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Role of tachykinin NK3 receptors in the release and effects of nerve growth factor in human isolated bronchi

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Abstract

The nerve growth factor (NGF) is a neurotrophic factor essential for the development and survival of neurons. It has also been identified as a mediator of inflammation and can cause airway hyperresponsiveness [Frossard et al., Eur. J. Pharmacol. 500, 453 (2004)]. Evidence in rodents suggests a link between tachykinins, the sensory nerves, and NGF. Recent evidence shows that NGF is released by the proinflammatory cytokine interleukin-1β and induces hyperresponsiveness to the tachykinin NK1 receptor agonist [Sar^9,$Met(O_2)^{11}$]SP in isolated human bronchi. The aim of this study was to determine the role of sensory nerves through the effect of the tachykinin NK3 receptor antagonist SR142801 in the interleukin-1β effects and/or the NGF-induced airway hyperresponsiveness. SR142801 (0.1 μM) abolished the interleukin-1β (10 ng/ml, 21 °C, 15 h)-induced increased NGF release from isolated human bronchi *in vitro* ($P<0.05$). In organ bath studies, SR142801 also abolished the interleukin-1β-induced airway hyperresponsiveness to [Sar^9,$Met(O_2)^{11}$]SP (0.1 μM) ($P<0.05$). SR142801 also inhibited the NGF-induced airway hyperresponsiveness ($P<0.01$). This study suggests tachykininergic sensory nerves to be involved in the interleukin-1β-induced NGF release and airway hyperresponsiveness.

Keywords: Nerve growth factor; Airway hyperresponsiveness; Tachykinin; Interleukin-1β; Neuroimmune interaction

1. Introduction

Chronic airway inflammation is an essential feature of asthma and chronic obstructive pulmonary disease (COPD). It is accompanied by enhanced production of proinflammatory cytokines in resident and inflammatory cells and bronchoalveolar lavage from symptomatic asthma patients (Broide et al., 1992; Sousa et al., 1996) and patients with COPD (Rusznak et al., 2000). Among these cytokines, interleukin-1β has a major role in the initiation and persistence of inflammation (Dinarello, 1996) and especially in the pathogenesis of chronic inflammatory diseases of the lung (Lappalainen et al., 2005). Previous reports show that interleukin-1β induces airway hyperresponsiveness in several animal models (Hernandez et al., 1991; Van Oosterhout and Nijkamp, 1993; Tsukagoshi et al., 1994) and in the isolated human bronchus (Molimard et al., 1998; Barchasz et al., 1999). The mechanism of this hyperresponsiveness is unclear but may involve various mediators. One of these is nerve growth factor (NGF). In experiments with human airway cells in culture, interleukin-1β induces the release of NGF from airway epithelial cells (Pons et al., 2001; Fox et al., 2001), airway smooth muscle cells (Freund et al., 2002), and fibroblasts (Olgart and Frossard, 2001). It can also induce NGF release from the isolated human bronchus (Frossard et al., 2005).

NGF is a neurotrophic factor essential for the development and survival of neurons (for reviews: Levi-Montalcini et al., 1996; Frossard et al., 2004) and, according to recent suggestions, an important mediator of inflammation (for reviews:

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Bonini et al., 1999; Frossard et al., 2004). Animal studies suggest that NGF in the airways contributes to the development of airway hyperresponsiveness since NGF blocking antibodies abolish the bronchial hyperresponsiveness created in allergen-sensitized and challenged mice (Braun et al., 1999) and rats (Glaab et al., 2003). Bronchial hyperresponsiveness also accompanies tissue-specific overexpression of NGF in the airways (Hoyle et al., 1998), and NGF by itself induces hyperresponsiveness in guinea-pig airways *in vivo* (de Vries et al., 2001) and *in vitro* (de Vries et al., 1999) and in the human bronchus *in vitro* (Frossard et al., 2005).

Finally, several lines of evidence suggest that NGF is associated with sensory nerves and their mediators. NGF is able to sensitize neurons and enhance production of tachykinins from sensory nerves (Hunter et al., 2000; Hoyle et al., 1998). Several reports show that the tachykinin NK_3 receptor antagonists SR142801 (Daoui et al., 1997, 1998; Nenan et al., 2001), SB223,412 and SB235,375 (Daoui et al., 2001; Hay et al., 2002; Mukaiyama et al., 2004) have anti-inflammatory effects. Conversely, tachykinin NK_3 receptor agonists have proinflammatory effects (Daoui et al., 2000, 2001), as does the upregulation of tachykinin NK_3 receptors in inflammatory conditions (Braun et al., 1999). These receptors are also involved in local sensory nerve transmission or regulation (Canning et al., 1998; Myers et al., 1996, 2005). The aim of this study was to determine whether the tachykinin NK_3 receptors played a role in (1) NGF release and/or (2) hyperresponsiveness to the [Sar^9,$Met(O_2)^{11}$]SP induced by interleukin-1β in the isolated human bronchus. To do so, we have studied the effect of the tachykinin NK_3 receptor antagonist SR142801 (Emonds-Alt et al., 1995) on both effects. We also studied the effect of SR142801 on hyperresponsiveness induced by NGF itself.

2. Materials and methods

2.1. Preparation of human bronchial tissue

Bronchial tissue was surgically removed from 31 patients with lung cancer (22 men, 9 women, mean age 63.1 ± 2.0 years; all patients were smokers or ex-smokers). The use of human lung tissue for *in vitro* experiments was approved by the local ethics committee. Just after resection, segments of the resected bronchi as far away as possible from the malignant lesion were placed in oxygenated Krebs–Henseleit solution (composition mM: NaCl 119, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11.7). After removal of adhering lung parenchyma and connective tissue, rings of each bronchus were prepared (5–7 mm length × 0.5–1 mm diameter) and divided into paired groups.

2.2. Study of the effect of interleukin-1β

Bronchial ring segments from one group (control group) were placed in 1 ml Krebs–Henseleit solution at room temperature (21 °C) for 15 h. Ring segments from a second group (pretreated group) were incubated (15 h at room temperature) with interleukin-1β (10 ng/ml Krebs–Henseleit solution), as previously reported (Molimard et al., 1998; Barchasz et al., 1999) with and without the tachykinin NK_3 receptor antagonist, SR142801 (0.1 μM) for 15 h at room temperature. After incubation, the bronchi were taken for contractile studies; the supernatant was kept in aliquots at −80 °C until NGF was measured.

2.3. Study of the effects of NGF

Bronchial ring segments were placed in Krebs–Henseleit solution at +4 °C overnight and used for contractile studies after pre-treatment with exogenous NGF (1 ng/ml) or saline for 30 min with or without SR142801 for 1 h before contraction was induced by addition of [Sar^9,$Met(O_2)^{11}$]SP in the organ baths.

2.4. Functional procedure

Bronchial ring segments were suspended on hooks in 5-ml organ baths containing Krebs–Henseleit solution, gassed with 95% O_2 − 5% CO_2 and maintained at 37 °C. Each preparation was connected to a force displacement transducer (UF1, Piodem, Canterbury, Kent, UK) and EMKA amplifier (EMKA Technology, Les Ulis, France). Isometric tension changes were recorded on a polygraph. Preparations were suspended with an initial tension of 1.5 g in organ baths, and were equilibrated for 60 min. Krebs–Henseleit solution was changed every 10 min for the first 30 min of the steady-state period before data acquisition began. A load of 1.0–1.5 g was maintained throughout the first 30 min of the equilibrium period. Contractile response to the tachykinin NK_1 receptor agonist, [Sar^9,$Met(O_2)^{11}$]SP (0.1 μM), was then measured; 15 min later, acetylcholine 3 mM was directly added into the bath. [Sar^9,$Met(O_2)^{11}$]SP contraction was recorded only once for each ring segment to avoid the rapid desensitization of tachykinin NK_1 receptors previously reported in human bronchi (Naline et al., 1996). Furthermore, the 0.1 μM concentration of [Sar^9,$Met(O_2)^{11}$]SP was selected as that which yielded the maximal contractile response without interfering with tachykinin NK_2 receptors (Naline et al., 1996).

2.5. Quantification of NGF protein by ELISA

NGF was quantified in the supernatant of isolated human bronchi. We used a commercially available highly sensitive, NGF-specific, two-site enzyme-linked immunosorbent assay (ELISA kit) and followed the manufacturer's instructions (Promega, Madison, WI, USA). Briefly, 96-well immunoplates (Maxisorp™, Nunc, Roskilde, Denmark) were coated with a polyclonal goat anti-human NGF antibody in a coating buffer (25 mM carbonate buffer, pH 9.7). After overnight incubation at +4 °C, plates were washed (20 mM Tris–HCl, 150 mM NaCl with 0.05% (v/v) Tween®-20; Sigma Aldrich) and incubated in a blocking buffer for 1 h. The supernatants and the standard recombinant human NGF dilutions in Krebs–Henseleit were incubated at 37 °C for at least 6 h and then washed. Rat monoclonal anti-NGF antibody (0.25 μg/ml) was added for overnight incubation at +4 °C, and washed. Anti-rat horseradish peroxidase-conjugated IgG was added and incubated for 2.5 h.

The substrate (3,3′,5,5′-tetramethylbenzidine 0.02% and hydrogen peroxidase 0.01%) was then added. The colorimetric reaction was stopped after 10 min by adding phosphoric acid (1 M), and the optical density was measured in duplicate at 450 nm. The technique made it possible to detect NGF in the range of 3.9 to 500 pg/ml.

2.6. Expression of results and statistical analysis

All values in the text and in the figures are expressed as means±S.E.M. Contractile responses were expressed in tension (g) or in percentages of the contraction induced by acetylcholine 3 mM. NGF protein levels were expressed as pg NGF/mg wet weight tissue or as a percentage of control secretion. Statistical analysis of the data was performed using analysis of variance and Student's *t*-test for paired data. Data were considered significantly different when $P<0.05$.

2.7. Drugs

The drugs used were: [Sar^9,Met(O$_2$)^{11}]SP and recombinant human interleukin-1β (Bachem, Bubendorf, Switzerland), nerve growth factor (NGF, R&D, UK), and (*S*)-(*N*)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-*N*-methylacetamide (SR142801, Sanofi Synthelabo Recherche, Montpellier, France). Interleukin-1β and NGF were dissolved in distilled water at a concentration of 5 μg/ml and 20 μg/ml, respectively and kept in aliquots at −80 °C until used. All drugs were first dissolved in distilled water and then further diluted in Krebs solution.

3. Results

3.1. Bronchial hyperresponsiveness induced by interleukin-1β

In control experiments (without incubation with interleukin-1β), [Sar^9,Met(O$_2$)^{11}]-SP induced a contraction that was not modified by SR142801 (0.1 μM, 15 h , 21 °C) (2.44±0.20 g in control *vs* 2.38±0.15 g in the presence of SR142801, $n=12$).

Bronchi incubated overnight with interleukin-1β (without SR142801) became hyperresponsive to [Sar^9,Met(O$_2$)^{11}]SP in the functional studies. Response was 58.9±18.3% higher than in the control experiments ($P<0.05$, $n=13$) (Fig. 1). Under similar conditions, responses to acetylcholine 3 mM did not change: 4.48±0.20 g, $n=13$ (without) *vs* 4.10±0.18 g, $n=13$ (with interleukin-1β). SR 142801 (0.1 μM) incubated with interleukin-1β for 15 h totally suppressed the interleukin-1β-induced airway hyperresponsiveness (Fig. 1).

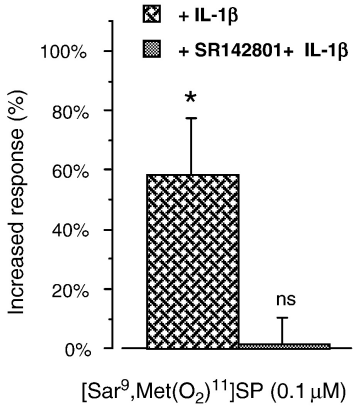

Fig. 1. Effect of interleukin-1β (10 ng/ml, 15 h, 21 °C) on the contractile response to [Sar^9,Met(O2)^{11}]-SP (0.1 μM) of the human isolated bronchi with or without the tachykinin NK$_3$ receptor antagonist SR142801 (0.1 μM, 15 h, 21 °C). Results are means±S.E.M. of experiments performed in duplicate on bronchi from 13 patients, and expressed as percentage of increase from control values. Significant differences are shown as * with $P<0.05$.

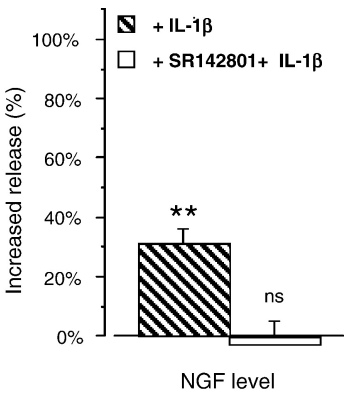

Fig. 2. Effect of interleukin-1β (10 ng/ml, 15 h, 21 °C) on NGF release from human isolated bronchi with or without the tachykinin NK$_3$ receptor antagonist SR142801 (0.1 μM, 15 h, 21 °C). Results are means±S.E.M. of 9 experiments in duplicate on bronchi from 9 patients, and expressed as percentage of increase from control values. Significant differences from controls are shown as ** with $P<0.01$.

3.2. NGF release by interleukin-1β

The level of NGF in the control incubation medium (15 h at 21 °C) was 2.60±0.49 pg/mg wet weight tissue. Interleukin-1β (10 ng/ml) incubated for 15 h at 21 °C induced a significant increase (31.1±5.0%, $n=9$, $P<0.01$) in the levels of NGF measured in the incubation medium. SR142801 incubated with

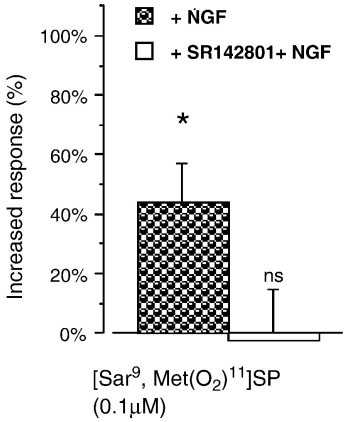

Fig. 3. Effect of SR142801 (0.1 μM, 1 h, 37 °C) on the increased response to [Sar^9,Met(O2)^{11}]-SP (0.1 μM) by NGF (1 ng/ml, 30 min) in the human isolated bronchi. Results are means±S.E.M. of experiments performed in duplicate on bronchi from 11 patients, and expressed as percentage of increase from control values. Significant increase is shown as * $P<0.05$.

interleukin-1β for 15 h totally abolished this increase of NGF levels from the isolated human bronchus (Fig. 2).

3.3. Bronchial hyperresponsiveness induced by NGF

Bronchi incubated with exogenous NGF (1 ng/ml, 30 min at 37 °C) became hyperresponsive to [Sar^9,$Met(O_2)^{11}$]-SP. Response was increased by 43.9±13.1% ($n=11$, $P<0.05$) (Fig. 3). SR142801, added to the bath 30 min before NGF, abolished the hyperresponsiveness induced by NGF on (Sar^9, $Met(O_2)^{11}$)-SP response (Fig. 3).

4. Discussion

We report here that the tachykinin NK_3 receptor antagonist SR142801 abolishes the potentiation of the [Sar^9,$Met(O_2)^{11}$] SP-induced contraction by both interleukin-1β and the neurotrophic factor NGF. It also abolishes the interleukin-1β-induced NGF release in the isolated human bronchus. These findings suggest that the tachykinin NK_3 receptor plays a role in these effects in the airways.

Although the distribution of the tachykinin NK_3 receptor was identified early on in the central nervous system of rodent (Ding et al., 1996; Mileusnic et al., 1999) and man (Buell et al., 1992; Mileusnic et al., 1999), early studies did not succeed in detecting it in the lungs (Bai et al., 1995; Baluk and Mc Donald, 1998). However, Pinto et al. (2004) using a reverse transcription-polymerase chain reaction method, recently pinpointed the presence of its mRNA in human airways and pulmonary arteries and veins. In addition, evidence from several types of functional studies in animals shows that the tachykinin NK_3 receptor may play a significant role in controlling pulmonary function and increases the neuronal activity and responsiveness of target cells. For example, aerosol administration of NKB and of the tachykinin NK_3 receptor selective agonists in guinea pigs elicits airway hyperresponsiveness (Daoui et al., 2000) and potentiation of histamine-induced airway microvascular leakage (Daoui et al., 2001), respectively. These effects are abolished by the the tachykinin NK_3 receptor-antagonists SR142801 and SB223,412 (Daoui et al., 2000, 2001). Moreover, in guinea pigs, SR142801, SB235,375 and SB223,956, respectively, inhibit induction of airway hyperresponsiveness to a cholinergic agonist by substance P, citric acid, fenoterol and allergen (Daoui et al., 1997; Hay et al., 2002; Pinto et al., 2002; Mukaiyama et al., 2004), as well as potentiation of the histamine-induced microvascular permeability induced by citric acid (Daoui et al., 1998). In sensitized mice, aerosol exposure to SR142801 significantly reduces recruitment of inflammatory cells – neutrophils and eosinophils – in the airways, after antigen challenge (Nenan et al., 2001). Finally, the tachykinin NK_3 receptor antagonists SR142801, SSR146977 and SB235,375 inhibit citric acid-induced coughing in guinea pigs (Daoui et al., 1998; Emonds-Alt et al., 2002; Hay et al., 2002) and pigs (Moreaux et al., 2000). Hay et al. (2002) suggest that since SB235,375 is characterized by a low penetration into the central nervous system, its effect on citric acid-induced coughing or airway hyperresponsiveness is exerted through the peripheral nervous system.

From these evidence, the tachykinin NK_3 receptor antagonist SR 142801 was used to study the relation between interleukin-1β-releasing NGF and the sensory nerves in more detail. Our demonstration of its blockade of bronchial hyperresponsiveness complements that previously reported by de Vries et al. (1999) who found that NGF-induced airway hyperresponsiveness in the guinea pig was blocked by a mechanism dependent on the NK_1 receptor. Our finding that the tachykinin NK_3 receptor antagonist SR142801 abolished NGF-induced hyperresponsiveness, as well as NGF release by interleukin-1β, is consistent with previous reports of reduction of bronchial inflammation and hyperresponsiveness through the tachykinin NK_3 receptor-dependent mechanisms (Daoui et al., 2000, 2001; Hay et al., 2002; Mukaiyama et al., 2004).

However, the mechanism by which SR142801 inhibits the airway hyperresponsiveness induced by interleukin-1β and NGF and the release of NGF by interleukin-1β remains unclear. NGF sensitizes neurons and enhances tachykinin production in sensory neurons (Hunter et al., 2000). The tachykinin NK_3 receptor is involved in the control of neural activity: electrophysiologic studies show that substance P and neurokinin B or the selective agonist for the tachykinin NK_3 receptor [$Asp^{5,6}$, Methyl-Phe^8]SP (5-11), but not neurokinin A, induce depolarization of guinea-pig bronchial parasympathetic ganglion neurons and that neurokinin B is 60 times more potent and five times more efficient than substance P for that purpose (Myers et al., 1996). The tachykinin NK_3 receptor plays a similar role in the regulation of parasympathetic ganglionic neurotransmission in the human bronchus (Myers et al., 2005). Furthermore, the tachykinin NK_3 receptor antagonist SR142801 reduces both the capsaicin-evoked slow excitatory post-synaptic potential of guinea-pig bronchial and tracheal parasympathetic neurons (Myers et al., 1996) and the relaxation of the guinea-pig trachea elicited by antidromic stimulation of capsaicin-sensitive sensory vagal afferent nerves (Canning et al., 1998).

NGF also exerts early apparently local effects that do not require either transport of proteins to the soma or transcriptional mechanisms. de Vries et al. (2001) reported this effect in the guinea-pig trachea *in vitro*, where NGF induces hyperresponsiveness to histamine within 30 min. It also occurs in skin hyperalgesia: Rueff and Mendell (1996) examined the response of nociceptive afferents in an isolated skin-nerve preparation and showed that NGF, applied directly to the receptive field for 20 min, lowered the threshold of thermal stimulation. Shu and Mendell (1999a) looked at short-acting effects and showed that NGF applied for 10 min on dorsal root ganglion neurons in culture abolished the tachyphylaxis observed in response to capsaicin or even potentiated these responses. These results, considered with the data we report here, suggest that NGF induces early posttranslational changes in neurons and cells and that these may be involved in the neuronal "sensitization" within the tissue (Shu and Mendell, 1999a,b; Nicholas et al., 1999; Woolf and Costigan, 1999). They also suggest NGF-induced neuronal hyperexcitability, similar to hyperalgesia (Shu and Mendell, 1999b), as a possible cause for the bronchial hyperresponsiveness observed *in vitro* and a role for the tachykinin NK_3 receptor antagonists in its inhibition.

In conclusion, our results confirm that NGF released by interleukin-1β may be involved in the airway hyperresponsiveness induced by this cytokine. Furthermore, the inhibitory effect caused by the tachykinin NK_3 receptor antagonist SR142801 suggests an involvement of sensory nerves in the interleukin-1β-induced release of NGF and its effect in airway hyperresponsiveness. These data add to the growing body of evidence of neuroimmune cross-talk in the airways, a mechanism close to that of hyperalgesia, involved in NGF-induced bronchial hyperresponsiveness.

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