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Central antitussive activity of the NK_1 and NK_2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat

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1 The purpose of this study was to investigate the antitussive activity and sites of action of the NK_1 and NK_2 tachykinin receptor antagonists, CP-99,994, SR 48968, and the racemate of SR 48968, SR 48212A in the cat and guinea-pig.

2 Guinea-pigs were dosed subcutaneously (s.c.) with CP-99,994, SR 48212A or SR 48968 one hour before exposure to aerosols of capsaicin (0.3 mM) to elicit coughing. Coughs were detected with a microphone and counted.

3 Intracerebroventricular (i.c.v.) cannulae were placed in the lateral cerebral ventricles of anaesthetized guinea-pigs. Approximately one week later, the animals were dosed with CP-99,994 or SR 48212A (i.c.v.) and exposed to aerosols of capsaicin (0.3 mM) to elicit coughing.

4 Cough was produced in anaesthetized cats by mechanical stimulation of the intrathoracic trachea and was monitored from electromyograms of respiratory muscle activity. Cannulae were placed for intravenous (i.v.) or, in separate groups of animals, intravertebral arterial (i.a.) administration of CP-99,994, SR 48212A or SR 48968. Dose-response relationships for i.v. and i.a. administration of each drug were generated to determine a ratio of i.v. ED_{50} to i.a. ED_{50}, known as the effective dose ratio (EDR). The EDR will be 20 or greater for a centrally active drug and less than 20 for a peripherally active drug.

5 In the guinea-pig, CP-99,994 (0.1–30 mg kg^{-1}, s.c.), SR 48212A (1.0–30 mg kg^{-1}, s.c.), and SR 48968 (0.3–3.0 mg kg^{-1}, s.c.) inhibited capsaicin-induced cough in a dose-dependent manner. Capsaicin-induced cough was also inhibited by i.c.v. administration of CP-99,994 (10 and 100 μg) or SR 48212A (100 μg).

6 In the cat, both CP-99,994 (0.0001–0.3 mg kg^{-1}, i.a., $n=5$; 0.003–3.0 mg kg^{-1}, i.v., $n=5$) and SR 48212A (0.003–1.0 mg kg^{-1}, i.a., $n=5$; 0.01–3.0 mg kg^{-1}, i.v., $n=5$) inhibited mechanically induced cough by either the i.v. or i.a. routes in a dose-dependent manner. SR 48968 (0.001–0.3 mg kg^{-1}, i.a., $n=5$; 0.03–1.0 mg kg^{-1}, i.v., $n=5$) inhibited cough when administered by the i.a. route in a dose-dependent manner, but had no effect by the i.v. route up to a dose of 1.0 mg kg^{-1}. Intravenous antitussive potencies (ED_{50}, 95% confidence interval (CI)) of these compounds were: CP-99,994 (0.082 mg kg^{-1}, 95% CI 0.047–0.126), SR 48212A (2.3 mg kg^{-1}, 95% CI 0.5–20), and SR 48968 (>1.0 mg kg^{-1}, 95% CI not determined). The intra-arterial potencies of these compounds were: CP-99,994 (1.0 μg kg^{-1}, 95% CI 0.4–1.8), SR 48212A (25 μg kg^{-1}, 95% CI 13–52), and SR 48968 (8.0 μg kg^{-1}, 95% CI 1–32). The derived EDRs for each compound were: CP-99,994, 82; SR 48212A, 92; and SR 48968, >125.

7 We concluded that CP-99,994 and SR 48968 inhibit cough in the guinea-pig and cat by a central site of action. In the cat, the antitussive action of these compounds appears to be solely by a central site.

Keywords: Cough; antitussive; tachykinin receptor antagonists; CP-99,994; SR 48968

Introduction

Cough is the most common manifestation of pulmonary disease and the most common reason why sick patients visit physicians in the United States (Choudry & Fuller, 1992; National Ambulatory Medical Care Survey, 1992). Cough can be the primary or sole manifestation of bronchitis, upper respiratory infections or asthma (Braman & Corrao, 1987; O'Connell *et al*., 1991). In patients with chronic bronchitis, chronic productive cough is the primary clinical manifestation (American Thoracic Society Committee on Diagnostic Standards, 1962). The reason that cough is so important in pulmonary disease is that this defensive reflex is the primary mechanism for the removal of mucus and foreign matter from the upper respiratory tract (Basser *et al*., 1989).

Although the beneficial role of cough in host defense is well known, chronic cough is associated with significant morbidity and a variety of compounds have been used to suppress this reflex (Braman & Corrao, 1987). These compounds are generally classified as central or peripheral antitussives (Braman & Corrao, 1987). Central antitussive agents, such as codeine and dextromethorphan, penetrate the central nervous system (CNS) upon systemic administration and inhibit the responsiveness of the central neural elements eliciting cough (Chou & Wang, 1975; Bolser & DeGennaro, 1994; Bolser *et al*., 1994). Peripheral antitussive agents, such as benzonatate and BW443C, exhibit little or no penetration of the CNS after systemic administration but inhibit the responsiveness of pulmonary vagal afferents that elicit cough (Korpas & Tomori, 1979; Adcock *et al*., 1988; Adcock, 1991; Bolser *et al*., 1994).

Recent work has demonstrated antitussive activity of NK_1 and NK_2 tachykinin receptor antagonists in models of irritant-

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and antigen-induced cough in the guinea-pig (Advenier *et al*., 1993; Ujiie *et al*., 1993; Ogawa *et al*., 1994; Sekizawa *et al*., 1995). The site(s) of action of NK_1 and NK_2 tachykinin receptor antagonists to inhibit cough is(are) unknown, although two studies have suggested that the effects of two peptide-based tachykinin receptor antagonists are restricted to peripheral sites (Ujiie *et al*., 1993; Ogawa *et al*., 1994; Sekizawa *et al*., 1995). However, two selective NK_1 and NK_2 tachykinin receptor antagonists, CP-99,994 (NK_1) and SR 48968 (NK_2), have been shown to have CNS actions on other systems following systemic administration (McLean *et al*., 1993; Stratton *et al*., 1993; Bristow & Young, 1994). The extent to which antitussive activity of NK_1 and NK_2 antagonists can represent an action at central sites is unknown. We speculated that CP-99,994 and SR 48968 would have central components to their antitussive action in models of cough in the guinea-pig and cat. A preliminary account of this work has been published (Bolser *et al*., 1995b).

Methods

Capsaicin-induced cough in the guinea-pig

The methods used in this study are identical to those described previously (Bolser *et al*., 1993; 1994). Awake Dunkin-Hartley guinea-pigs (Harlan-Sprague Dawley, 400–800 g) were placed in a cylindrical transparent plastic chamber (12 in × 4 in) and exposed individually to aerosols of capsaicin (0.3 mM) to produce cough (Bolser *et al*., 1993; 1994). Coughs were detected by a microphone in the chamber and this microphone was connected to a chart recorder. Capsaicin exposure occurred for 4 min. The capsaicin aerosol was produced by a jet nebulized at an airflow of 4 l min^{-1}. The volume of capsaicin nebulized per exposure was approximately 1.6 ml. The number of coughs occurring during this period was counted by visual inspection of the chart record. Each animal was exposed only once to capsaicin.

The antitussive activities of (+),(2**R**,3**R**)-3-(2-methoxybenzyl-amino)-2-phenylpiperidine (CP-99,994), (±)-N-methyl-[4-(4-acetylamino-4-phenyl piperidino)-2-(3, 4-dichloro-phenyl)-butyl]benzamide] (SR 48212A) and (+)-N-methyl- [4-(4-acetylamino-4-phenyl piperidino)-2-(3, 4-dichloro-phenyl)butyl]benzamide] (SR 48968) were evaluated by systemic (s.c.) or central (i.c.v.) administration of each compound. For systemic administration, each animal was dosed subcutaneously 1 h before capsaicin challenge. In separate groups of animals, single i.c.v. cannulae were implanted into the lateral ventricles of anaesthetized (ketamine, 30 mg kg^{-1} xylazine, 5 mg kg^{-1}, i.m.) guinea-pigs (Bolser *et al*., 1994). The animals were allowed to recover 1 week before challenge with capsaicin. Each animal was dosed i.c.v. 5 min before capsaicin exposure. For both systemic and central experiments, each animal was dosed only once with 1 dose of a single compound or vehicle.

Mechanically induced cough in cats

Cats were anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.p.). Supplementary amounts of anaesthetic were administered as necessary (5 mg kg^{-1}, i.v.). Atropine sulphate (1 mg kg^{-1}, i.v.) was administered to block reflex airway secretions. The trachea, femoral artery and femoral vein were cannulated in all animals. In some animals, the left vertebral artery was cannulated (Chou & Wang, 1975; Bolser, 1991; Bolser *et al*., 1993; 1994; 1995a).

Electromyograms (EMG) from the diaphragm and rectus abdominis muscles were recorded with bipolar tungsten wire electrodes. The EMGs were amplified, filtered (0.5–10 KHz), and integrated with a resistance-capacitance circuit (100 ms time constant). The integrated EMGs were displayed on a chart recorder.

Cough was defined as a large burst of EMG activity in the diaphragm immediately followed by a burst of EMG activity in the rectus abdominis muscle (Bolser *et al*., 1993; 1994; 1995b). Coughing was produced by mechanical stimulation of the intrathoracic trachea with a thin flexible polyethylene cannula for 10 s per trial.

The antitussive activity of CP-99,994, SR 48968 and SR 48212A was evaluated from cumulative dose-response curves obtained after i.v. and, in separate groups of animals, intravertebral artery (i.a.) administration of each compound. Control values were obtained by averaging the number of coughs during five consecutive mechanical stimulus trials after vehicle administration. One minute elapsed between stimulus trials. Stimulus trials were applied at 1 min intervals after each dose of compound for a total of five stimulus trials between doses. The cough response after each dose of compound was determined by averaging the number of coughs observed during the five stimulus trials. Approximately five min elapsed between each dose of compound.

Statistics

Effective doses for 50% inhibition (ED_{50}) of cough frequency were obtained by regression analysis of dose-response relationships. Effective dose-ratios (EDR) were generated for each compound in the cat experiments (Chou & Wang, 1975; Domino *et al*., 1985; Bolser *et al*., 1994; 1995a). The EDR was defined as the ED_{50} for i.v. activity divided by the ED_{50} for i.a. activity of the compound. This ratio will be 20 or greater for a centrally-acting compound and less than 20 for a peripheral antitussive compound (Chou & Wang, 1975; Bolser *et al*., 1994; 1995a). Data are expressed as mean ± s.e.mean or mean and 95% confidence interval (CI). Student's *t* test (Mann-Whitney test for non-parametric data) or one-way analysis of variance were used to evaluate differences between means. *Post hoc* analysis of the data for analysis of variance was conducted by the Bonferroni method. $P<0.05$ was considered significant.

Compounds

CP-99,994, SR 48968, and SR 48212A were synthesized at Schering-Plough Research Institute (Kenilworth, NJ, U.S.A.). Atropine sulphate and capsaicin were obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Capsaicin was dissolved in 1% ethanol, 1% Tween 20 and 98% physiological saline. CP-99,994, SR 48968 and atropine sulphate were dissolved in physiological saline. SR 48212A was dissolved in β-cyclodextrin (Research Biochemicals Inc., Natick, MA, U.S.A.). Doses were calculated as their free base.

Results

Antitussive activity of CP-99,994, SR 48968 and SR 48212A after systemic or central administration in the guinea-pig

The cough response to increasing doses of capsaicin (0.01–0.3 mM) was determined (Table 1). Doses higher than 0.3 mM were not used because preliminary experiments indicated frank distress among the animals. Capsaicin increased cough frequency in a dose-dependent manner. The highest dose of capsaicin (0.3 mM) was chosen to induce cough in guinea-pigs receiving tachykinin antagonists because it elicited cough in every guinea-pig tested and in other studies this dose was shown to produce consistent cough responses (Bolser *et al*., 1993; 1994).

CP-99,994 (0.1–30 mg kg^{-1}, s.c.), SR 48968 (0.3–3.0 mg kg^{-1}, s.c.) and SR 48212A (1.0–30 mg kg^{-1}, s.c.) significantly inhibited capsaicin-induced cough in a dose-dependent manner (Table 2). At the highest dose of CP-99,994 tested (30 mg kg^{-1}), seizure-like effects were observed. Potencies of these compounds were: SR 48968 (ED_{50} = 2.2 mg kg^{-1}, s.c.,

Table 1 Effect of capsaicin inhalation on the cough response in the guinea-pig

Capsaicin dose (mM)[a]	n	*Frequency of coughs*
0	6	0±0
0.01	6	5±1*
0.03	6	6±1*
0.1	6	11±3*
0.3	6	15±2*

Data shown are means±s.e.mean. [a]Capsaicin was administered by aerosol for 4 min. Vehicle-treated animals are designated by a dose of zero. *$P<0.05$ relative to vehicle-treated animals.

Table 2 Effect of systemic administration of CP-99,994, SR 48968 and SR 48212A on capsaicin-induced cough in the guinea-pig

Compound	*Dose*[a] (mg kg^{-1})	n	*Frequency of coughs*
CP-99,994	0	6	13±2
	0.3	6	9±1
	1.0	6	6±1*
	3.0	6	4±0*
	0	18	16±1
	1.0	18	9±1*
	3.0	18	8±1*
	10.0	17	7±1*
SR 48212A	0	12	15±1
	1.0	12	12±2
	3.0	12	8±2*
	10.0	12	7±1*
	0	6	19±1
	30.0	6	11±1*
SR 48968	0	12	10±1
	0.3	12	10±1
	1.0	12	6±1*
	3.0	12	5±1*

Data shown are means±s.e.mean. [a]Compounds were administered subcutaneously 1 h before capsaicin challenge. Vehicle treated groups are designated by a dose of zero. *$P<0.05$ relative to vehicle-treated animals challenged on the same day.

95% CI 1.3–6.8), CP-99,994 (ED_{50}=3.0 mg kg^{-1}, s.c., 95% CI 1.0–6.8) and SR 48212A (ED_{50}=6.9 mg kg^{-1}, s.c. 95% CI 2.6–54).

Both CP-99,994 (10 and 100 μg) and SR 48212A (10 and 100 μg) significantly inhibited capsaicin-induced cough after i.c.v. administration (Table 3). Both doses of CP-99,994 were active to inhibit cough, but only the highest dose of SR 48212A had significant antitussive activity. The maximum observed inhibition of cough by each of these compounds at the highest dose administered was 50–60%. SR 48968 was not administered centrally.

Intravenous and intra-arterial administration of CP-99,994, SR 48212A and SR 48968 in the cat

Control cough frequencies were not significantly different between animals dosed by the i.v. or i.a. routes. After vehicle administration, mechanical stimulation of the intrathoracic airway elicited 8±1 coughs per stimulus trial in animals that received CP-99,994 i.v. and 8±1 coughs in animals that received CP-99,994 i.a. ($P<0.5$). Animals that received SR 48212A i.v. coughed 6±1 times per stimulus trial after vehicle administration, compared to 9±3 times in animals dosed with SR 48212A i.a. ($P<0.2$). The number of coughs elicited per stimulus trial in animals that received SR 48968 i.v. was 9±2, compared to 8±2 in animals dosed with SR 48968 i.a. ($P<0.4$).

Table 3 Effect of central administration of CP-99,994 and SR 48212A on capsaicin-induced cough in the guinea-pig

Compound	*Dose*[a] (μg)	n	*Frequency of coughs*
CP-99,994	0	22	14±2
	10	12	9±2*
	100	18	7±1*
SR 48212A	0	22	17±2
	10	12	13±3
	100	12	8±2*

Data shown are means±s.e.mean. [a]Compounds were administered i.c.v. 5 min before capsaicin challenge. Vehicle treated groups are designated by a dose of zero. *$P<0.05$ relative to vehicle-treated animals challenged on the same day.

Figure 1 shows cumulative dose-response relationships for intravenous and intra-arterial administration of CP-99,994, SR 48212A and SR 48968. Both CP-99,994 and SR 48212A inhibited cough in a dose-dependent manner when given either by the i.v. or i.a. routes (Figure 1a, b). Additional experiments were conducted with SR 48968, the active isomer of SR 48212A. SR 48968 inhibited cough in a dose-dependent manner by the i.a. route, but was inactive by the i.v. route up to the maximum dose tested of 1000 μg kg^{-1} (Figure 1c).

CP-99,994 was much more potent when given by the i.a. route (ED_{50}=1 μg kg^{-1}, 95% CI=0.4–1.8, n=5) than the i.v. route (ED_{50}=82 μg kg^{-1}, 95% CI 47–126, n=5). The EDR for CP-99,994 was 82. SR 48212A also was much more potent when given by the i.a. route (ED_{50}=25 μg kg^{-1}, 95% CI 13–52, n=5) than the i.v. route (ED_{50}=2.3 mg kg^{-1}, 95% CI 0.5–20, n=5). The EDR for SR 48212A was 92. SR 48968 was very potent at inhibiting cough by the i.a. route (ED_{50}=8 μg kg^{-1}, 95% CI 1–32, n=5). Because SR 48968 did not inhibit cough by the intravenous route (n=5), the precise EDR and 95% confidence intervals could not be determined. However, a predicted EDR based on the highest intravenous dose given (1000 μg kg^{-1}) was calculated to be greater than 125.

Discussion

The major findings of this study are that CP-99,994, SR 48212A and SR 48968 possess antitussive activity in the cat and guinea-pig. In the guinea-pig, these compounds inhibit cough following systemic or central administration. In the cat, CP-99,994, SR 48212A and the active isomer SR 48968, were at least 80 fold more potent at inhibiting cough when given by the intra-arterial route, than the intravenous route.

Antitussive action of tachykinin NK_1 and NK_2 receptor antagonists

This study provides the first evidence that the nonpeptide tachykinin NK_1 receptor antagonist, CP-99,994, has antitussive activity in the guinea-pig. Other investigators have shown that inhalation of FK 888, a peptide NK_1 antagonist, in the guinea-pig will inhibit irritant-induced cough (Ujiie *et al*., 1993; Sezikawa *et al*., 1995). Furthermore, our results extend this previous work by demonstrating antitussive activity of an NK_1 antagonist in the cat. Our results are not consistent with the findings of Girard *et al*. (1995), who showed no direct antitussive activity of the NK_1 antagonist, SR 140333, in the guinea-pig. One possible explanation for this apparent discrepancy is that SR 140333 and CP-99,994 may bind to different NK_1 receptor subtypes (Maggi *et al*., 1993), each of which has a different effect on the cough reflex. Alternatively, SR 140333 may not penetrate the CNS to inhibit cough centrally whereas CP-99,994 has a central site of action (see below).

Advenier and coworkers (Advenier *et al*., 1993; Girard *et al*., 1995) have shown antitussive activity of the NK_2 tachykinin receptor antagonist, SR 48968, in the guinea-pig. Our findings confirm their observations in the guinea-pig and additionally show antitussive activity of this compound in the cat.

Evidence for a central site of action for NK_1 and NK_2 tachykinin receptor antagonists in the guinea-pig

Results from the present study are consistent with the idea that tachykinins are involved in the production of cough in the guinea-pig. For example, cough can be elicited in the guinea-pig by inhalation of substance P (Sekizawa *et al*., 1995). Inhibition of the degradation of tachykinins by neutral endopeptidase inhibitors will potentiate irritant-induced cough in this species (Kohrogi *et al*., 1988; Ujiie *et al*., 1993). Finally, NK_1, NK_2, or dual NK_1/NK_2 tachykinin receptor antagonists inhibit irritant-induced cough in the guinea-pig (Ujiie *et al*., 1993; Advenier *et al*., 1993; Ogawa *et al*., 1994; Sekizawa *et al*., 1995).

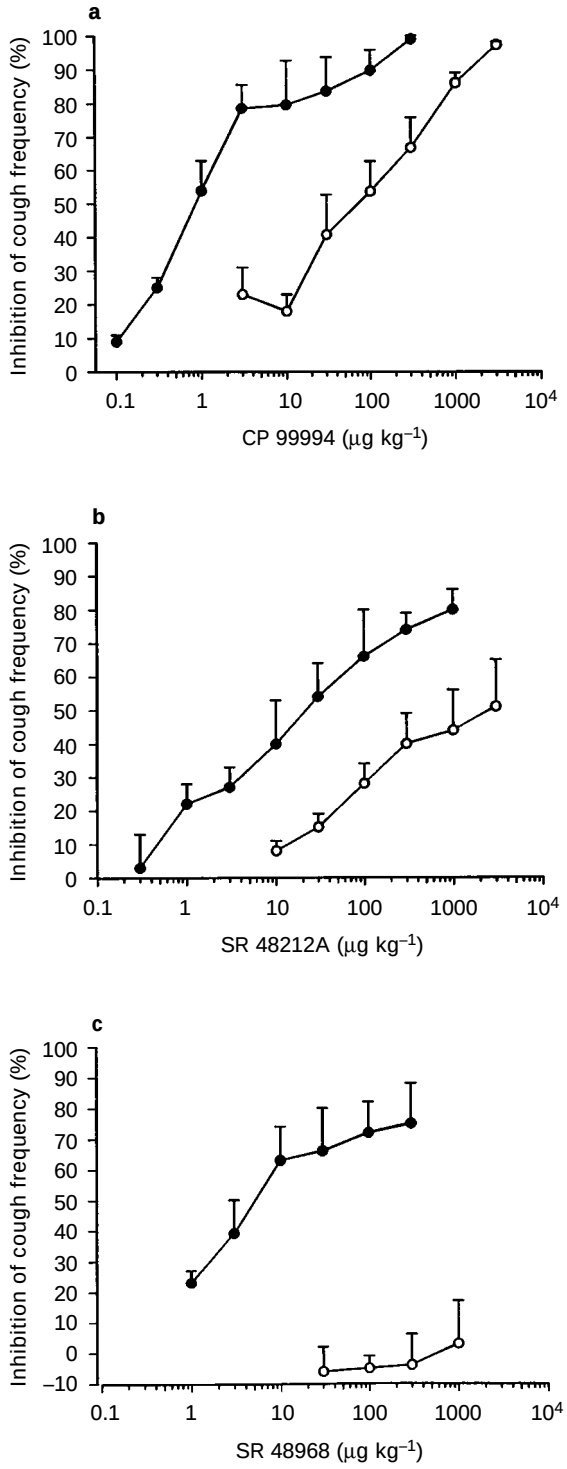

Figure 1 Antitussive effects of intra-arterial and intravenous administration of NK_1 and NK_2 tachykinin receptor antagonists in the cat. Cumulative dose-response relationships for i.v. (○) and i.a. (●) administration of CP-99,994 (a), SR 48212A (b) and SR 48968 (c) are shown.

The site at which tachykinins or their antagonists act to produce or inhibit cough has generally been considered to be peripheral, primarily because the compounds in question were peptides and were administered by inhalation (Ujiie *et al*., 1993; Ogawa *et al*., 1994; Sekizawa *et al*., 1995). However, the possibility that NK_1 and NK_2 tachykinin receptor antagonists could inhibit cough by a central site of action has not been addressed. This is the first study demonstrating that tachykinin NK_1 and NK_2 receptor antagonists can inhibit cough by a central site of action. In the guinea-pig, both CP-99,994 and SR 48212A inhibited capsaicin-induced cough after central administration. The doses of CP-99,994 and SR 48212A necessary to inhibit capsaicin-induced cough by the i.c.v. route were much lower than the minimally-active systemic doses (1.0 mg kg^{-1}, s.c. for CP-99,994 and 3.0 mg kg^{-1} for SR 48212A). This finding indicates that there was no peripheral component to the antitussive action of these compounds after central administration. Both NK_1 and NK_2 tachykinin receptor antagonists also inhibited capsaicin-induced cough after systemic administration. Although we cannot rule out a peripheral component to the antitussive action of these compounds by the systemic route of administration, we propose that the site of action of these antagonists after systemic administration is primarily central. A peripheral action of either antagonist would require peripheral tachykinin release to be an essential component in the tussigenic action of capsaicin. While the peripheral release of tachykinins may be elicited by inhalation of capsaicin in this model, no direct evidence exists that the tussigenic activity of capsaicin is mediated by the peripheral release of tachykinins. In fact, in an *in vitro* preparation of guinea-pig airway, nanomolar concentrations of capsaicin or bradykinin vigorously stimulate C-fibres within a few seconds of application, indicating direct stimulation of these afferent fibres (Fox *et al*., 1993).

Evidence for a central site of action of NK_1 and NK_2 tachykinin receptor antagonists in the cat

The effective dose-ratio of i.v. to i.a. potencies has been used to obtain information regarding the sites of action of antitussive compounds in the cat (Chou & Wang, 1975; Domino *et al*., 1985; Bolser *et al*., 1994; 1995a). Historically, when this ratio is less than 20, the compound is considered to have a peripheral site of action; conversely, when this ratio is greater than 20, the compound is considered to have a central site of action (Chou & Wang, 1975). Previous findings from this laboratory are consistent with the idea that centrally active antitussive compounds have EDRs of approximately 20 or greater (Bolser *et al*., 1994; 1995a). However, our findings also indicate that peripherally active antitussive compounds, such as the μ-opioid agonist BW 443C, have EDRs much less than 20 (approximately 3) (Bolser *et al*., 1994; 1995a). Therefore, our previous results indicate that the EDR is a rigorous method of discriminating antitussive compounds that have solely peripheral activity from those with a central component to their site(s) of action. However, one of the limitations of this method has been the lack of information on its ability to differentiate between compounds with solely a central site of action from those with both central and peripheral sites of action to inhibit cough. For example, codeine is a classical centrally acting antitussive drug with EDRs of 20–26 in the cat (Chou & Wang, 1975; Bolser *et al*., 1994). However, some investigators have shown that codeine may have a peripheral site of action in the guinea-pig (Karlsson *et al*., 1990).

In the present study, the tachykinin NK_1 and NK_2 receptor antagonists displayed EDRs in excess of 80. These EDRs are the highest that have been obtained for any antitussive and indicate a central site of action for these compounds. Previously, the highest EDR obtained was approximately 40 for the centrally-active γ-aminobutyric acid$_B$ ($GABA_B$) receptor agonist, baclofen (Bolser *et al*., 1994). The high EDR for baclofen in the cat is consistent with data from the guinea-pig showing that this $GABA_B$ receptor agonist has solely a central site of action (Bolser *et al*., 1994). We suggest that the very high EDRs of these NK_1 and NK_2 tachykinin receptor antagonists provide evidence for solely a central site of action of these compounds in the cat.

This idea is also supported by several other observations. First, SR 48968 was inactive when given intravenously up to doses of 1.0 mg kg^{-1}. This finding suggests that SR 48968 has no peripheral site of action in this model. This compound was only active when it was delivered directly to the brainstem circulation via the vertebral artery. SR 48212A was active when given intravenously, but it was dissolved in β-cyclodextrin, which is known to enhance the central penetration of other compounds after intravenous administration (Frijlink *et al*., 1991). The intravenous activity of SR 48212A was probably due to enhancement of central penetration of this compound by the β-cyclodextrin vehicle. Second, cough was elicited by a punctate mechanical stimulus applied to the intrathoracic airway in the cat. For a tachykinin receptor antagonist to inhibit mechanically-induced cough at a peripheral site, tachykinins must be released by the stimulus and activate sensory afferents to elicit the reflex. There is no evidence that mechanical stimuli of this nature elicit the release of tachykinins from pulmonary or bronchial C-fibres. However, it is known that this sort of mechanical stimulus will vigorously stimulate pulmonary rapidly adapting receptors (Mills *et al*., 1969), which are probably responsible for the production of cough in this model (Tomori & Widdicombe, 1969; Korpas & Tomori, 1979). Therefore, it is unlikely that antagonism of peripheral tachykinin receptors would influence the production of cough in the cat model. However, we cannot rule out a peripheral action of NK_1 and NK_2 tachykinin receptor antagonists to inhibit cough produced by chemical stimuli or in situations in which cough is produced during neurogenic airway inflammation.

In the guinea-pig, subcutaneous administration of SR 48968 inhibited capsaicin-induced cough at doses of 1 and 3 mg kg^{-1}, but in the cat intravenous administration of 1 mg kg^{-1} of this compound had no effect on mechanically-induced cough. There are at least three possible explanations for this apparent discrepancy. Firstly, SR 48968 may penetrate the CNS more readily in the guinea-pig than the cat and therefore inhibit cough at lower doses. Secondly SR 48968 may have a higher binding affinity to the NK_2 receptor in the guinea-pig than the cat. To our knowledge, there is no information on the pharmacological properties of the cat NK_2 receptor. Thirdly, the experimental protocols for the cat and guinea-pig experiments were different. SR 48968 was administered subcutaneously with a 1 h pretreatment time in the guinea-pig, whereas this compound was administered intravenously in the cat and the cough response was evaluated within five min of injection. It is likely that the pharmacokinetics of SR 48968 administration in each model were very different. Differences in plasma pharmacokinetics could easily account for the observation that SR 48968 was active in one cough model at 1 mg kg^{-1}, but inactive at that same dose in another cough model. Although we cannot rule out the first two possible explanations, we favour the third explanation.

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