Neurokinin B- and specific tachykinin NK3 receptor agonists-induced airway hyperresponsiveness in the guinea-pig

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1 The aim of this study was to determine whether neurokinin B (NKB) or specific agonists of tachykinin NK3 receptors, [MePhe7]NKB and senktide, were able to induce airway hyperresponsiveness in guinea-pigs. The effects of these compounds were compared to those of substance P (SP), neurokinin A (NKA) and the preferential tachykinin NK1 ([Sar9,Met(0)2]SP) or NK2 (βAla8)NKA (4-10) receptor agonists.

2 In guinea-pigs pretreated with phosphoramidon (10^{-4} M aerosol for 10 min) and salbutamol (8.7 × 10^{-3} M for 10 min), all tachykinins administered by aerosol (3 × 10^{-7} to 10^{-4} M) induced airway hyperresponsiveness 24 h later, displayed by an exaggerated response to the bronchoconstrictor effect of acetylcholine (i.v.). The rank order of potency was: [βAla8]NKA (4-10) > NKA = NK2 = senktide = [MePhe7]NKB = [Sar9,Met(0)2]SP > SP.

3 Airway hyperresponsiveness induced by [MePhe7]NKB was prevented by the tachykinin NK3 (SR 142801) and NK2 (SR 48968) receptor antagonists.

4 Bronchoconstriction induced by tachykinins administered by aerosol was also determined. SP, NKA, NKB and the tachykinin NK1 and NK2 receptor agonist induced bronchoconstriction. The rank order of potency was: NKA = [βAla8]NKA (4-10) > NK2 = NK1 = senktide = [MePhe7]NKB = [Sar9,Met(0)2]SP. Under similar conditions, and for concentrations which induce airway hyperresponsiveness, senktide and [MePhe7]NKB failed to induce bronchoconstriction.

5 It is concluded that tachykinin NK3-receptor stimulation can induce airway hyperresponsiveness and that this effect is not related to the ability of tachykinins to induce bronchoconstriction.

Keywords: Tachykinins; airway hyperresponsiveness; tachykinin NK3 receptors

Abbreviations: NKA: neurokinin A; NKB: neurokinin B; SP: substance P

Introduction

Tachykinins, a group of neuropeptides including substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are the transmitters of sensory neurones which, in the lung, innervate all compartments of the airway wall from the trachea down to the bronchioles (Baluk & McDonald 1998; Ellis & Undem 1994; Lundberg 1996; Lundberg & Saria 1987). The activation of C-fibre afferent nerves in airways leads to a local release of tachykinins that are responsible for several biological effects: bronchospasm, increase in microvascular permeability, vasodilatation, stimulation of glandular secretions, facilitation of cholinergic neurotransmission, recruitment and activation of inflammatory cells. Sensory nerves also mediate respiratory defence reflexes, such as coughing and sneezing (Ellis & Undem, 1994; Maggi et al., 1993; Widdicombe, 1995).

The biological actions of tachykinins are mediated via three types of receptors, denoted tachykinin NK1, NK2 and NK3 which have the highest affinity for SP, NKA and NKB, respectively. This receptor classification has been established from receptor-binding and functional studies using selective agonists or antagonists for tachykinin receptors (Regoli et al., 1994). It has now been recognized that the expression of tachykinin NK3 receptor is confined mainly to the central and peripheral nervous system, whilst tachykinins NK1 and NK2 receptors are expressed both in the nervous system and in target organs, including airways (Baluk et al., 1996; Guard & Watson, 1991; Maggi, 1993; Myers & Undem, 1993).

Several experimental reports using different animal species have suggested that tachykinins are involved in airway hyperresponsiveness, an enhanced bronchoconstrictor response to many different stimuli and a key feature of asthma. Airway hyperresponsiveness is associated with inflammation in the airways and relates closely to the severity of asthma, the frequency of symptoms, and the need for treatment (Barnes, 1989; Boushey et al., 1980; O’Byrne, 1988). Indeed, exposure to a single aerosol of SP elicited 24 h later airway hyperresponsiveness to exogenous bronchoconstrictor agents in guinea-pigs (Boichot et al., 1993). Similar data were observed in asthmatic patients (Cheung et al., 1994). NKA also enhanced methacholine response up to 4 weeks in monkeys (Tamura et al., 1989). Conversely, chronic treatment with high doses (i.p.) of capsaicin which depletes tachykinins from sensory nerves, or single pretreatments with the tachykinin NK1 [CP 96345, SR 140333], NK2 [SR 48968, MEN 10,627] or NK1+NK2 [MDL 105212; FK 224] receptor antagonists have been reported to prevent airway hyperresponsiveness in various experimental models in guinea-pigs, mice or monkeys (see reviews Advenier et al., 1997; Kraneveld et al., 1997; Spina et al., 1998).

We have recently demonstrated that the NK3 receptor antagonist, SR 142801 (Osanetant) (Emonds-Alt et al., 1995) was also able to inhibit in guinea-pig airway hyperresponsiveness induced by substance P (Daoui et al., 1997) or citric acid (Daoui et al., 1998), and to prevent in human isolated bronchi hyperresponsiveness induced by interleukin 1-β or by passive sensitization (Vincent et al., 1999). To our knowledge, no
studies have been performed in order to determine if agonists for NK3 receptors may induce airway hyperresponsiveness as previously reported for substance P and NKA.

The aim of this study was to determine whether NKB or the specific agonists of NK, receptors, [MePhe7]NKB or senktide, were able to induce airway hyperresponsiveness in guinea-pigs. We also compared the potency of NKB and tachykinin NK3 agonists with those of SP, NKA and of tachykinin NK4 and NK2 receptor agonists.

Methods

Airway hyperresponsiveness to acetylcholine
Exposure to tachykinins or tachykinin receptor agonists aerosol. Tricoloured unanaesthetized, unrestrained male or female guinea-pigs (300 – 400 g), were placed in Plexiglas chamber (30 × 25 × 15 cm) and exposed successively to a nebulized aqueous solution of salbutamol (8.7 × 10^-3 M, 10 min) or phosphoramidon (10^-7 M, 10 min) in order to prevent tachykinins- or tachykinin receptor agonist-induced bronchoconstriction and tachykinin metabolism; 5 min later the animals were exposed to a single aerosol of tachykinins or tachykinin receptor agonists at various concentrations (3 × 10^-7 to 10^-4 M) or vehicle solution as control group for 30 min (Figure 1). An ultrasonic nebulizer (Aerodynamic mean mass median particle diameter of 0.5 to 5 μm, NEB99, Devilbiss, Somerset, PA, U.S.A.) was used. Previous studies have shown that phosphoramidon and/or salbutamol when used alone or in combination were not able to induce airway hyperresponsiveness (Girard et al., 1996; Daoui et al., 1997, 1998).

Assessment of the in vivo bronchopulmonary reactivity. 24 h after exposure to tachykinins or tachykinin receptor agonists (Figure 1), animals were anaesthetized with urethane (1.25 g kg^-1, i.p.) and placed on a heated blanket (Homeothermic blanket system, Havard Apparatus Ltd, Kent, U.K.). A jugular vein was cannulated for injection of acetylcholine. A tracheal cannula was inserted and artificial ventilation was maintained by means of a constant volume ventilator. Animals were ventilated with room air at a rate of 60 breath per min and at a tidal volume of approximately 10 ml kg^-1. Airway function was assessed by measuring changes in pleural pressure, which can be regarded as an indicator of airway resistance at least in guinea-pigs (Santing et al., 1992). Pleural pressure was determined with a catheter fitted with a 16 G needle inserted into the 6th or 7th intercostal space and connected to a pressure transducer (P23XL, Viggo-Spectramed, Bilthoven, Netherlands). The pleural pressure increase was evaluated as the difference between the baseline value and the maximum response (the peak value) after tachykinin or tachykinin receptor agonist aerosol.

After a 30 min resting period, artificial ventilation was stopped, and the tracheal cannula was connected in spontaneously breathing animals directly to the nebulizer. Aerosols of tachykinin or tachykinin receptor agonist solutions (3 × 10^-7 to 10^-4 M) were administered for 2 min and about 0.3 ml of the solution was nebulized per min. After the pleural pressure was returned to baseline or stabilized, artificial ventilation was set running again. Preliminary experiments have shown that responses were reproducible at least three times at 30 min intervals. Also we have demonstrated that no significant changes were produced by 0.9% saline aerosol (0.3 ml min^-1) administration. The bronchopulmonary responses were expressed as per cent changes vs acetylcholine (500 μg kg^-1, i.v.) administered at the end of the experiment, in spontaneously breathing animals.

Statistical analysis of results

Data are expressed as means ± s.e.mean. EC30 value is the dose which provokes an increase in airway inflation pressure of 30% of the maximal effect (Girard et al., 1996; Daoui et al., 1997, 1998). Statistical analysis of the results was assessed by a two-way analysis of variance (ANOVA) followed by a Student’s t-test for paired or unpaired data. Probability values of P < 0.05 were considered significant.

Drugs

The substances used were: urethane (Prolabo, Paris, France); histamine dihydrochloride, phosphoramidon, salbutamol sulphate (Sigma, St Louis, MO, U.S.A.); acetylcholine hydrochloride (PCH, Paris, France); substance P, [Sar^9, Met(O2)^10]substance P, neurokinin A, [βAla^10]neurokinin A (4-10) (Bachem, Paris, France); neurokinin B, [MePhe^7]neurokinin B, senktide (Novabiochem, Paris, France); neurokinin B, MePhe^7]neurokinin B, senktide (Novabiochem, Paris, France); SR 48968 [(S)-N-methyl-N-[4-acetylamino-4-phenylpiperidino-2-(3,4-dichlorophenyl)butyl]benzamid] (saredutant) used as hydrochloride, SR 140333 [(S)-1-[2-(3,4-dichlorophenyl)-1-(3-isopropoxyphenylacetyl)piperidin-3-y1]ethyl]-4-phenyl-1-azoniacyclclo[2.2.2]octane, chloride (chloride of nortipitramine) and SR 142801 [(R)-(N-h)1-[3-(3,4-dichlorophenyl)piperidin-3-yl]propyl-4-phenylpiperidin-4-yl]-N-methylacetamide (osanetant) used as hydrochloride (Sanofi Recherche, Montpellier, France). All drugs were dissolved in saline, except SR 48968, SR 140333 and SR 142801 which were dissolved in ethanol and then in diluted saline, and neurokinin B and [MePhe^7]neurokinin B which were dissolved in acetic acid (100%) and then diluted in saline. The maximum amount of ethanol injected (20 μl per 100 g body weight) did not modify the respiratory responses to acetylcholine, the development of...
Figure 1  Experimental protocol of induction of airway hyperresponsiveness and measurement of airway inflation pressure in guinea-pigs.

Figure 2  Cumulative contractile concentration-response curves for acetylcholine (10–200 µg kg⁻¹) in anaesthetized guinea-pigs, 24 h after aerosols of salbutamol (8.7 x 10⁻³ M, 10 min), phosphoramidon (10⁻⁴ M, 10 min) and saline (NaCl 9 %, 30 min) or SP, NKA, NKB, [Sar⁹, Met(O₂)¹¹]SP, [βAla⁸]NKA (4-10), [MePhe⁷]NKB and senktide (3 x 10⁻⁷ to 10⁻⁴ M, 30 min). Values are means ± s.e.mean, n are reported in Tables 1 and 2. AIP: airway inflation pressure. Significant difference from control shown as: *P < 0.05 and **P < 0.01.
airway hyperresponsiveness and bronchoconstriction at the dilution used.

Results

Comparison of the ability of the tachykinins and tachykinin receptor agonists to induce hyperresponsiveness when given by aerosol

Airway hyperresponsiveness developed consistently 24 h after a single tachykinin or tachykinin receptor agonist (3 x 10⁻⁷ to 10⁻⁴ M) exposure in guinea-pigs pretreated with phosphoramidon, as evidenced by a significant leftward shift in dose response curves to acetylcholine-induced bronchoconstriction in comparison with matched saline controls (Figure 2). The maximum bronchoconstrictor responses to acetylcholine (E₉₀, at 500 µg kg⁻¹) were similar in animals exposed to tachykinins, tachykinin receptor agonists or saline (Tables 1 and 2). ED₉₀ values for acetylcholine were significantly lower in animals pretreated with salbutamol, phosphoramidon and exposed to tachykinins or tachykinin receptor agonists than in saline exposed animals control, showing a maximal increase in sensitivity of approximately 2 fold.

Relative potency of agonists

The relative potencies of the tachykinins and their selective analogues were compared using data derived from ED₉₀ values (Tables 1 and 2). Significant increases in airway responsiveness were observed from 10⁻⁴ M for [βAla]²NKA (4-10), from 10⁻³ M for NKA, NKB, [MePhe]²NKB, senktide and [Sar⁹, Met(O₂)¹¹]²SP and for 10⁻⁴ SP for SP. The rank order of potency was: [βAla]²NKA (4-10) > NKA = NKB = [MePhe]²NKB = senktide = [Sar⁹, Met(O₂)¹¹]²SP > SP (Tables 1 and 2).

Effects of SR 140333 (NK₂ antagonist), SR 49868 (NK₃ antagonist) or SR 142801 (NK₃ antagonist) on [MePhe]²NKB-induced hyperreactivity

Airway hyperresponsiveness to acetylcholine following exposure to [MePhe]²NKB was abolished by a single dose of the tachykinin NK₂ or NK₃ receptor antagonists SR 49868 and SR 142801 (1 mg kg⁻¹, i.p.), administered 45 min before [MePhe]²NKB exposure (Table 3). In contrast after the administration of the selective NK₁ agonist SR 140333 (1 mg kg⁻¹, i.p.), the ED₉₀ for acetylcholine did not appear significantly different between control animals and animals pretreated with [MePhe]²NKB. Only a partial inhibition was observed.

Comparison of the bronchoconstrictor response to tachykinin and selective tachykinin receptor agonists in guinea-pigs in vivo

In control animals that received successive administrations of a 0.9 % NaCl aerosolized solution no significant changes in the baseline was observed. The effects of various tachykinins and selective receptor agonists were then examined. Without prior treatment with phosphoramidon (10⁻⁴ M, aerosol for 10 min), the guinea-pigs did not respond to tachykinin or tachykinin receptor agonist aerosolized solution at concentrations up to 3 x 10⁻⁴ M. After pretreatment with phosphoramidon, the guinea-pigs responded to SP, NKA, NKB, neurokinin B-aerosol exposure on bronchoconstriction

Table 1 Effects of substance P-, neurokinin B-aerosol and acetylcholine-induced bronchoconstriction

<table>
<thead>
<tr>
<th>Bronchoconstrictive agents</th>
<th>Aerosol concentration</th>
<th>n</th>
<th>Acetylcholine</th>
<th>E₉₀±s.e.mean</th>
<th>E₉₀±s.e.mean</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(µg kg⁻¹)</td>
<td>(cmH₂O)</td>
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<tr>
<td>Control</td>
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</tr>
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Neurokinin A

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<tr>
<td>3 x 10⁻⁵ M</td>
<td>8</td>
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<td></td>
<td>28.8±4.6***</td>
<td>34.4±2.2</td>
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<tr>
<td>3 x 10⁻⁵ M</td>
<td>6</td>
<td></td>
<td>29.3±10.4**</td>
<td>32.5±2.1</td>
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Neurokinin B

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<tbody>
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<td>3 x 10⁻⁶ M</td>
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<td></td>
<td>54.4±7.4</td>
<td>30.5±21.1</td>
<td></td>
</tr>
<tr>
<td>10⁻⁵ M</td>
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<td>37.5±4.5**</td>
<td>24.5±4.2</td>
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<td>3 x 10⁻⁵ M</td>
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<td></td>
<td>34.7±5.6**</td>
<td>32.1±5.3</td>
<td></td>
</tr>
<tr>
<td>10⁻⁴ M</td>
<td>4</td>
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<td>29.5±4.8***</td>
<td>36.9±6.2</td>
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</tr>
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</table>

Definition of abbreviations: n = number of experiments; ED₉₀ = dose of acetylcholine giving 30% increase in airway inflation pressure; E₉₀ = increase in airway inflation pressure induced by acetylcholine 500 µg kg⁻¹. Values are mean ± s.e.mean. Significant differences from control are: *P<0.05; **P<0.01; ***P<0.001.

Table 2 Effects of different selective tachykinin receptor agonists on acetylcholine-induced bronchoconstriction

<table>
<thead>
<tr>
<th>Bronchoconstrictive agents</th>
<th>Aerosol concentration</th>
<th>n</th>
<th>Acetylcholine</th>
<th>E₉₀±s.e.mean</th>
<th>E₉₀±s.e.mean</th>
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<td></td>
<td></td>
<td>(µg kg⁻¹)</td>
<td>(cmH₂O)</td>
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<tr>
<td>Control</td>
<td>14</td>
<td></td>
<td>71.3±6.7</td>
<td>34.7±3.3</td>
<td></td>
</tr>
<tr>
<td>[Sar⁹, Met(O₂)¹¹]²SP</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>30.7±6.2</td>
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<td>3 x 10⁻⁶ M</td>
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<td></td>
<td>46.6±5.4**</td>
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</tr>
<tr>
<td>[βAla³]²NKA (4-10)</td>
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<td>3 x 10⁻⁷ M</td>
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<td></td>
<td>59.3±7.2</td>
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<tr>
<td>10⁻⁶ M</td>
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<td>50.8±2.4*</td>
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<tr>
<td>3 x 10⁻⁷ M</td>
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<td>55.2±6.7</td>
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<tr>
<td>3 x 10⁻⁷ M</td>
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<td>[MePhe⁷]²NKB</td>
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<td>59.1±7.5</td>
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<td>61.7±7.3</td>
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<td>10⁻⁶ M</td>
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<td>31.1±5.0***</td>
<td>34.8±3.7</td>
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</tbody>
</table>

Senktide

| Substance P                |                      |   |               |              |              |
| 10⁻⁶ M                    | 10                   |   | 52.9±6.2      | 36.2±3.8     |              |
| 10⁻⁶ M                    | 6                     |   | 29.1±6.5***   | 33.8±6.3     |              |

Definition of abbreviations: n = number of experiments; ED₉₀ = dose of acetylcholine giving 30% increase in airway inflation pressure; E₉₀ = increase in airway inflation pressure induced by acetylcholine 500 µg kg⁻¹. Values are mean ± s.e.mean. Significant differences from control are: *P<0.05; **P<0.01; ***P<0.001.

[Sar⁹, Met(O₂)¹¹]²SP and [βAla³]²NKA (4-10) with an immediate bronchoconstriction. The rank order of potency to induce bronchoconstriction was: [βAla³]²NKA (4-10) > NKA > NKB > SP > [Sar⁹, Met(O₂)¹¹]²SP. Under similar conditions [MePhe⁷]²NKB and senktide had no effect (Figure 3).

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In the present study, we found that NKB and the tachykinin NK3 receptor agonist, [MePhe7]NKB (4-10) and senktide are also able to induce airway hyperresponsiveness in guinea-pigs pretreated with phosphoramidon. However, in terms of potency, the selective agonist for tachykinin NK2 receptor [βAla8]NKA (4-10) appears the most effective, since it significantly elicits a significant leftward shift of the dose-response curve to ACh, from the concentration of $10^{-6}$ M. We also observed that [MePhe7]NKB and senktide showed a similar effect as NKA, whereas NKB and [Sar9, Met(O2)11]SP were more effective than SP. The activity of NKB could be mediated through the effect on NK3 and/or NK2 receptors regarding the nonselective activity of this compound on NK3 receptors (Regoli et al., 1994). Nevertheless, the involvement of NK3 receptors in the effects of [MePhe7]NKB and senktide is strongly suggested by the high selectivity of these agonists on NK3 receptors in several radioligand binding and functional assays (Regoli et al., 1994).

The development of bronchial hyperresponsiveness induced by tachykinins and selective agonists for tachykinin receptors is not related to their bronchoconstrictor effects. Indeed, in this study the guinea-pigs are pretreated by the potent bronchodilator drug, salbutamol, in order to avoid all spasmogenic activities during the aerosol administration of tachykinin and tachykinin selective agonist. Moreover, [MePhe7]NKB and senktide do not elicit a bronchoconstrictor response by themselves. The dissociation between the bronchoconstrictor activity and the induction of bronchial hyperresponsiveness is also demonstrated by the use of [βAla8]NKA (4-10) and NKA. Both compounds elicit similar bronchoconstrictor effects (Chan et al., 1994; Yuan et al., 1994 and this study), but [βAla8]NKA (4-10) induced a more marked leftward shift of the dose-response curve to ACh than NKA. Similar observations and conclusions may be proposed in view of the respective efficacy of [Sar9, Met(O2)11]SP and SP in the induction of bronchoconstriction and airway hyperresponsiveness.

Discussion

Tachykinin NK3 receptor stimulation induces airway hyperresponsiveness

Tachykinins induce various effects in the bronchopulmonary system and they are recognised to be involved in the pathogenesis of airway hyperresponsiveness in animal models (see introduction and reviews of Advenier et al., 1997; Kraneveld et al., 1997; Spina et al., 1998). Indeed, it has been previously reported that aerosol exposure of SP induces the development of airway hyperresponsiveness in guinea-pigs (Boichot et al., 1993; Daoui et al., 1997). Similar results were obtained in asthmatic patients (Cheung et al., 1994). Moreover, NKA also elicits airway hyperresponsiveness in monkeys (Tamura et al., 1989) but no studies have been conducted to date that evaluate the capacity for NK3 receptor agonists to induce the development of airway hyperresponsiveness.
was abolished by the tachykinin NK3 receptor antagonist, SR 142801 (osanetan), but also by the tachykinin NK2 receptor antagonist, SR 48968 (saredutant). Similar observations were previously reported on airway hyperresponsiveness induced by SP or citric acid (Daoui et al., 1997, 1998). This later compound has been demonstrated to release endogenous tachykinins from capsaicin sensitive nerve endings (Belmonte et al., 1990; Fox et al., 1995; Geppetti et al., 1991; Steen et al., 1992). In contrast to the inhibitory activity of SR 142801, the effect of SR 48968 and other NK2 receptor antagonists on the development of bronchial hyperresponsiveness have been clearly demonstrated in sensitized and challenged guinea-pigs (Boichot et al., 1995; Kudlacek et al., 1996) or after exposure to toluene diisocyanate (Marek et al., 1996); cold air (Yoshihara et al., 1996); ozone (Masson et al., 1996) or PAF (Perretti & Manzini, 1993) in guinea-pigs.

The tachykinin NK3 receptor antagonist, SR 140333, only elicited a partial inhibition of [MePhe7]NKB. In previous reports, we observed that SR 140333 did not prevent in guinea-pigs airway hyperresponsiveness induced by SP (Boichot et al. 1996) or by an allergen challenge in sensitized animals (Boichot et al., 1995). The effects of SR 140333 is however debated since Schuiling et al. (1999) reported a preventive effect of this drug in the latter model. These discrepancies could be explained by the different protocols and spasmogenic agents used in both cases.

**Hypothesis on the mechanism of action of tachykinin NK3 agonists**

To date, it is difficult to provide the exact mechanism and the site of action of NK3 agonists in the development of airway hyperresponsiveness. Indeed, airway hyperresponsiveness is a complex process which involves multiple cell interactions and several mediators. Firstly, it seems that the action of NK3 agonists is mainly due to the NK3 receptor activation pathway. Secondly, this activity may involve neuronal receptors rather than post-junctional effector sites. Thirdly, a cascade of physiopathological process associated with the successive stimulation of tachykinin receptors may also be proposed.

The activity of NKB, [MePhe7]NKB and senktide involve the NK3 receptor pathway as suggested by the high selectivity of these agonists on this receptor subtype, but also by the inhibitory activity of the selective NK3 antagonist, SR 142801. The compound selectivity has been demonstrated by radioligand binding and well characterized in vitro functional assays for tachykinin receptors (Beaujouan et al., 1997; Daoui et al., 1997; Emonds-Alt et al., 1995; Nguyen-Le et al., 1996; Oury-Donat et al., 1995; Patacchini et al., 1995). In vivo, the selectivity of SR 142801 is clearly suggested by two assays: in contrast to SR 48968, SR 142801 (1 mg kg⁻¹) did not inhibit bronchoconstriction induced by [Nle10]NKA (4-10) in anaesthetized guinea-pigs (Daoui et al., 1997); and unlike SR 140333, SR 142801 (1 mg kg⁻¹) failed to inhibit the hypotension induced by [Sar²,Met(O₂)⁴]SP in guinea-pigs and dogs (Emonds-Alt et al., 1993, 1995; Roccon et al., 1996).

A direct priming effect of NK3 receptor stimulation on target cells is unlikely, since a low number of NK3 tachykinin receptor has been identified in lung (Baluk et al., 1996). In agreement with previous studies (Ellis et al., 1993; Killingsworth & Shore, 1995; Maggi et al., 1991), our results demonstrating that [MePhe7]NKB and senktide do not present bronchoconstrictor activity in the guinea-pig suggest that NK3 receptor stimulation does not lead to the contraction of airway smooth muscle. A direct participation of NK3 receptors in the impairment of vessels and endothelial cells, leading to microvascular leakage and airway obstruction is also excluded since SR 142801 failed to inhibit tachykinin and capsaicin-induced plasma extravasation which is mainly mediated by NK1 receptors and suppressed by SR 140333 (Inoue et al., 1996). Finally, no effect of tachykinin NK3 receptor stimulation has been demonstrated in mucus or in inflammatory cells (Ellis & Undem, 1994; Maggi et al., 1993; Rogers, 1995).

Tachykinin NK3 receptor may increase neural activity and responsiveness of target cells. Several electrophysiological studies have reported that tachykinins elicit an important activity on the control of various neuronal and ganglionic potentials at the periphery and, among tachykinins, neurokinin B and stimulation of tachykinin NK3 receptors seems to play a predominant role. This has been suggested by studies showing that substance P and neurokinin B (but not neurokinin A) induced depolarization of guinea-pig bronchial parasympathetic ganglion neurones, and that neurokinin B was 60-fold more potent and five time more efficient than substance P (Myers & Undem, 1993). Neurokinin B and [Asp⁵,⁶, metylPhe⁹]SP(5-11) (a selective agonist for NK3 receptors) induced a decrease in membrane resistance (Myers & Undem, 1993). Interestingly, the capsaicin-evoked slow excitatory postsynaptic potential of guinea-pig bronchial and tracheal parasympathetic ganglion neurons (Myers et al., 1996) and the relaxation of the guinea-pig trachea elicited by antidromic stimulation of capsaicin-sensitive vagal afferent nerves were reduced by SR 142801 (Canning et al., 1998). A similar control of neuronal transmission and reflexes by NK3 receptor has also been evidenced in gastrointestinal tract (Johnson et al., 1996, 1998; Mawe, 1995; Zhao et al., 1995). On the basis of these data, however it is not clear whether peripheral neuronal electric activities mediated by tachykinin NK3 receptors may lead to the modulation of airway hyperresponsiveness to ACh. Hence, the importance of the role of tachykinins in nodose ganglia has been recently strengthened in the airway hyperresponsiveness induced in the guinea-pig (Fischer et al., 1996; Weinreich et al., 1997), but until now no evidence for a role of NK3 at this site of action has been demonstrated.

Finally, the mechanism of the prevention of airway hyperresponsiveness induced either by tachykinin NK3 agonists (the present study), SP (Daoui et al., 1997) or citric acid (Daoui et al., 1998) by SR 48968 and SR 142801 is unclear and suggest the involvement of various physiopathological serial process. For example, a costimulation of NK1 + NK2 receptor or NK₁ + NK3 receptor has been reported for intestinal motility (Croci et al., 1995). An interrelationship between different tachykinins has been also suggested. Indeed, Schmid et al. (1998) showed that NK3 receptors mediate enhancement of substance P release from rat capsaicin-sensitive spinal cord afferent terminals.

In conclusion, the present study demonstrates the potent ability of neurokinin B and tachykinin receptor agonists [MePhe7]NKB and senktide to induce airway hyperresponsiveness and the inhibitory effect of the selective NK3 receptor antagonists (SR 142801) on [MePhe7]NKB-induced hyperresponsiveness in guinea-pigs. For concentrations that induced airway hyperresponsiveness, senktide and [MePhe7]NKB failed to induce bronchoconstriction. Our data suggest that NK3 receptor stimulation can induce airway hyperresponsiveness and this effect is not related to the ability of tachykinins to induce bronchoconstriction.
References


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