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European Journal of Pharmacology 363 (1998) 49–55

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Antiemetic effects of sendide, a peptide tachykinin NK_1 receptor antagonist, in the ferret

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Received 16 September 1998; revised 20 October 1998; accepted 23 October 1998

Abstract

The antiemetic activity of sendide, a new peptide tachykinin NK_1 receptor antagonist, against cisplatin-induced emesis was investigated using ferrets. The frequency of cisplatin (10 mg/kg, i.p.)-induced retching (104.6 ± 14.3/6 h) and vomiting (19.0 ± 3.0/6 h) was significantly reduced by pretreatment with sendide (3.0 mg/kg, s.c.) (14.0 ± 8.1/6 h and 1.8 ± 1.2/6 h, respectively). Intravenous bolus injection of substance P (1–10 μg/kg) or 5-hydroxytryptamine (5-HT) (10–50 μg/kg) produced a dose-dependent increase in the abdominal afferent vagus nerve activity. The change from pre-injection level in the afferent nerve activity induced by substance P (1 μg/kg, i.v.) ($453.7 \pm 51.5\%$) was significantly reduced by pretreatment with either sendide (100 μg/kg, i.v.) ($276.1 \pm 50.1\%$, $P < 0.05$) or granisetron, a 5-HT_3 receptor antagonist (1 mg/kg, i.v.) ($146.3 \pm 14.0\%$, $P < 0.01$). The amount of 5-HT released into the solution during a 1-h exposure to 2-methyl-5-HT (10^{-6} M), a 5-HT_3 receptor agonist, was significantly increased ($317.9 \pm 46.7\%$, $P < 0.05$) compared with that of the control tissues ($160.4 \pm 8.1\%$). The 2-methyl-5-HT-induced 5-HT release was significantly inhibited by administration of sendide (10^{-6} M) ($174.0 \pm 21.6\%$, $P < 0.05$) or granisetron (10^{-6} M) ($186.6 \pm 27.3\%$, $P < 0.05$). Since sendide does not penetrate the central nervous system, these results suggest that the antiemetic effects of sendide are due to the inhibition of NK_1 and 5-HT_3 receptors on the emetic peripheral detector sites. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Sendide; Tachykinin NK_1 receptor antagonist; Antiemetic activity; Cisplatin; Abdominal afferent vagus nerve activity

1. Introduction

Substance P has been implicated as a primary afferent transmitter of noxious stimulation. It is reported that tachykinin NK_1 receptor antagonists have a variety of pharmacological effects such as analgesic (Ma and Woolf, 1997; McLean et al., 1998), hypotensive (Diz et al., 1998; Emanueli et al., 1998), anti-asthmatic (Ichinose et al., 1996) and antiemetic (Watson et al., 1995a,b). The non-peptide tachykinin NK_1 receptor antagonist, CP-99,994 [(+)-(2*S*, 3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine], has proved to have broad-spectrum antiemetic effects against cytotoxics, central, peripheral and mixed emetic agonists and motion sickness (Watson et al., 1995a,b). Yet, CP-99,994 has been shown to have no effect on laryngeal, respiratory or cardiovascular reflexes that are known to be mediated through the same region of the brainstem that is responsible for emetic reflexes (Watson et al., 1995a,b). Sakurada et al. (1992) developed a peptide selective tachykinin NK_1 receptor antagonist containing D-amino acid peptide (sendide) (Tyr-D-phe-phe-D-His-Leu-Met-NH_2) as an analogue of substance P. It is suggested that the antinociception assessed in the capsaicin test with sendide may be due to blockade of the tachykinin NK_1 receptor in the spinal cord (Sakurada et al., 1993, 1994a,b). A small volume of sendide administered in the cisterna magna (i.c.v.) inhibited intraduodenal hypertonic saline-induced retching and vomiting in halothane-anesthetized ferrets (Davidson et al., 1995). No reports are available concerning the antiemetic activity of sendide via peripheral administration.

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PII: S0014-2999(98)00784-5

Resinferatoxin, a potent capsaicin analogue, and CP-99,994 are both capable of inhibiting morphine-induced emesis, suggesting a role for substance P in the modulation of the emetic response (Andrews and Bhandari, 1993; Bountra et al., 1993). Endogenous opioids and receptor sites are present in the nucleus tractus solitarius, and stimulation of the vagus nerve can result in analgesia (Randich and Gebhart, 1992). Furthermore, μ-opioid receptors are located presynaptically on vagus afferent fibers (Dashwood et al., 1988). μ-Opioid-receptor agonists do not control substance P release (or other neurotransmitter substances) in the vomiting center. We previously demonstrated that abdominal vagotomy reduced the frequency of cisplatin-induced emesis by 85% and simultaneously inhibited the cisplatin-induced increase in 5-hydroxytryptamine (5-HT) level of the area postrema (Endo et al., 1992). It is proposed that the vomiting center receives an input from the afferent discharges of the vagal fibers, which evoke an emetic reflex. The nucleus tractus solitarius, a brain region where abdominal vagal afferent fibers terminate, has been shown to have a high density of 5-HT_3 receptor binding sites and to be innervated by substance P-containing vagal afferent fibers (Sanger, 1992; Otsuka and Yoshioka, 1993). The vagus is the major nerve involved in the detection of emetic stimuli and it contains about 80–90% afferent fibers in its abdominal course (Andrews, 1992). In the intestine, the enterochromaffin cell has been proposed as another detector cell for emetic stimuli. We speculate that tachykinin NK_1 receptor antagonists may act to interfere with the integration of information between emetic peripheral detector sites before they input to the vomiting center. Using ferrets, an animal model of emesis, the antiemetic activity of sendide against cisplatin was investigated. We also examined the effects of sendide on abdominal afferent vagus nerve activity and 5-HT release from the isolated ileum in the ferret.

2. Materials and methods

2.1. Animals and behavioral experiments

Experiments were performed using ferrets weighing an average of 1.64 (1.5–1.9) kg. Adult male fitch ferrets (*Mustela putorius furo* L.) were supplied by Marshall Research Animals (North Rose, NY, USA). This study was conducted in accordance with the Guideline for The Care and Use of Laboratory Animals by the Animal Research Committee in Health Sciences University of Hokkaido.

The ferrets were injected subcutaneously with sendide or vehicle (physiological saline) 30 min before the intraperitoneal administration of cisplatin (10 mg/kg, i.p.). After treatment, the animals were returned to individual observation cages for the assessment of retching and/or vomiting during the subsequent 6-h period, according to the method of Stables et al. (1987). During this time period, cat chow (Purina Taiyo, Japan) and water were available ad libitum.

2.2. Measurement of abdominal afferent vagal activity

Ferrets were anesthetized with urethane (500 mg/kg, i.p.) and α-chloralose (50 mg/kg, i.p.), and immobilized with gallamine triethiodide (10 mg/kg, i.v.) under artificial respiration. Electrocardiogram and blood pressure were recorded continuously during the course of the experiment on a bioamp and recorder (Nihon-Kohden, AP-641G, Japan). An arterial blood pressure transducer (Nihon-Kohden, TP-400T, Japan) was attached to a polyethylene catheter that was placed in the left carotid artery, as described previously (Minami et al., 1994). Respiration was maintained through a tracheal cannula connected to a respirator (Harvard Apparatus, model 683, USA). Using an expired gas monitor (Nippondenki San-ei, IH26, Japan), ventilation was adjusted to maintain an end tidal O_2 and CO_2 at approximately 15% and 5%, respectively (Endo et al., 1995; Minami et al., 1997; Yoshioka et al., 1992). Rectal temperature was maintained between 37 and 38°C with a heating pad (Natsume homoethermin blanket control, KN-474, Japan). Afferent abdominal vagus nerve activity was recorded from the peripheral cut end of the nerve with bipolar platinum–iridium wire electrodes (Yoshioka et al., 1992). The nerve was immersed in a pool of warm paraffin oil. Nerve activity was amplified, passed through a filter (time constant of 6.7 ms, and a high cutoff filter of 1000 Hz) and displayed on a thermal array recorder (Nihon-Kohden, RTA-1300A, Japan). In order to avoid tachyphylaxis on abdominal afferent nerve activity with the administration of sendide and/or 5-HT, a minimum of 10 min was allowed between injections of each dose.

2.3. Measurement of 5-HT release from the isolated ileum

Ferret tissues, including the heart, were isolated from animals anesthetized with urethane (500 mg/kg, i.p.) and α-chloralose (50 mg/kg, i.p.). According to the method of Milano et al. (1991), a 3-cm long (weight 1.0–1.5 g) section was dissected 20 cm from the pylorus. These isolated ileal segments were placed in organ baths which contained modified Krebs solution: NaCl 120; KCl 5.0; $CaCl_2$ 2.5; $MgSO_4$ 1.0; $NaHPO_4$ 1.0; glucose 11.0 mM, pH 7.4 and aerated with 95% O_2 and 5% CO_2. After a 60-min equilibration period, tissue bathing buffer solution was collected in 20 ml fractions. The amount of 5-HT released from the ileum was measured using high performance liquid chromatography (Eicom, EP-10, Japan) with an electrochemical detector (Eicom, ECD-100, Japan) (Minami et al., 1988). Protein assays were performed by the method of Lowry et al. (1951) with bovine serum albumin as the standard.

Table 1
The inhibitory effects of sendide (s.c.) on cisplatin-induced emesis in ferrets

Dose (mg/kg)	No. of animals retching/tested	No. of retching/6 h	No. of vomiting/6 h	Latency to emesis (min)	Duration of emesis (min)
Cisplatin (10, i.p.)	9/9	136.4 ± 19.7	24.9 ± 24.5	96.4 ± 2.2	155.0 ± 20.8
Cisplatin + Sendide (1.0, s.c.)	5/5	105.6 ± 29.0	10.0 ± 2.5	104.4 ± 7.3	88.2 ± 23.3
Cisplatin + Sendide (3.0, s.c.)	4/4	76.3 ± 15.5[a]	9.5 ± 3.2[a]	107.0 ± 6.5	132.8 ± 10.5

The data represent the mean ± S.E. from four to nine animals.
Values are significantly different ([a]$P < 0.05$) from those for cisplatin alone.

2.4. Drugs

In order to obtain a stable solution with reproducible emetic activity, commercial cisplatin (Nippon Kayaku, Tokyo, Japan) was used in this study. Granisetron hydrochloride (SmithKline Beecham, Tokyo, Japan) and 5-HT creatinine sulfate (Sigma, St. Louis, MO, USA) were dissolved in normal saline. An equal volume of physiological saline was administered to control animals. Sendide (Sakurada et al., 1992) was prepared in the Department of Pharmacology, Tohoku College of Pharmacy (Sendai, Japan) and was supplied by Asahi Glass (Tokyo, Japan). The 5-HT_3 receptor agonist, 2-methyl-5-hydroxytryptamine maleate (Research Biochemicals, Natick, MA, USA), was dissolved in the above mentioned modified Krebs solution. Substance P (Research Biochemicals, Natick, MA, USA), chymostatin (0.1 mg/ml) (Peptide Institute, Osaka, Japan) and soybean trypsin inhibitor (0.1 mg/ml) (Sigma, St. Louis, MO, USA) were dissolved in the same buffer and concomitantly superfused. Chymostatin and soybean trypsin inhibitor were used as peptidase inhibitors for our in vitro study.

2.5. Statistical analysis

All values are given as mean ± S.E. The significance of differences between treatment effects was assessed using Student's *t*-test. Analysis of variance, followed by the Bonferroni modified *t*-test (Wallenstein et al., 1980), was used for comparisons of more than two groups. A $P < 0.05$ was considered to be statistically significant.

Table 2
Effects of intravenous injection of substance P, sendide and granisetron on abdominal vagus nerve activity in anesthetized ferrets

Compounds	Dose (μg/kg, i.v.)	% Increase from pre-injection level
Vehicle		104.7 ± 8.8 ($n = 7$)
Sendide	100	98.4 ± 4.9 ($n = 14$)
Granisetron	1000	93.0 ± 8.0 ($n = 7$)
Substance P	1	453.7 ± 51.1 ($n = 6$)[b]
	5	676.8 ± 74.5 ($n = 6$)[c]
	10	857.7 ± 173.8 ($n = 6$)[b]

The data represent the means ± S.E. for five to fourteen animals.
Values are significantly different ([b]$p < 0.01$, [c]$p < 0.001$) from those for the vehicle.
In order to avoid tachyphylaxis, a minimum of 10 min was allowed between injection of each dose.

3. Results

3.1. Emetic effects of cisplatin and the antiemetic effects of sendide

3.1.1. Effects of sendide on cisplatin-induced emesis in ferrets during a 6-h observation period

The frequency of cisplatin-induced retching and vomiting over 6 h was significantly reduced by pretreatment with sendide (3.0 mg/kg, s.c.) (Table 1). There were no significant differences between the two groups in terms of latency to first emesis or duration of emesis induced by cisplatin during the 6-h observation period.

3.2. Effects of sendide on abdominal afferent vagus nerve activity

3.2.1. Effects of substance P, 5-HT, sendide and granisetron on abdominal afferent vagus nerve activity in the anesthetized ferret

Intravenous bolus injection of substance P (1–10 μg/kg, i.v.) produced a dose-dependent increase in abdominal afferent vagus nerve activity (Table 2). 5-HT also

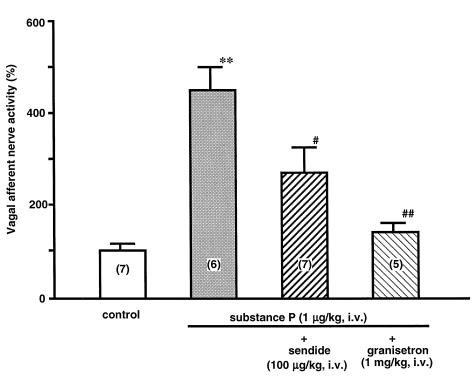

Fig. 1. Effects of sendide on substance P-induced increase in abdominal afferent vagus nerve activity in the anesthetized ferret. Each bar represents the mean ± S.E. for the number of animals shown in brackets. Significant differences (** $P < 0.01$) among control animals and (# $P < 0.05$, ## $P < 0.01$) the substance P (1 μg/kg, i.v.) group are shown, respectively.

produced a dose-dependent increase in abdominal afferent nerve activity.

3.2.2. Effects of sendide on substance P- and 5-HT-induced increase of abdominal afferent vagus nerve activity in the anesthetized ferret

As shown in Fig. 1, the increase in abdominal afferent nerve activity of the vagus (453.7 ± 51.5% from pre-injection level) induced by substance P (1 μg/kg, i.v.) was significantly inhibited by sendide (100 μg/kg, i.v.) (276.1 ± 50.1%). Intravenous administration of granisetron (1 mg/kg, i.v.) (146.3 ± 14.0%) also significantly inhibited the increase brought about by substance P. Furthermore, the increase in abdominal afferent nerve activity of the vagus induced by 5-HT (25 μg/kg, i.v.) (552.0 ± 57.0% from pre-injection level) was significantly inhibited by sendide (100 μg/kg, i.v.) (448.0 ± 50.0% from pre-injection level, $P < 0.05$). A spinal cut (between the 2nd and 3rd cervical cord) did not alter the effects of sendide on abdominal afferent nerve activity.

3.3. Effects of sendide on 5-HT release

3.3.1. Effects of sendide on the 5-HT release induced by 2-methyl-5-HT

As shown in Fig. 2, 2-methyl-5-HT, a 5-HT_3 receptor agonist, induced a concentration-dependent increase of 5-HT release from the ferret isolated ileum. The amount of 5-HT released into the solution during a 1 h exposure to 2-methyl-5-HT (10^{-6} M) was significantly increased (317.9 ± 46.7%, $P < 0.05$) compared with that of the control tissues (160.4 ± 8.1%). Sendide (10^{-8}–10^{-6} M) itself did not affect 5-HT release. The 2-methyl-5-HT (10^{-6} M)-induced 5-HT release was significantly inhibited by both sendide (10^{-6} M) and granisetron (10^{-6} M) (Fig. 2) administration. The interaction between the NK_1 and 5-HT_3 receptors was investigated during 5-HT release from the isolated ileum. Substance P (10^{-8}–10^{-5} M), with or without protease inhibitors such as soybean trypsin inhibitor (1–100 μg/ml) and chymostatin (1–100 μg/ml), did not affect 5-HT release.

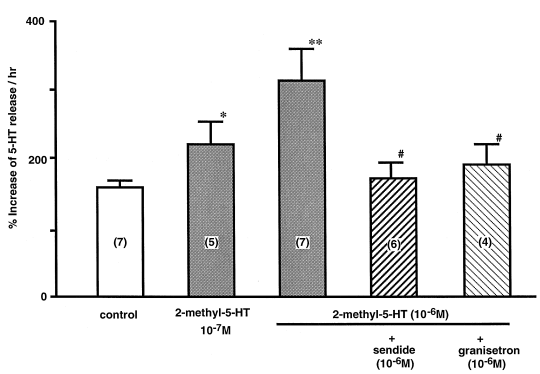

Fig. 2. Effects of sendide on the 5-HT release induced by 2-methyl-5-HT in the isolated ileum of the ferret. Each bar represents the mean ± S.E. for the number of animals shown in brackets. Significant differences (* $P < 0.05$, ** $P < 0.01$) among control animals and (# $P < 0.05$) the 2-methyl-5-HT (10^{-6} M) group are shown, respectively.

4. Discussion

This paper is the first to describe a significantly reduced frequency in cisplatin-induced emesis caused by the peptide tachykinin NK_1 receptor antagonist, sendide, in the ferret. No significant differences were observed between the sendide group and the control group for either latency to first emesis or duration of emesis induced by cisplatin during the 6-h observation. In contrast, a significant delay in the latency to retching was produced at doses of 1 and 3 mg/kg of CP-99,994, a non-peptide tachykinin NK_1 receptor antagonist (Tattersall et al., 1993). Since sendide is a peptide, it may be a short-acting antiemetic and its application may thus be limited.

Next, in order to elucidate the antiemetic involvement of peripheral sites, we determined the effect of sendide on afferent vagal nerve activity. The most important result was that sendide inhibited both the substance P- and the 5-HT-induced increase in abdominal vagal nerve activity in anesthetized ferrets. Furthermore, granisetron, a 5-HT_3 receptor antagonist, also significantly inhibits substance P-induced nerve changes. Although intrathecal administration of sendide has antinociceptive effects, sendide does not easily penetrate the central nervous system as it is a peptide tachykinin NK_1 receptor antagonist (Sakurada et al., 1992). Since these effects of sendide were not altered by a spinal cut, the site of action was thought to be a peripheral one. Furthermore, we have reported from a preliminary study that CP-99,994, a non-peptide tachykinin NK_1 receptor antagonist, significantly inhibited the increased abdominal afferent vagal nerve activity induced by either substance P or 5-HT (Endo et al., 1998). There are, however, no reports available showing that either CP-99,994 or sendide lacks affinity for 5-HT_3 receptors. These results suggest that tachykinin NK_1 receptor antagonists produce an antiemetic action on the abdominal afferent vagus nerve by blocking the effects of substance P and 5-HT.

In the guinea pig ileum, substance P induces physiological activity via the NK_1 receptors, neurokinin A induces activity via the tachykinin NK_2 receptors, and neurokinin B induces activity via the NK_3 receptors (Ramírez et al., 1994). It has been previously reported that substance P may be associated with the depolarization of 5-HT_3 receptors and that neurokinin B may excite 5-HT_4 receptors (Ramírez et al., 1994). Substance P could be involved in the response in several roles: as co-transmitter (Nilsson and Holmgren, 1989), as an intermediate transmitter with the final effect being due to 5-HT (Holmgren et al., 1985), or by potentiating the effect of a non-peptide transmitter as

demonstrated with bombesin and acetylcholine in cod and trout stomachs (Thorndyke and Holmgren, 1990). In order to purge toxins from the gastrointestinal tract, tachykinin NK_1 receptors may act cooperatively with 5-HT_3 receptors on the abdominal afferent vagal nerves as a defense mechanism.

As the first synapse in the pathway is within the brainstem, a central site of action has been proposed for the antiemetic activity of CP-99,994 (Watson et al., 1995a,b). Andrews (1994) pointed out that the tachykinin NK_1 receptor antagonist differs from the 5-HT_3 receptor antagonists which appear to block emesis mediated by vagal afferent pathways activated by the local release of 5-HT in the gut wall. However, no anatomical correlate has been identified: the vomiting center, or nucleus tractus solitarius, is regarded as the area that integrates all the disparate emetic inputs and coordinates the generation of the sensory, visceral and somatic outputs that comprise nausea and vomiting (Watson et al., 1995a,b). Substance P has been proposed to be an important neurotransmitter in primary sensory neurons involved in nociception (Pernow, 1983). Our results suggest that sendide could block the first input of substance P, including emetic and painful information, to the abdominal afferent vagal nerves. As lesion studies have shown that the emesis induced by a variety of foods and drugs is reduced or abolished by vagotomy, it is likely that it is these mucosal afferents that are responsible (Wang and Borison, 1952; Andrews et al., 1990). The fact that abdominal vagotomy inhibits 85% of the cisplatin-induced emesis indicates that abdominal vagal afferent nerves seem to be a major pathway for cisplatin-induced emesis (Endo et al., 1992). Emesis caused by cisplatin, cyclophosphamide or copper sulfate is associated with an increase in the concentration of 5-HT in the intestinal mucosa (Endo et al., 1990a,b) and in the area postrema (Endo et al., 1992). The activity of tryptophan hydroxylase, the rate-limiting enzyme for the synthesis of 5-HT, in the area postrema increases significantly in cisplatin-treated ferrets as compared with that in the non-drug control group (Endo et al., 1993). We have demonstrated that electrical stimulation of the abdominal vagal afferents also induces an increase in the concentration of 5-HT in the area postrema region (Minami et al., 1995a). Vagotomy clearly inhibits the increase of 5-HT in the area postrema (Endo et al., 1992). Also, pretreatment with ondansetron diminishes the area postrema-5-HT increase, but does not alter the increase in ileal 5-HT levels (Endo et al., 1992). In other words, the increase in 5-HT levels induced by anticancer drugs in the vomiting center might be inhibited by the chemical vagotomy caused by 5-HT_3 receptor antagonists. In the acute emesis caused by anticancer agents, the 5-HT_3 receptor antagonists exert an antiemetic effect by interrupting 5-HT action mainly at the abdominal vagal afferent fibers (Andrews, 1992). Our studies confirmed that cytotoxic drugs induce acute emesis mainly through actions on the gastrointestinal tract.

The basic mechanism in emesis might be the toxic action of cancer chemotherapeutic agents on the rapidly dividing cells (Esseboom et al., 1995). Anticancer drugs congregate in tissues with a rapid turnover, such as the gastrointestinal tract, including the enterochromaffin cells and impair the epithelium of the mucous membrane in the acute phase. 5-HT plays an important role in the production of cytotoxic drug-induced emesis (Miner and Sanger, 1986; Costall et al., 1986). In addition to increasing 5-HT synthesis, cytotoxic drugs cause 5-HT release from the enterochromaffin cells (Endo et al., 1993; Racké and Schwörer, 1991; Milano et al., 1991). There is a complex pattern of mechanisms involved in the regulation of 5-HT release from the intestinal mucosa (Racké and Schwörer, 1991; Minami et al., 1995b). It is uncertain how cytotoxic drug-induced 5-HT release is brought about. 5-HT release can be modulated by a variety of heteroreceptors (Racké and Schwörer, 1991; Schwörer et al., 1987; Racké et al., 1988). Thus 5-HT can cause both direct activation of the afferents and long-lasting sensitization to other stimuli (Andrews and Hawthorn, 1988; Andrews et al., 1988). Stimulation of the afferent vagal nerve fibers or 5-HT entering the circulation appears to act on the area postrema.

Next, in order to elucidate the relationship between tachykinin NK_1 and 5-HT_3-receptors, we determined the effect of sendide on 5-HT release induced by 2-methyl-5-HT. These experiments demonstrated that the 2-methyl-5-HT-induced increase in 5-HT levels in the isolated ferret ileum was significantly inhibited by sendide. We have obtained similar results with CP-99,994 (Endo et al., 1998). Our experimental results, together with the finding of afferent vagal nerve activity and 5-HT release from the isolated ileum, indicated a close relationship between tachykinin NK_1 receptors and 5-HT_3 receptors at the peripheral sites of action.

Substance P has aroused interest as a blood pressure regulator because of experimental evidence that: (1) it localizes in brain areas involved in cardiovascular control, such as the nucleus tractus solitarius and hypothalamus (Folkers et al., 1984); (2) our group found that intracerebroventricular administration of substance P produces a rise in blood pressure (Togashi et al., 1986); and (3) electrical or chemical stimulation of the ventral medulla oblongata causes a blood pressure rise, accompanied by an increase in substance P release into the cerebrospinal fluid (Helke et al., 1982). We previously reported that peptide antagonists, spantide and SPA-80, administered intrathecally, produce a decrease in adrenal nerve activity and blood pressure (Togashi et al., 1986). There are no clinically important hypotensive drugs among the tachykinin NK_1 receptor antagonists. However, angiotensin-II-induced effects on substance P release from brain slices of the medulla oblongata are linked to acute cardiovascular actions of the peptide through the tachykinin NK_1 receptors (Diz et al., 1998). Since the so called vomiting center includes the nucleus tractus solitarius, centrally acting

tachykinin NK_1 receptor antagonists may induce hypotension as a side-effect. In the present study, relatively higher doses of sendide (1–3 mg/kg, i.v.) did not induce hypotension in anesthetized ferrets. These results indicate that sendide has a peripheral site of action.

Sakurada et al. (1993, 1994a,b) suggest that the antinociceptive effects of sendide may be due to blockade of the tachykinin NK_1 receptors in the spinal cord. The present results demonstrated that sendide significantly reduced the frequency of cisplatin-induced emesis in the ferret. Post-operative nausea and vomiting may be related to the control of pain following surgical procedures (Baxendale et al., 1993). Sendide may have potential as an antiemetic for the clinical treatment of postoperative nausea and vomiting. On the other hand, the retching response to mechanical stimulation in the anesthetized suncus is not blocked by granisetron, CP-99,994 or morphine but is blocked by the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) (Andrews, 1994). Further study is needed to elucidate whether tachykinin NK_1 receptor antagonists are effective to reduce post-operative nausea and vomiting.

In conclusion, the antiemetic effect of sendide involves the peripheral gastrointestinal tract as its site of action. In order to purge toxins from the gastrointestinal tract, tachykinin NK_1 receptors may act cooperatively with 5-HT_3 receptors on the abdominal afferent vagal nerves as a defense mechanism.

Acknowledgements

The authors are greatly indebted to Mr. Hideya Yokota and Miss Yumi Teramoto for their technical assistance. The authors wish to thank SmithKline Beecham (Tokyo, Japan) and Asahi Glass (Tokyo, Japan) for generously providing granisetron and the sendide compounds, respectively. This work was supported in part by Grants-in-Aid for High Technology Research Programs from the Ministry of Education, Science, Sports and Culture of Japan.

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