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Anti-emetic Effect of Mosapride Citrate Hydrate, a 5-HT_4 Receptor Agonist, on Selective Serotonin Reuptake Inhibitors (SSRIs)-Induced Emesis in Experimental Animals

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Abstract. Although selective serotonin reuptake inhibitors (SSRIs) are widely used to treat depression, they frequently cause gastrointestinal adverse effects, such as nausea and emesis. In the present study, we investigated the anti-emetic effect of mosapride, a 5-HT_4 receptor agonist, on SSRIs-induced emesis in *Suncus murinus* and dogs. We also examined the effect of mosapride on SSRIs-induced delay in gastric emptying and increase in gastric vagal afferent activity in rats. Oral administration of paroxetine, but not its subcutaneous administration, dose-dependently caused emesis in both animals. Mosapride inhibited paroxetine-induced emesis in *Suncus murinus* and dogs with ID_{50} values of 7.9 and 1.1 mg/kg, respectively. The anti-emetic effect of mosapride was partially inhibited by SB207266, a selective 5-HT_4 antagonist. Intragastric administration of paroxetine increased gastric vagal afferent discharge in anesthetized rats. Mosapride failed to suppress this increase. On the other hands, mosapride improved the delay in gastric emptying caused by paroxetine in rats. We have shown in this study that oral administration of SSRIs causes emesis and activates gastric vagal afferent activity in experimental animals and that mosapride inhibits SSRIs-induced emesis, probably via improvement of SSRIs-induced delay in gastric emptying. These findings highlight the promising potential of mosapride as an anti-emetic agent.

Keywords: mosapride citrate hydrate, 5-HT_4 receptor agonist, emesis, anti-emetic effect, selective serotonin reuptake inhibitors (SSRIs)

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat anxiety and depression owing to lack of serious side effects, such as dry mouth and cardiotoxicity, which are often observed with tricyclic antidepressants (1). Inhibition of neuronal 5-HT uptake is the main mechanism of action of numerous antidepressant drugs such as fluoxetine, fluvoxamine, paroxetine, sertraline, and others (2). While these SSRIs have been found to be clinically effective, their beneficial action is occasionally associated with nausea and emesis, which limits their use or prompt the discontinuation of these drugs (3).

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SSRIs-induced nausea and vomiting are probably due to increased serotonin levels in the gastrointestinal tract as well as in the CNS caused by obstruction of 5-HT reuptake. Although the 5-HT_3 receptor antagonist ondansetron is believed to be efficacious in reducing fluvoxamine-induced emesis (4), its decrease of vomiting incidence is only partial. It has also been reported that cisapride, a 5-HT_4 agonist with 5-HT_3 antagonistic activity, produces rapid relief from nausea elicited by initiation of treatment with SSRI (5). While SSRIs-induced emesis is shown to be mediated at least in part via 5-HT_3 and 5-HT_4 receptors, the mechanism underlying this adverse event has not yet been clearly elucidated.

Mosapride citrate hydrate (mosapride), a 5-HT_4 receptor agonist, is a gastroprokinetic agent indicated for the treatment of gastrointestinal (GI) symptoms such as heartburn, nausea/vomiting associated with chronic

gastritis, and functional dyspepsia (6 − 9). Clinically, mosapride has been found to be useful in reducing fluvoxamine-induced nausea and emesis (10). However, there is no report showing that mosapride has a beneficial effect on SSRIs-induced vomiting and its underlying mechanism in experimental animals. To clarify the beneficial effects of mosapride in animals, we investigated in this study the anti-emetic effect of mosapride on SSRIs-induced emesis in *Suncus murinus* (a house musk shrew) and dogs. As previous reports have shown that emetogenic agents increase gastric vagal afferent activity and delay gastric emptying in rats (11 – 13), we also examined in this study the effect of mosapride on SSRI-induced delay in gastric emptying and increase in gastric vagal afferent activity in rats.

Materials and Methods

Animals

Male *Suncus murinus* (Jic:SUN-Her; Clea Japan, Tokyo) weighing 50 – 73 g, Sprague-Dawley rats (Japan SLC, Inc., Shizuoka) weighing 280 – 330 g, and beagle dogs (Nosan-Beagle; Naruku, Inc., Chiba) weighing 8 – 13 kg were used in this study. The *Suncus murinus* were individually housed in stainless steel cages, and the rats were housed in groups of 2 – 3 in polycarbonate cages kept in a temperature (23°C ± 3°C)- and humidity (55% ± 15%)-controlled animal room under a 12:12 h light-dark cycle. Dogs were individually housed in stainless steel cages kept in a temperature (18°C – 28°C)- and humidity (40% – 80%)-controlled animal room. Standard food (CIEA-312 for *Suncus murinus* and CE-2 for rats, Clea Japan) and tap water were available ad libitum to all *Suncus murinus* and rats. For dogs, standard food (250 g per day, DS-A; Oriental Yeast Co., Ltd., Tokyo) was given in the morning, and tap water was available ad libitum. All experiments in this study were approved by the Institutional Animal Care and Use Committee at the Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd.

Drugs

Paroxetine hydrochloride (Paxil®, or extracted from Paxil®; GlaxoSmithKline KK, Tokyo), fluvoxamine maleate (extracted from Lubox®; Astellas Pharma, Inc., Tokyo), and sertraline maleate (extracted from Jzoloft®; Pfizer Japan, Inc., Tokyo) were used as SSRIs. Mosapride [(±)-4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl] benzamide citrate dehydrate] was synthesized at our plant. Ondansetron, domperidone, and SB207266 were synthesized in our laboratories. Other compounds used in this study were purchased commercially: 5-HT (Serotonin creatinine sulfate complex; Sigma-Aldrich, St. Louis, MO, USA).

SSRIs (paroxetine, fluvoxamine, sertraline) were dissolved in 40% polyethylene glycol (PEG#400) for oral or subcutaneous administration. Mosapride, ondansetron, and domperidone were suspended in 0.5% methyl cellulose solution for oral administration. SB207266, a selective 5-HT_4 receptor antagonist, was dissolved in saline for intraperitoneal administration. 5-HT was dissolved in saline and given intravenously.

Evaluation of vomiting (emesis) in Suncus murinus (shrews)

Immediately after oral or subcutaneous administration of SSRIs, the shrews were transferred to individual cages (17 × 28 × 13 cm) and observed for 1 h to assess vomiting behavior. Observation was directly performed by the experiment investigator. For each animal, the number of expulsive vomiting during the 1-h observation period was counted, and the latency to the first vomiting was recorded. Emetic tests for individual animals were spaced at least 14 days apart to permit full recovery and to avoid changes in susceptibility or tolerance.

In the antiemetic experiments, mosapride, ondansetron, or domperidone was orally administered 1 h before administration of SSRIs. SB207266 was also intraperitoneally administered 1 h before administration of SSRIs, that is, at the same time as mosapride. These drugs were administered to animals in a volume of 10 mL/kg.

Evaluation of vomiting (emesis) in dogs

After oral or subcutaneous administration of paroxetine to dogs, the number of expulsive vomiting by each dog was counted for a period of 1 h, and the latency to the first vomiting was recorded. Paroxetine was orally given as Paxil® tablet. In the antiemetic experiment, mosapride was orally administered to each dog in a volume of 1 mL/kg 1 h before administration of paroxetine. Emetic tests for individual animals were spaced at least 14 days apart to permit full recovery and to avoid changes in susceptibility or tolerance.

Preparation of rats for electrophysiological recording of vagal nerve activity

Under urethane (Sigma-Aldrich) anesthesia (1 g/kg, i.p.), the left carotid artery was cannulated with a heparinized polyethylene catheter (200 U/mL heparin in saline) for blood pressure monitoring, and the left femoral vein was cannulated for drug administration. Heart rate and blood pressure were continuously monitored to insure physiological stability of the preparations. A polyethylene catheter was inserted into the fundus for drug intragastric administration. Under a dissection microscope (Nikon SMZ, Tokyo), the nerve bundle of the left

gastric branch was split with a sharp blade over 3 mm in length. Fine vagal filaments were dissected from the main nerve trunk and placed on a platinum hook recording electrode, with perineural connective tissue placed on a reference electrode. All recordings were made from the peripheral cut end of the vagal nerve. The abdominal wound was covered with a saline-moistened gauze, and the rats were maintained at 37°C by a regulated heating pad.

Electrophysiological recording of vagal nerve activity in rats

Electrophysiological recordings of vagal nerve activity were conducted according to the method described in a previous report (14). The electrode was connected to a head stage (JB-101J; Nihon-Kohden, Tokyo) and the signal was differentially amplified 10,000 times and filtered with a bandwidth of 150 Hz to 1 KHz (AVB-11A, Nihon-Kohden). The neural output signals, together with the signal from a pressure transducer, were acquired by an interface (USA-II; Unique Medical Co., Ltd. Tokyo). The nerve signal was digitally sampled at 10 KHz, which was sufficient to allow spike discrimination. Nerve activity was analyzed after raw data were converted to standard pulses and counted (5 s bin width), or through an integration of the raw signal with a time constant of 1 s using the off-line software spike histogram extension to distinguish discharges from back-ground noise. Data were also recorded on tape for later analysis. Each drug was administered i.v. or i.g. via the inserted cannula.

Measurement of gastric emptying in rats

Gastric emptying of a semisolid meal was measured according to the method of Droppleman et al. (15). The rats were fasted for 18 h before all experiments. Test drug (paroxetine at 10 and 30 mg/kg, a combination of paroxetine at 30 mg/kg and mosapride at 1 − 10 mg/kg or vehicle) was orally administered before the test meal (2.5% cornstarch, 2.5% beef bouillon, 5% casein, and 2.5% powdered sugar in 5% aqueous methyl cellulose solution), which was given via a gastric tube (3 mL per animal). Ninety minutes after administration of the test meal, the stomach was removed and weighed, with and without the remaining luminal content. The amount of meal emptied per rat was calculated according to the method of Droppleman et al. (15).

Statistical analyses

Data are expressed as the mean ± S.E.M. Statistical analysis was performed using the SAS system (SAS Institute, Inc., Cary, NC, USA). Values of $P < 0.05$ were considered as statistically significant. In the emesis test, results are presented as the incidence of vomiting in which both the numbers of animals that vomited and those tested are shown. Differences in incidence of vomiting between the vehicle control group and each SSRI treatment group were analyzed by using Fisher's exact test. Latency to the first vomiting as well as the number of emetic episodes was determined for all animals that vomited. In the antiemetic experiment, differences between the vehicle control group and each mosapride-treated group were analyzed using Dunnett's multiple comparison test. Mosapride ID_{50} values, defined as the doses that cause 50% inhibition of the number of paroxetine-induced emetic episodes, were estimated using the Probit method. In the experiment for assessment of 5-HT_4 antagonistic activity, differences between the vehicle control group and mosapride-treated group and between the mosapride-treated group and SB207266/mosapride-treated group were analyzed by using Student's *t*-test. In the gastric emptying experiment, differences between the vehicle control group and paroxetine-treated group were analyzed by using Student's *t*-test, and differences between the paroxetine control group and mosapride treatment groups were analyzed by using Dunnett's multiple comparison test.

Results

Effect of oral administration of SSRIs in Suncus murinus and dogs

Table 1 shows the incidence of vomiting induced by oral administration of SSRIs in *Suncus murinus*. Oral administration of paroxetine, fluvoxamine, or sertraline caused emesis in the animals. Paroxetine (10 – 90 mg/kg) dose-dependently increased the incidence of vomiting, shortened the latency to the first emetic episodes, and increased total emetic episodes. At the dose of 60 mg/kg and over, paroxetine induced vomiting in all the shrews. Fluvoxamin (60 – 120 mg/kg) and sertraline (60 – 90 mg/kg) also increased the incidence of vomiting, and shortened the latency to the first emetic episode in *Suncus murinus*.

Table 2 shows the incidence of vomiting induced by oral administration of paroxetine in dogs. Oral administration of paroxetine (20 – 60 mg/dog) dose-dependently increased the incidence of vomiting in dogs.

Effect of subcutaneous administration of paroxetine in Suncus murinus and dogs

Table 3 shows the incidence of vomiting induced by subcutaneous administration of paroxetine in *Suncus murinus* and dogs. Subcutaneous administration of paroxetine didn't cause emesis in *Suncus murinus* or dogs.

Table 1. Vomiting induced by oral administration of SSRIs (paroxetine, fluvoxamine, sertraline) in *Suncus murinus*

Drugs	Dose (mg/kg, p.o.)	Number of animals vomited/tested	Latency of the first emetic episode (min)	Total emetic episodes
Vehicle (40% PEG)	—	0/6	—	—
Paroxetine	10	0/6	—	—
	30	2/6	19, 10	6, 8
	60	6/6**	13.0 ± 4.8	6.7 ± 0.5
	90	6/6**	8.7 ± 2.2	9.7 ± 1.6
Fluvoxamine	60	2/5	37, 7	5, 5
	90	2/5	2, 6	6, 8
	120	5/6*	10.2 ± 1.7	8.0 ± 1.0
Sertraline	60	3/4*	12.0 ± 5.6	7.3 ± 1.2
	90	9/10**	10.1 ± 4.3	7.4 ± 1.0

The incidence of vomiting is shown as the number of shrews that vomited / the number of shrews tested. *$P < 0.05$, **$P < 0.01$ vs. vehicle treatment, analyzed by Fisher's exact test. Values of the latency and the total emetic episodes during the 1 h of observation were calculated for the animals that vomited and expressed as mean ± S.E.M.

Table 2. Vomiting induced by oral administration of paroxetine in dogs

Drugs	Dose (mg/dog, p.o.)	Number of animals vomited/tested	Latency of the first emetic episode (min)	Total emetic episodes
Paroxetine	20	1/3	22	2
	40	2/3	20, 18	1, 2
	60	2/3	25, 12	3, 2

The incidence of vomiting is shown as the number of dogs that vomited / the number of dogs tested. Values of the latency and the total emetic episodes during the 1 h of observation were expressed for vomited animals.

Table 3. Vomiting induced by subcutaneous administration of paroxetine in *Suncus murinus* or dogs

Animals	Drugs	Dose (mg/kg, s.c.)	Number of animals vomited/tested
Suncus murinus	Paroxetine	10	0/3
		30	0/4
		60	0/4
Dogs	Paroxetine	0.1	0/3
		0.3	0/3
		1	0/3

The incidence of vomiting is shown as the number of animals that vomited / the number of animals tested.

Effect of mosapride on SSRI-induced emesis in Suncus murinus and dogs

Figure 1 shows the effect of oral administration of mosapride on paroxetine-induced emesis in *Suncus murinus*. Oral administration of mosapride dose-dependently reduced both the incidence of vomiting and the number of emetic episodes in paroxetine-treated *Suncus murinus* with ID_{50} values of 7.9 mg/kg. Figure 2 shows the effect of oral administration of mosapride on fluvoxamine or sertraline-induced emesis in *Suncus murinus*. Oral administration of mosapride (30 mg/kg) reduced fluvoxamine- or sertraline-induced emesis in *Suncus murinus*. At the dose of 30 mg/kg, mosapride inhibited the emesis caused by fluvoxamine by 52.2% and that caused by sertraline by 55.0%. The anti-emetic effect of mosapride on sertraline-induced emesis was statistically

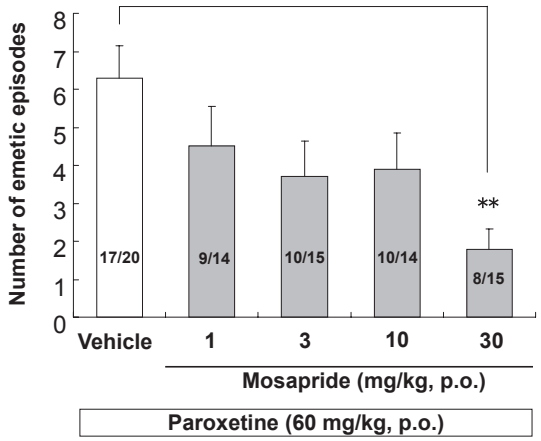

Fig. 1. Effects of mosapride on paroxetine-induced emesis in *Suncus murinus*. Each column represents the mean ± S.E.M. of the number of emetic episodes. The number in each column represents the incidence of vomiting as the number of animals that vomited / the number of animals tested. Mosapride or vehicle was orally administered to the animals. One hour later, paroxetine was orally administered and numbers of vomits were recorded for 1 h after paroxetine administration. $^{**}P < 0.01$, significantly different from the vehicle control group (Dunnett's multiple comparison test).

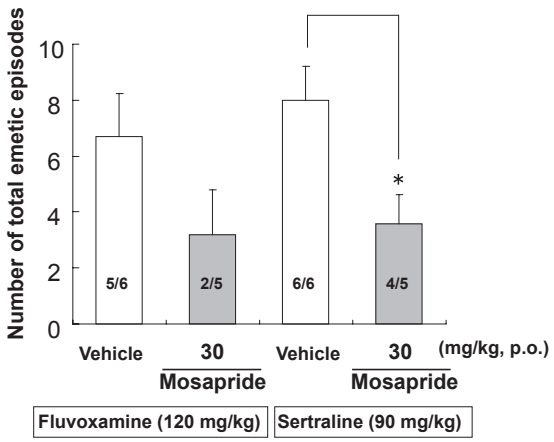

Fig. 2. Effects of mosapride on fluvoxamine or sertraline-induced emesis in *Suncus murinus*. Each column represents the mean ± S.E.M. of the number of emetic episodes. The number in each column represents the incidence of vomiting as the number of animals that vomited / the number of animals tested. Mosapride or vehicle was orally administered to the animals. One hour later, fluvoxamine or sertraline was orally administered and numbers of vomits were recorded for 1 h after each SSRI administration. $^{*}P < 0.05$, significantly different from the vehicle control group (Student's *t*-test).

significant. Figure 3 shows the effect of oral administration of mosapride on paroxetine (60 mg/dog)-induced emesis in dogs. Oral administration of mosapride dose-dependently reduced the number of paroxetine-induced emetic episodes and increased the latency to the first emetic episode with an ID_{50} value of 1.1 mg/kg. At the high dose of 30 mg/kg, mosapride completely inhibited emesis in all animals.

Effect of other anti-emetic agents on paroxetine-induced emesis in Suncus murinus

Figure 4 shows the effects of ondansetron (1, 10 mg/kg) and domperidone (10 mg/kg) on paroxetine-induced emesis in *Suncus murinus*. Ondansetron, a 5-HT_3 antagonist, and domperidone, a dopamine D_2–receptor antagonist, slightly, but not significantly, reduced the emesis induced by paroxetine.

Effect of SB207266 on the anti-emetic action of mosapride in Suncus murinus

Figure 5 shows the effect of SB207266, a selective 5-HT_4 receptor antagonist, on the antiemetic effect of mosapride in paroxetin-treated *Suncus murinus*. Mosapride (30 mg/kg) inhibited the emesis caused by paroxetine (60 mg/kg, p.o.). This anti-emetic effect was partially inhibited by SB207266. SB207266 given alone at 1 mg/kg, i.p. had no effect on paroxetine-induced emesis in the animals.

Effect of intragastric or intravenous administration of paroxetine on gastric vagal afferent activity in anesthetized rats

To assess the reliability of the experimental system used, we first examined activation of gastric vagal afferent by 5-HT or copper sulfate. Intravenous administration of 5-HT (3 – 30 μg/kg) evoked a dose-dependent, short-lasting transit vagal nerve discharge in anesthetized rats (data not shown). In addition, intragastric administration of copper sulfate (3 mL) increased gastric vagal afferent activity (data not shown).

As shown in Fig. 6A, intragastric administration of paroxetine (10 − 30 mg/kg) dose-dependently increased the gastric vagal afferent activity. On the other hand, intravenous administration of paroxetine (5, 10 mg/kg) did not increase gastric vagal afferent activity (Fig. 6B). Mosapride (30 mg/kg), given intragastrically at the same time as paroxetine, failed to affect paroxetine-induced increase in gastric vagal afferent activity in anesthetized rats (Fig. 6C).

Effect of mosapride on paroxetine-induced delay in gastric emptying in rats

As shown in Fig. 7, oral administration of paroxetine (10 and 30 mg/kg) delayed gastric emptying in rats. Mosapride (1 − 3 mg/kg, p.o.) dose-dependently shortened this delay.

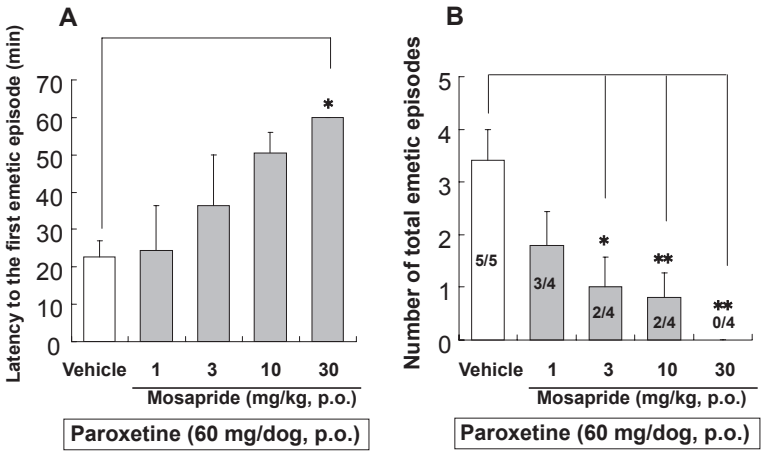

Fig. 3. Effects of mosapride on paroxetine-induced emesis in dogs. Each column of panel A represents the mean ± S.E.M. of latency to the first emetic episode (min), and each column of panel B represents the mean ± S.E.M. of the number of total emetic episodes. The number in each column of panel B represents the incidence of vomiting as the number of animals that vomited / the number of animals tested. Mosapride or vehicle was orally administered to dogs. One hour later, paroxetine was orally administered and the number of vomits was recorded for 1 h after paroxetine administration. $*P < 0.05$, $**P < 0.01$, significantly different from the vehicle control group (Dunnett's multiple comparison test).

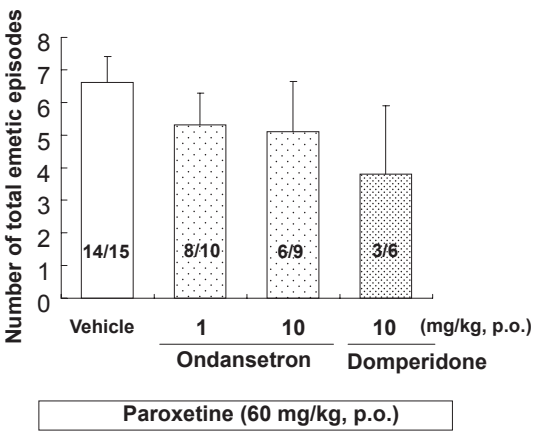

Fig. 4. Effects of ondansetron or domperidon on paroxetine-induced emesis in *Suncus murinus*. Each column represents the mean ± S.E.M. of the number of total emetic episodes. Number in each column represents the incidence of vomiting as the number of animals that vomited / the number of animals tested. Ondansetron, domperidone, or vehicle was orally administered to the animals. One hour later, paroxetine was orally administered and the number of vomits was recorded for 1 h after paroxetine administration.

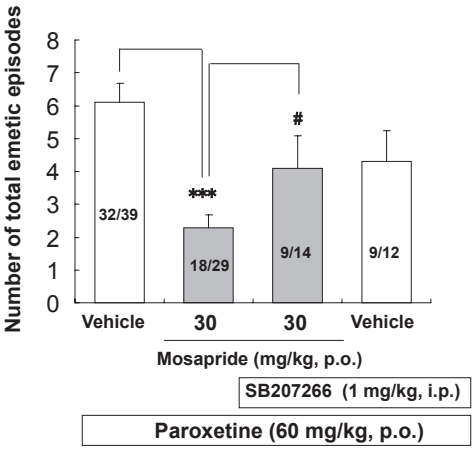

Fig. 5. Effects of SB207266, a 5-HT_4 receptor antagonist, on the anti-emetic effect of mosapride on paroxetine-induced emesis in *Suncus murinus*. Each column represents the mean ± S.E.M. of the number of total emetic episodes. Number in each column represents the incidence of vomiting as the number of animals that vomited / the number of animals tested. Mosapride or vehicle was orally administered to the animals and SB207266 simultaneously i.p. administered. One hour later, paroxetine was orally administered and the number of vomits was recorded for 1 h after paroxetine administration. $***P < 0.001$, significantly different from the vehicle control group (Student's *t*-test); $^{\#}P < 0.05$, significantly different from the mosapride-treatment group (Student's *t*-test).

Discussion

This study is the first to investigate the effect of mosapride, a 5-HT_4 receptor agonist, on SSRIs-induced emesis in experimental animals. Our findings reveal that oral administration of mosapride inhibits paroxetine, fluvoxamine, or sertraline-induced emesis in *Suncus murinus* and dogs. Previous studies have shown that mosapride, a gastroprokinetic agent, increases gastric emptying in rats and human and enhances motility in the upper GI tract in dogs (6, 7, 16). Taken together, these findings indicate that mosapride has, in addition to its beneficial gastroprokinetic effect on functional dyspepsia, a promising potential as an anti-emetic agent for SSRI treatment.

Suncus murinus (a house musk shrew) is a new animal model for research on emesis (17). Indeed, *Suncus murinus* positively responds to various emetic stimuli including motion, X-radiation, and emetogenic substances such as nicotine, copper salt, and cisplatin (18, 19). In our experiments, oral administration of a SSRI (paroxetine, fluboxamine, or sertraline) increased the incidence of vomiting in animals, shortened the latency to the first emetic episode, and increased total emetic episodes.

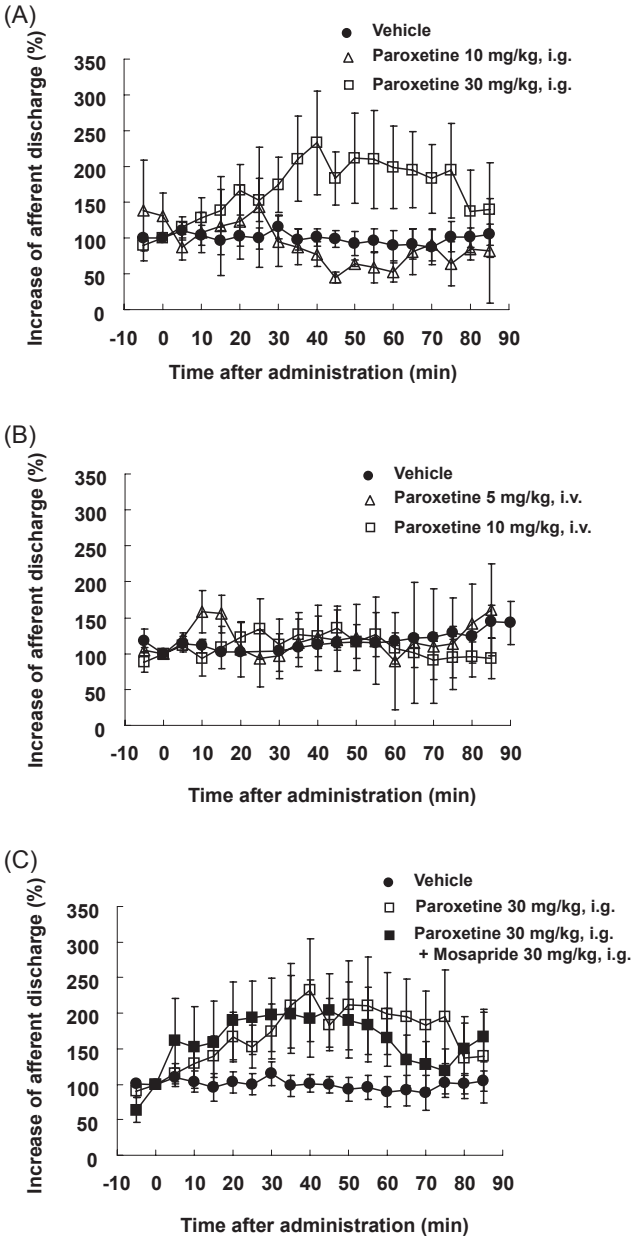

Fig. 6. Effects of paroxetine on gastric afferent discharge in anesthetized rats. Each point represents the mean ± S.E.M. of increase of afferent discharge (%) before administration of each drug (n = 5 − 6). A: Effects of intragastric administration of paroxetine (10 and 30 mg/kg) on afferent discharge. B: Effects of intravenous administration of paroxetine (5 and 10 mg/kg) on afferent discharge. C: Effect of mosapride (30 mg/kg) on paroxetine (30 mg/kg, i.g.)-induced activated gastric vagal afferent. Mosapride (30 mg/kg) was intragastrically administered simultaneously with intragastric administration of paroxetine (30 mg/kg).

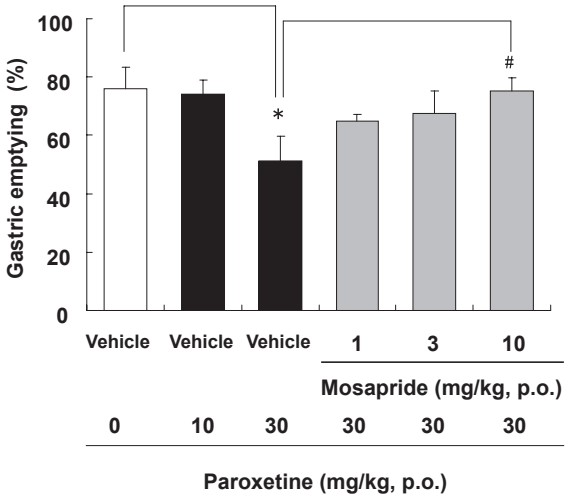

Fig. 7. Effect of oral administration of mosapride on paroxetine-induced gastric emptying in rats. Each column represents the mean ± S.E.M. of gastric emptying (%). Parovetine (10 or 20 mg/kg) or the combination of paroxetine (30 mg/kg) and vehicle or mosapride (1, 3, or 30 mg/kg) was orally administered before the test meal was given by a gastric tube in rats. Ninety minutes after administration of the test meal, the stomach was removed and gastric emptying was measured. $^{*}P < 0.05$, significantly different from the vehicle control group (Dunnett's multiple comparison test). $^{\#}P < 0.05$, significantly different from the paroxetine (30 mg/kg)-treatment group (Dunnett's multiple comparison test).

These findings are consistent with those of previous reports, indicating that *Suncus murinus* is a useful animal model when investigating SSRI-induced emesis (20, 21).

It has been reported that oral administration of fluvoxamin or fluxetine, but not their intraperitoneal administration, induces emesis in *Suncus murinus* (20). Therefore, we investigated in this study SSRI-inducing emesis using various routes of administration. Our results show that oral administration of paroxetine and other SSRIs induces emesis in *Suncus murinus* and dogs, but subcutaneous administration of paroxetine did not produce emesis in either type of animal (Tables 1 − 3). These findings are consistent with those of previous reports, indicating that only oral administration of SSRIs induces emesis in experimental animals (20). From these findings, it is possible that SSRIs induce vomiting by activation of the gastric afferent vagus nerve, but not via a systemic action.

It is known that the afferent vagal nerve plays an important role in emesis induced by peripherally acting stimuli such as copper sulfate and cytotoxic drugs. For example, vagal afferent discharge has been shown to be activated by cisplatine or copper sulfate in rats and ferrets (11, 12). Therefore, in this study, we conducted electrophysiological recording to assess the effect of a SSRI on the vagal afferent nerve as well as the effect of mosapride on SSRI-induced afferent nerve discharge in anesthetized rats. This provided insight into the possible mechanism

underlying emesis induced by SSRIs as well as the anti-emetic mechanism of mosapride. Our results showed that paroxetine, given intragastrically but not intravenously, increases vagal afferent discharge (Fig. 6). These findings are consistent with those of other studies, where only oral administration of a SSRI, not its systemic administration, caused emesis (20).

Torii et al (1991) reported that peripheral treatment with serotonin by itself via intraperitoneal, intravenous and subcutaneous routes elicits vomiting in *Suncus murinus*, probably through stimulation of peripheral 5-HT_3 receptors (22). We have also shown that systemic administration of 5-HT evokes a transient vagal afferent nerve discharge (data not shown). Moreover, it has been reported that 5-HT induced vagal afferent discharge is blocked by 5-HT_3 receptor antagonists (14, 22). On the other hand, our results show that only oral administration of paroxetine induces emesis that is slightly, but not significantly, inhibited by ondansetron, a 5-HT_3 receptor antagonist, or domperidone, a dopamine D_2–receptor antagonist (Fig. 4). Moreover, our results show that only oral administration of paroxetine increases gastric vagal afferent discharge (Fig. 6). From these findings, it is believed that the mechanism of SSRI-induced emesis and vagal afferent discharge is different from that of 5-HT. It has been indicated that another mechanism, different from that involving 5-HT_3 receptor, may be at least in part involved in emesis and activation of vagal afferent discharge induced by oral administration of SSRIs.

In our experiments, the anti-emetic effect of mosapride was partially inhibited by SB207266 at the dose of 1 mg/kg, i.p., which is potent enough to antagonize the 5-HT_4 receptors (23). From these findings, it is assumed that the anti-emetic effect of mosapride on SSRI-induced emesis involves, at least in part, activation of the 5-HT_4 receptor. However, it has been reported that zacopride, a 5-HT_3 antagonist and 5-HT_4 agonist, produces emesis in the ferret (24). Therefore, involvement of the 5-HT_4 receptor in the antiemetic effect of mosapride is unclear, and further studies are needed to elucidate the involvement of 5-HT_4 receptors in emesis.

As mosapride failed to affect paroxetine-induced increase in gastric vagal afferent discharge, it is believed that the anti-emetic effect of mosapride is not mediated by vagal afferent discharge. From these results, it is suggested that SSRI-induced emesis is mediated not only by increase of vagal afferent discharge but also by one or more other mechanisms.

Although the mechanism of the antiemetic effect of mosapride has not yet been clearly elucidated, it may be postulated that the gastroprokinetic effect of mosapride is involved in its antiemetic effect. It has been demonstrated that delayed gastric emptying frequently causes nausea and vomiting (13). In addition, it is reported that emetogenic agents, such as cisplatin, apomorphine, and copper sulfate, prevent GI motility and gastric emptying in experimental animals and humans (25, 26). In fact, it is reported that SSRIs inhibit GI motor activity through 5-HT_{2C} receptors (27). Our results also show that paroxetine delays gastric emptying in rats (Fig. 7). These findings indicate that delayed gastric emptying may play an important role in SSRI-induced emesis. In addition, we found that mosapride improves the delay in gastric emptying induced by paroxetine in rats. From these results, one possible explanation is that mosapride reduces SSRIs-induced emesis by enhancing delayed gastric motility, regardless of activation of gastric afferent nerve.

In conclusion, we have shown in this study that mosapride reduces SSRI-induced vomiting in *Suncus murinus* and dogs and that this reduction may partially involve 5-HT_4 receptors. Although the mechanism of the anti-emetic effect of mosapride has not yet been clearly elucidated, it may involve enhancement of delayed gastric motility. It is noteworthy that the anti-emetic dose of mosapride in this study relate well with its clinical dose, effective anti-emetic dose in a non-clinical study, and effective dose for functional dyspepsia (10, 28). These findings indicate that mosapride is a promising anti-emetic agent for SSRI treatment.

References

1 Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 2000;85:11–28.

2 Ortiz J, Artigas F. Effects of monoamine uptake inhibitors on extracellular and platelet 5-hydroxytryptamine in rat blood: different effects of clomipramine and fluoxetine. Br J Pharmacol. 1992;105:941–946.

3 McManis PG, Talley NJ. Nausea and vomiting associated with selective serotonin reuptake inhibitors; incidence, mechanisms and management. CNS Drugs. 1977;8:394–401.

4 Bailey JE, Potokar J, Coupland N, Nutt DJ. The 5-HT_3 antagonist ondansetron reduces gastrointestinal side effects induced by a specific serotonin re-uptake inhibitor in man. J Psychopharmacol. 1995;9:137–141.

5 Bergeron R, Blier P. Cisapride for the treatment of nausea produced by selective serotonin reuptake inhibitors. Am J Psychiatry. 1994;151:1084–1086.

6 Yoshida N, Ito T, Karasawa T, Itoh Z. AS-4370, a new gastrokinetic agent, enhances upper gastrointestinal motor activity in conscious dogs. J Pharmacol Exp Ther. 1991;257:781–787.

7 Yoshida N, Kato S, Ito T. Mosapride citrate. Drugs Future. 1993; 18:513–515.

8 Hongo M. Initial approach and pharmacotherapy for functional dyspepsia – a large clinical trial in Japan (abstr). Gastroenterology. 2006;130:A-506.

9 Mizuta Y, Shikuwa S, Isomoto H, Mishima R, Akazawa Y, Masuda J, et al. Recent insights into digestive motility in func-

tional dyspepsia. J Gastroenterol. 2006;41:1025–1040.
10 Okada T. Effectiveness of mosapride citrate to gastrointestinal side effects of fluvoxamine. Jpn J Psychiatric Treatment. 2001; 16:401–404. (text in Japanese)
11 Lanq IM. Noxious stimulation of emesis. Dig Dis Sci. 1994; 44(8 Suppl):58S–63S.
12 Carpenter DO. Neural mechanisms of emesis. Can J Physiol Pharmacol. 1990;68:230–236.
13 Cherian D, Parkman HP. Nausea and vomiting in diabetic and idiopathic gastroparesis. Neurogastroenterol Motil. 2012;24: 217–223.
14 Uneyama H, Niijima A, Tanaka T, Torii K. Receptor subtype specific activation of the rat gastric vagal afferent fibers to serotonin. Life Sci. 2002;72:415–423.
15 Droppleman DA, Gregory RL, Alphin RS. A simplified method for assessing drug effects on gastric emptying in rats. J Pharmacol Methods. 1980;4:227–230.
16 Mine Y, Yoshikawa T, Oku S, Nagai R, Yoshida N, Hosoki K. Comparison of effect of mosapride citrate and existing 5-HT_4 receptor agonists on gastrointestinal motility in vivo and in vitro. J Pharmacol Exp Ther. 1997;283:1000–1008.
17 Ueno S, Matsuki N, Saito H. Suncus murinus: a new experimental model in emesis reseach. Life Sci. 1987;41:513–518.
18 Matsuki N, Torii Y, Ueno S, Saito H. Suncus murinus as an experimental animal model for emesis and motion sickness. In: Bianchi AL, Grelot L, Miller AD, King GL, editors. Mechanisms and control of emesis. Montrouge: John Libbey Eurotext Ltd, 1992. p. 323–329.
19 Okada F, Saito H, Matsuki N. Blockade of motion- and cisplatine-induced emesis by a 5-HT_2 receptor agonist in Suncus murinus. Br J Pharmacol. 1995;114:931–934.
20 Fujiwara M, Yamashita N, Hayashi A, Imanishi T, Ichimaru Y, Baba J. Emetic reaction induced by a selective serotonin reuptake inhibitor, fluboxamine, in Suncus murinus. Pharmacometrics. 2000;59:39–46. (text in Japanese with English abstract)
21 Fujiwara-Sawada M, Imanishi T, Yoshida A, Baba J. Possible involvement of peripheral serotonin 5-HT_3 receptors in fluvoxamine-induced emesis in Suncus murinus. J Pharm Pharmacol. 2003;55:271–274.
22 Torii Y, Saito H, Matsuki N. 5-Hydroxytryptamine is emetogenic in the house musk shrew, *Suncus murinus*. Naunyn Schmiedebergs Arch. Pharmacol. 1991;344:564–567.
23 Gaster LM. SB-207266. Drug Future. 1997;22:1325–1332.
24 Bhandari P, Andrews PLR. Preliminary evidence for the involvement of the putative 5HT-4 receptor in zacopride and copper sulfate-induced vomiting in the ferret. Eur J Pharmacol. 1991; 204:273–280.
25 King GL. Animal models in the study of vomiting. Can J Physiol Pharmacol. 1990;68:260–268.
26 Lang IM, Marvig J. Functional localization of specific receptors mediating gastrointestinal motor correlates of vomiting. Am J Physiol. 1989;256:G92–G99.
27 Fujitsuka N, Asakawa A, Hayashi M, Sameshima M, Amitani H, Kojima S, et al. Selective serotonin reuptake inhibitors modify physiological gastrointestinal motor activities via 5-HT2c receptor and acyl ghrelin. Biol Psychiatry. 2009;65:748–759.
28 Curran MP, Robinson DM. Mosapride in gastrointestinal disorders. Drugs. 2008;68:981–991.