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# The broad-spectrum anti-emetic activity of the novel non-peptide tachykinin $NK_1$ receptor antagonist GR203040

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1 Following our earlier observations that the tachykinin $NK_1$ receptor antagonist CP-99,994 is an effective anti-emetic in ferrets, we have examined the anti-emetic effects of a more potent and novel $NK_1$ receptor antagonist, GR203040, against various emetic stimuli in the ferret, dog and house musk shrew (*Suncus murinus*).

2 In ferrets, GR203040 (0.1 mg $kg^{-1}$ s.c. or i.v.) is effective against emesis induced by radiation, cisplatin, cyclophosphamide, copper sulphate, ipecacuanha or morphine.

3 In animals in which emesis had been established with cisplatin, GR203040 (1 mg $kg^{-1}$ s.c.) was fully effective as an interventional treatment. No further emesis was seen in animals treated with GR203040 whilst saline-treated animals continued to vomit.

4 GR203040 (0.1 mg $kg^{-1}$ s.c.) retains anti-emetic efficacy in the ferret, even when given as a 6 h pretreatment, indicating that this compound has a long duration of action. The compound is also effective orally at the same dose, when given as a 90 min pretreatment.

5 GR203040 (0.1 mg $kg^{-1}$ i.v.) is fully effective against ipecacuanha-induced emesis in the dog.

6 GR203040 is effective against motion- and cisplatin-induced emesis in *Suncus murinus*. These effects were seen at doses an order of magnitude greater than those shown to be effective against cisplatin in the ferret.

7 In conclusion, GR203040 is a novel anti-emetic agent, and the broad spectrum of anti-emetic activity, together with activity observed in three species, suggests that this compound is worthy of clinical investigation.

**Keywords:** GR203040; tachykinin $NK_1$ receptor; emesis; anti-emetic; cisplatin; motion sickness; substance P

## Introduction

In the treatment of malignant disease, potentially curative chemotherapy and radiotherapy treatments are commonly associated with a wide range of adverse events. These often include intractable nausea and vomiting, which can challenge patient compliance with a treatment regimen. Other forms of emesis, including those experienced post-operatively or in anticipation of cytotoxic treatment, can also present as serious problems. In a substantial proportion of patients, the recently introduced 5-hydroxytryptamine$_3$ (5-$HT_3$) receptor antagonists provide relief from the emesis and nausea produced by cytotoxic therapy. However, these agents are less effective at blocking the emesis produced by other stimuli. In an experimental context, 5-$HT_3$ receptor antagonists are very effective anti-emetic agents against cisplatin- or radiation-induced emesis, but are ineffective against orally administered copper sulphate (Rudd *et al.*, 1990; Kamato *et al.*, 1991), or systemic administration of morphine (Thompson *et al.*, 1992; Pitkanen *et al.*, 1993). Moreover, 5-$HT_3$ receptor antagonists have been shown to be ineffective against the emesis evoked by motion in both animals and man (Lucot, 1989; Stott *et al.*, 1989).

The neuropeptide substance P is an important neurotransmitter substance, being localized to many neuronal structures, particularly nerve fibres and cell bodies of sensory nerves. Substance P is thought to play a fundamental role in the transmission of sensory information, particularly that associated with noxious stimuli, from the periphery to central structures. Immunohistochemical techniques have demonstrated the presence of substance P-containing nerve fibres in regions of the hindbrain, including those known to be involved in the emetic reflex in cat, rat and man (Maley & Elde, 1982; Yamazoe *et al.*, 1984; McRitchie & Törk, 1994). Furthermore, substance P has been demonstrated to be co-localized with 5-HT within the enterochromaffin cells of the gastrointestinal tract (Sundler *et al.*, 1977; Sjoland *et al.*, 1983). The release of 5-HT from such structures is thought to be of prime importance in the cascade of events resulting in emesis following administration of a number of chemotherapeutic regimes (Cubeddu *et al.*, 1992). These data strongly suggest that substance P could be involved at any of a number of stages in the emetic pathway. Our initial discovery that the tachykinin $NK_1$ receptor antagonist, CP-99,994, was effective in inhibiting emesis induced by a wide range of emetogens in ferrets confirmed the involvement of this receptor in the emetic pathway (Bountra *et al.*, 1993). However, racemic CP-99,994 lacks potency *in vivo*, where a dose of 3 mg $kg^{-1}$ is necessary to inhibit emesis in the ferret. In the current study, we have investigated the effects of a recently described novel antagonist with high affinity for the tachykinin $NK_1$ receptor, GR203040 (Beattie *et al.*, 1995), in a range of animal models of emesis.

## Methods

### *Profile of anti-emetic activity in the ferret*

Adult male ferrets, body weight range 1.0 to 1.7 kg, were used to investigate the anti-emetic effects of GR203040 against emesis induced by morphine, ipecacuanha, copper sulphate, cyclophosphamide, cisplatin and X-irradiation. Each animal received a dose of either GR203040 (0.1 mg $kg^{-1}$) or vehicle

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control solution subcutaneously 30 min before administration of an emetogen, except in the cases of radiation, where the dose of GR203040 was administered as a 90 min pretreatment, and of cisplatin, where the dose was given intravenously concurrently with the emetogen. All doses of GR203040 and vehicle control were administered in a volume of 1 ml $kg^{-1}$. The numbers of retches and vomits occurring following administration of the emetogen were recorded. Retching was defined as rhythmic inspiratory movements against a closed glottis, and vomiting as forced expulsion of upper gastrointestinal contents. The doses of emetogen, routes of administration and observation periods are shown in Table 1.

The oral doses of ipecacuanha and copper sulphate were administered *via* an oro-gastric tube, and the subcutaneous dose of morphine into the nape of the neck. A Seifert Isovolt 420 X-ray source, pre-set to deliver 2Gy over approximately 5 min, was used to deliver whole-body irradiation. For intravenous administration of drugs, animals were anaesthetized with 2–3% halothane carried in 70% nitrous oxide, 30% oxygen in a semi-closed circuit. A polythene cannula (Portex, PP60) was implanted into an external jugular vein, and exteriorised at the nape of the neck before the animals were allowed to recover. The cannulae were filled with a solution of heparin (250 iu $ml^{-1}$ in 0.9% saline) and closed with a stainless-steel plug. A minimum of 48 h was allowed between surgery and experimental use.

### *Dose-response relationship and duration of action in ferrets*

Adult male ferrets, body weight range 1.0 to 1.7 kg were used for these experiments. Emesis was induced by whole-body exposure to X-irradiation as described above. Doses of GR203040 (0.03–1.0 mg $kg^{-1}$ s.c.) were administered either 6, 3 or 1.5 h before, or immediately after, irradiation. In other experiments, GR203040 (0.1 and 0.3 mg $kg^{-1}$ p.o.) was administered 1.5 h before irradiation. A control group of ten animals received NaCl (Sodium Chloride Intravenous Infusion BP, 1 ml $kg^{-1}$ s.c.) immediately after irradiation. The numbers of retches and vomits occurring in the 2 h post-dosing period were recorded.

### *Activity against established emesis in the ferret*

Adult male ferrets, body weight range 1.0 to 1.4 kg were used for this experiment. Emesis was induced by intraperitoneal administration of cisplatin (200 mg $m^{-2}$ body surface area). GR203040 (1 mg $kg^{-1}$ s.c.) or vehicle control solution, was administered 60 min after the first emetic response to cisplatin. The numbers of retches and vomits occurring over the subsequent 7 h period were recorded.

### *Anti-emetic activity in the dog*

Four adult male beagle dogs (initial body weight range 8.1 to 10.4 kg) were housed singly for these experiments. The animals were fed 200 g of dog meat (Pedigree Chum Original) 30 min before intravenous dosing. Drinking water was available at all times, but any uneaten food was removed after dosing with either GR203040 or vehicle control. The animals were dosed into the cephalic vein of a fore-limb in a volume of 0.5 ml $kg^{-1}$. Fifteen minutes after the intravenous dose, each animal received an oral dose of ipecacuanha (0.7 mg total alkaloids $kg^{-1}$), administered by oro-gastric tube in a dose volume of 0.5 ml $kg^{-1}$, and washed-in with 10 ml of water. The number of emetic episodes occurring in the following 90 min period, and the latency to first emesis were recorded. Emetic episodes were defined as retches and vomits occurring within a 1 min period. The experiment was of a cross-over design in which each animal was dosed on three separate occasions. Two animals received vehicle control injection on the first and third occasions, and GR203040 on the second occasion, whilst the other two animals received GR203040 on the first and third occasions, and vehicle control on the second. A period of at least ten days was allowed between treatments.

### *Motion-induced emesis in the house musk shrew* (Suncus murinus)

*Suncus murinus* is a small insectivore that has been shown previously to exhibit emesis when exposed to linear reciprocating motion (Ueno *et al.*, 1988). Adult male (body-weight range 55–87 g) and female (35–47 g) animals were used. Each animal received a dose of either GR203040 (1 or 3 mg $kg^{-1}$ s.c.) or vehicle control in a volume of 4 ml $kg^{-1}$, 15 min before motion testing. The animals were placed in a perspex chamber (11 cm wide × 22 cm long × 11 cm high) that was attached to the platform of a Taitec Recipro Shaker (model NR1, Taitec Corporation, Japan) set to execute a linear horizontal movement of 4 cm at a frequency of 1 Hz along the long axis of the chamber. The animals were allowed approximately 3 min to become accustomed to the chamber before exposure to motion for a period of 5 min, during which the number and timing of any emetic episodes were recorded. An emetic episode usually consisted of a short period of rapid retching (frequency >1 Hz) followed by a vomit. The experiment was of a cross-over design, with animals exposed to motion testing following treatment with vehicle control on one occasion, and following treatment with GR203040 on another. An interval of 12 days was allowed between treatments. Animals that failed to exhibit at least one emetic episode on the 'control' occasion were classed as 'non-responders', and were excluded from analysis.

### *Cisplatin-induced emesis in the house musk shew* (Suncus murinus)

Fifteen adult male (body-weight range 43–76 g) and 15 adult female (34–46 g) *Suncus murinus* were used. Each animal received a dose of either GR203040 (1, 3 or 10 mg $kg^{-1}$ s.c.) or vehicle control in a volume of 4 ml $kg^{-1}$ immediately before cisplatin injection. Cisplatin was administered in a dose of

**Table 1** Range of emetogens administered to ferrets

| *Emetogen* | *Dose* | *Dose volume* | *Route* | *Observation period* (h) |
|---|---|---|---|---|
| Morphine | 0.5 mg $kg^{-1}$ | | s.c. | 1\over 2 |
| Ipecacuanha | 2.0 mg $kg^{-1}$ | 1.43 ml $kg^{-1}$ | oral | 3 |
| Copper sulphate | 40.0 mg $kg^{-1}$ | 5 ml $kg^{-1}$ | oral | 2 |
| Cyclophosphamide | 200 mg $kg^{-1}$ | 5 ml $kg^{-1}$ | i.p. | 7 |
| Cisplatin[a] | 200 mg $m^{-2}$ | 100 ml $m^{-2}$ | i.p. | 81\over 2 |
| X-irradiation[b] | 2Gy | – | whole body | 2 |

[a]Cisplatin was administered according to body surface aea.
[b]Radiation was delivered over 5 min from a Seifert 420 X-ray source.

80 mg $kg^{-1}$ i.p., and the numbers of emetic episodes occurring during the following 3 h were recorded. In preliminary experiments this dose of cisplatin was found to be necessary to induce emesis in all animals tested; lower doses being effective in only a proportion of animals.

### *Statistical analysis*

Group results are expressed as mean and s.e.mean values. Either Student's *t* test or the Wilcoxon signed rank test was used as a measure of significance, depending on group size and distribution of data.

### *Materials*

Cyclophosphamide, cisplatin powder for injection and cupric sulphate pentahydrate were freshly prepared as solutions in water (Water for Injections BP). GR203040 ((2S, 3S)-2-methoxy-5-tetrazol-1-yl-benzyl)-(2-phenyl-piperidin-3-yl)-amine, Figure 1) and morphine sulphate pentahydrate were freshly prepared as solutions in sodium chloride (NaCl Intravenous Infusion BP). Ipecacuanha (Emetic Draught Paediatric BPC) was used undiluted. All doses are calculated in terms of base.

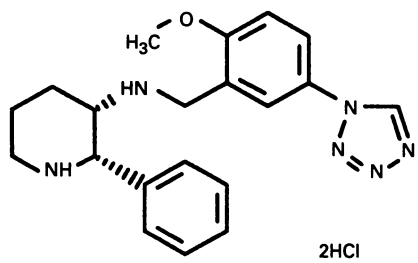


**Figure 1** Structural formula of GR203040.

## Results

### *Profile of antiemetic activity in ferrets*

All the agents administered to the ferrets evoked a profound emetic response. The numbers of retches and vomits observed after administration of each of the emetogens in combination with either GR203040 or vehicle control are shown in Table 2. GR203040 at a dose of 0.1 mg $kg^{-1}$ (either s.c. or following cisplatin, i.v.) was effective at inhibiting emesis induced by all the emetogens tested ($P<0.05$, unpaired *t* test).

### *Dose-response relationship and duration of action in ferrets*

The anti-emetic activity of GR203040 (0.1 mg $kg^{-1}$ s.c.) when administered over a range of doses and intervals before X-irradiation, is shown in Table 3. The effects of a single dose (0.1 mg $kg^{-1}$ s.c.) given at a range of pretreatment times, are illustrated in Figure 2. GR203040 inhibited the emesis evoked by whole body X-irradiation and retained a large measure of its anti-emetic properties, even when administered 6 h before radiation.

**Table 2** Numbers of retches and vomits observed in vehicle-treated and GR203040-treated (0.1 mg $kg^{-1}$) ferrets following a range of emetogens

| | *Vehicle control ** | | | *GR203040** | | |
|---|---|---|---|---|---|---|
| *Emetogen* | *Retches* | *Vomits* | n | *Retches* | *Vomits* | n |
| Morphine | 33.5±3.66 | 2.8±1.03 | 4 | 0.8±0.75† | 0.0† | 4 |
| Ipecacuanha | 82.0±11.50 | 9.0±2.04 | 4 | 5.8±2.53† | 1.8±1.11† | 4 |
| Copper sulphate | 165.8±49.59 | 14.8±2.53 | 4 | 22.5±2.78† | 8.0±2.48 | 4 |
| Cyclophosphamide | 102±22.28 | 17.8±2.39 | 4 | 6.8±3.82† | 1.0±0.00† | 4 |
| Cisplatin | 88.0±12.45 | 8.3±1.33 | 4 | 18.3±8.77† | 1.7±1.11† | 7 |
| Radiation | 66.9±8.03 | 7.2±1.08 | 10 | 2.7±2.66† | 0.3±0.33† | 3 |

Values are means and s.e.mean. *Subcutaneous route; intravenous in cisplatin-induced emesis.
†Indicates a significant difference from vehicle control, $P<0.05$, unpaired *t* test.

**Table 3** Emesis over a 2 hour period following whole body irradiation (2Gy) in the ferret

| *Dose* (mg $kg^{-1}$) | *Route* | *PTT* (min) | *Mean retches* | *Mean vomits* | n |
|---|---|---|---|---|---|
| Control | s.c. | 0 | 66.9±8.03 | 7.2±2.66 | 10 |
| 0.03 | s.c. | 0 | 46.0 | 7.5 | 2 |
| 0.1 | s.c. | 0 | 0.0 | 0.0 | 3 |
| 0.3 | s.c. | 0 | 0.0 | 0.0 | 1 |
| 0.03 | s.c. | 90 | 26.0 | 4.0 | 2 |
| 0.1 | s.c. | 90 | 2.7 | 0.3 | 3 |
| 0.3 | s.c. | 90 | 0.0 | 0.0 | 1 |
| 0.1 | s.c. | 180 | 9.0 | 2.0 | 3 |
| 0.3 | s.c. | 180 | 0.7 | 0.0 | 4 |
| 1 | s.c. | 180 | 0.0 | 0.0 | 1 |
| 0.1 | s.c. | 360 | 20.0 | 5.7 | 3 |
| 0.3 | s.c. | 360 | 10.7 | 2.0 | 3 |
| 0.1 | p.o. | 90 | 12.5 | 3.0 | 2 |
| 0.3 | p.o. | 90 | 0.0 | 0.0 | 3 |

GR203040 was given at various pretreatment times before irradiation (PTT).

*Activity against established emesis in the ferret*

The results of this experiment are illustrated in Figure 3. Over the 60 min period following the first emetic episode, the control group had retched 79±17.4 times and vomited 11±2.3 times. In the same period the group that were to receive GR203040 treatment retched 87±20.4 times and vomited 11±2.5 times. In contrast, over the 6 h period following treatment, while the control group retched a further 53±15.1 times and vomited a further 5±1.3 times, no further emesis was observed in the GR203040-treated group, indicating that GR203040 is fully effective in treating established emesis.

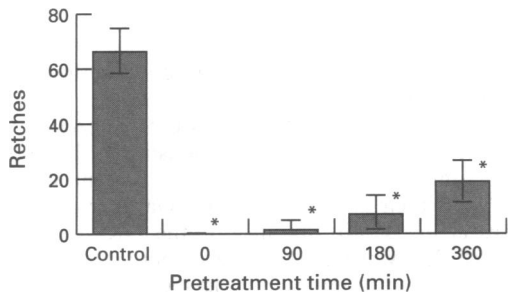


**Figure 2** Effects of GR203040 (0.1 mg kg$^{-1}$ s.c.), administered at various pretreatment intervals on radiation-induced emesis in ferrets. Values are mean and s.e.mean, $n=10$ control, 3 per treated group. *Indicates a significant difference from control, $P<0.05$.

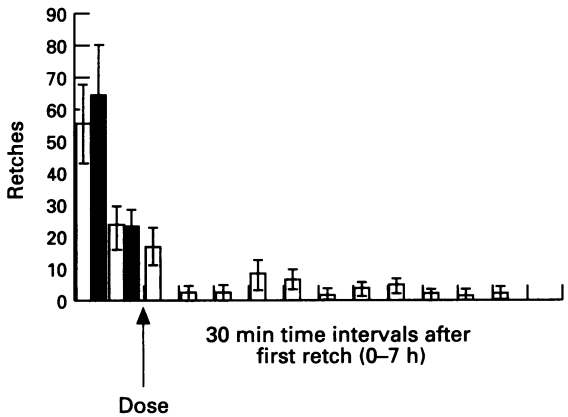


**Figure 3** Effects of GR203040 (1 mg kg$^{-1}$ s.c.), given 60 min after the first retch in ferrets treated with cisplatin, 200 mg m$^{-2}$ i.p. Open columns: control; solid columns: effects of GR203040. Data shown are means±s.e.mean.

*Anti-emetic activity in the dog*

The results of the experiment in which emesis was induced by oral administration of ipecacuanha are shown in Table 4. All the dogs experienced emesis on the control (saline pretreated) occasions. GR203040 completely inhibited emesis at intravenous doses of 0.1 mg kg$^{-1}$ and above.

*Motion-induced emesis in the house musk shrew* (Suncus murinus)

The emetic response of animals subjected to motion testing are shown in Table 5. GR203040 (1 and 3 mg kg$^{-1}$ s.c.) produced an inhibition in the number of emetic episodes that was significant at the higher dose (Wilcoxon signed rank test, $P<0.05$). Similarly, at the highest dose the mean latency to first emetic episode was significantly increased (Wilcoxon signed rank test, $P<0.05$).

*Cisplatin-induced emesis in the house musk shrew* (Suncus murinus)

The results from these experiments are illustrated in Figure 4. Subcutaneous doses of GR203040 above 1 mg kg$^{-1}$ progressively reduced the numbers of emetic episodes experienced by animals receiving cisplatin (80 mg kg$^{-1}$ i.p.). However, whilst the degree of inhibition of emesis was profound, GR203040 did not completely abolish emesis in any of the animals at the doses used. The doses of GR203040 required to inhibit cisplatin-induced emesis in *Suncus murinus* were comparable to doses inhibiting motion-induced emesis in this species, but an order of magnitude greater than needed to inhibit cisplatin-induced emesis in the ferret.

## Discussion

In the present experiments we have demonstrated that GR203040, a novel and high affinity tachykinin $NK_1$ receptor antagonist, is capable of exerting anti-emetic effects against a

**Table 4** Effects of intravenous GR203040 on ipecacuanha-induced emesis in dogs

| | | *Response* | | *Control response* | |
|---|---|---|---|---|---|
| *Treatment* | *Dog* | *Episodes* | *Latency* (min) | *Episodes* | *Latency* (min) |
| GR203040 | 4FB8 | 0 | | 2 | 19 |
| 0.3 mg kg$^{-1}$ | 4FB7 | 0 | | 1 | 15 |
| GR203040 | 4EC3 | 0 | | 3,2 | 18,15 |
| 0.1 mg kg$^{-1}$ | 4FB9 | 0 | | 2,1 | 18,27 |
| GR203040 | 4FB8 | 1 | 32 | 2 | 19 |
| 0.03 mg kg$^{-1}$ | 4FB7 | 0 | | 1 | 15 |

**Table 5** Numbers of emetic episodes and latencies to first emesis in *Suncus murinus* exposed to linear reciprocating motion

| *GR203040* (1 mg kg$^{-1}$) | | | | *GR203040* (3 mg kg$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|
| *Saline* | | *Treated* | | *Saline* | | *Treated* | |
| *Episodes* | *Latency* (s) | *Episodes* | *Latency* (s) | *Episodes* | *Latency* (s) | *Episodes* | *Latency* (s) |
| 6.8±2.46 | 120±44.5 | 4.0±1.58 | 128±54.3 | 4.9±2.38 | 126±25.9 | 1.1±0.34 | 191±20.6 |

Values are means and s.e.mean, $n=4-7$.

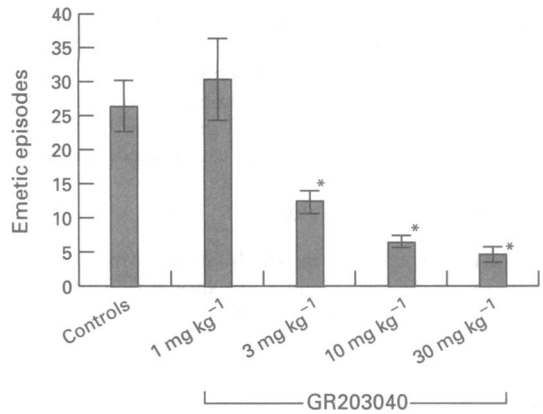


**Figure 4** Effects of GR203040 (1–30 mg kg$^{-1}$ s.c.) in cisplatin-induced emesis in *Suncus murinus*. Values are mean and s.e.mean, $n=10$ control, 4 per treated group. *Indicates a significant difference from control, $P<0.05$.

wide range of emetogens in the ferret. Specifically, GR203040 at a dose of 0.1 mg kg$^{-1}$ s.c. profoundly inhibited emesis induced by the chemotherapeutic agents cisplatin and cyclophosphamide, as well as the emesis induced by high-dose whole-body X-irradiation. Furthermore, GR203040 produced a greater than 80% inhibition of emesis induced by administration of ipecacuanha, morphine and copper sulphate. Importantly, emesis resulting from administration of the latter two agents has been previously shown to be refractory to treatment with 5-$HT_3$ receptor antagonists in ferret, dog and man (Rudd *et al.*, 1990; Kamato *et al.*, 1991; Thompson *et al.*, 1992; Pitkanen *et al.*, 1993). GR203040 was also fully effective at inhibiting established emesis evoked by cisplatin; there was rapid cessation of retching and vomiting in animals treated with GR203040, whereas saline-treated animals continued to exhibit a profound emetic response. Following intravenous administration, GR203040 was also fully effective at blocking emesis evoked in the dog by an oral dose of ipecacuanha; the minimally effective dose being between 0.03 and 0.1 mg kg$^{-1}$, which closely correlates with the anti-emetic potency seen in the ferret.

Currently, the only other tachykinin $NK_1$ receptor antagonist that has been examined for anti-emetic activity is CP-99,994. This compound has been demonstrated to be a broad-spectrum anti-emetic agent against a wide range of emetic stimuli (Bountra *et al.*, 1993; Tattershall *et al.*, 1993; 1994). However, this compound has relatively low potency, a subcutaneous or intravenous dose of 3 mg kg$^{-1}$ being required to inhibit emesis. Clearly, GR203040 has a broad spectrum of anti-emetic activity, and is approximately 30 times more potent that CP-99,994 in inhibiting emesis.

To extend further our knowledge of the anti-emetic profile of $NK_1$ receptor antagonists, we examined GR203040 in a model of motion-induced emesis. In this model, GR203040 at 3.0 mg kg$^{-1}$ s.c. profoundly inhibited the emesis induced by reciprocating motion in the house musk shrew, *Suncus murinus*. The emesis seen in this model has been shown to be sensitive to agents, such as muscarinic cholinoceptor and histamine $H_1$ receptor antagonists, known to inhibit motion sickness in man (Ueno *et al.*, 1988). The doses of GR203040 required to inhibit this kind of emesis in *Suncus murinus* are at least 10 times greater than those doses determined as anti-emetic in the ferret or dog. The observation that GR203040 is effective in inhibiting cisplatin-induced emesis in *Suncus murinus*, at doses comparable to those effective in motion-induced emesis in the same species, may indicate a lack of sensitivity of *Suncus murinus* to $NK_1$ receptor antagonists. To date, the $NK_1$ receptor found in *Suncus murinus* has not been characterized. It is likely that GR203040 will be effective at lower doses against motion-induced emesis in other species.

The site of action of GR203040 has not yet been precisely determined. However, it has been demonstrated that $NK_1$ receptor antagonists need to gain access to the central nervous system to exert their anti-emetic effect (Gardner *et al.*, 1994; Hargreaves *et al.*, 1994). Specifically, the $NK_1$ receptor antagonist GR82334, which is a peptidic compound that does not penetrate the blood-brain barrier, is ineffective as an anti-emetic agent unless administered directly into the hindbrain (Gardner *et al.*, 1994). Similarly, the quarternary compound, L-743,310, has been shown to penetrate into the CNS only poorly, and this compound is inactive against cisplatin-induced emesis in the ferret (Hargreaves *et al.*, 1994). Conversely, CP-99,994, which freely crosses into the brain, is an effective anti-emetic agent when given either centrally or peripherally (Gardner *et al.*, 1994; Hargreaves *et al.*, 1994). From these observations and the data contained within this study, it is likely that GR203040 is able to penetrate into the CNS in the ferret, dog and *Suncus murinus*. Whilst the precise site of action of GR203040 has not been determined, autoradiographic analysis of the binding of radiolabelled substance P has demonstrated dense binding in the medullary nuclei known to be associated with the emetic reflex (Maley & Elde, 1982; Maley *et al.*, 1983; Yamazoe *et al.*, 1984; Riche *et al.*, 1990). Recently, high levels of binding of radiolabelled substance P have been demonstrated in the nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagus nerve (DMNV) of the ferret (Maubach *et al.*, 1995; Watson *et al.*, 1995).

In conclusion, GR203040 is a potent anti-emetic agent with a broad spectrum of anti-emetic activity. This compound is active against emesis induced by agents refractory to current anti-emetic therapies. The anti-emetic activity of the tachykinin $NK_1$ receptor antagonists appears to depend on their penetration of the CNS. The likely site of action of GR203040 is the NTS and the DMNV, and probably it is activity in these important integrative nuclei that underpins the broad spectrum of activity. Importantly, GR203040 is highly effective at abolishing established retching and vomiting, strongly suggesting that this agent would be a useful interventional treatment in the control of emesis. GR203040 is orally active and appears to have a long duration of action, at least in the ferret. Anti-emetic activity in three species strongly suggests that GR203040 is worthy of clinical investigation for anti-emetic activity against a range of emetic stimuli.

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