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Communication

Possible involvement of peripheral serotonin 5-HT$_3$ receptors in fluvoxamine-induced emesis in *Suncus murinus*

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Abstract

Selective serotonin reuptake inhibitors fluvoxamine and fluoxetine, as well as serotonin (5-HT), induced vomiting in *Suncus murinus* (a house musk shrew). Fluvoxamine- and fluoxetine-induced vomiting gradually decreased with their repeated administration. Vomiting induced by serotonin also decreased with repeated treatment with serotonin. In these shrews, fluvoxamine-induced vomiting was partially inhibited. Fluvoxamine might induce vomiting, at least partially, by indirectly activating peripheral 5-HT$_3$ receptors, since serotonin has been reported to induce vomiting by activating peripheral 5-HT$_3$ receptors and granisetron, a 5-HT$_3$ antagonist, partially suppressed fluvoxamine-induced vomiting in our previous finding. In addition, fluvoxamine-induced vomiting was impaired more effectively using a step-wise dose-up schedule of fluvoxamine than a fixed high-dose schedule. Therefore, a careful dosing strategy starting with a low dose might be effective for avoiding emesis associated with the clinical use of fluvoxamine.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat depression owing to the lack of serious side effects, such as dry mouth and cardiotoxicity, which are often observed with tricyclic antidepressants (Hiemke & Hartter 2000). SSRIs are also effective in specific anxiety disorders other than depression, such as obsessive–compulsive disorder and panic disorder (Nutt et al 1999). While SSRIs have been found to be quite effective, their clinical application is occasionally associated with nausea and emesis and these adverse effects limit their use (McManis & Talley 1997).

Suncus murinus (a house musk shrew), used in this study, is a species of insectivore and was described as a new animal model for research on emesis (Ueno et al 1987). Indeed, *Suncus murinus* has a capability of vomiting in response to various emetic stimuli including motion, X-radiation and emetogenic substances such as nicotine, copper salt and cisplatin (Matsuki et al 1992; Okada et al 1995). Recently, we reported that the oral administration of two SSRIs, fluvoxamine and fluoxetine, induced vomiting in *Suncus murinus* (Fujiwara et al 2000). Although the vomiting induced by fluvoxamine was not effectively suppressed by available antiemetics, tolerance against vomiting developed in almost 50% of the shrews after the repeated administration at a fixed dose of fluvoxamine (Fujiwara et al 2000). Whereas the mechanism of vomiting induced by SSRIs including fluvoxamine remains unclear, it was reported that serotonin (5-HT) induced vomiting by activating peripheral 5-HT$_3$ receptors (Torii et al 1991) and serotonin-induced vomiting also produced tolerance (Selve et al 1994). Therefore, as the first aim of this study, we examined whether fluvoxamine produced vomiting in the shrews that had developed tolerance to serotonin-induced vomiting to evaluate the possible involvement of peripheral 5-HT$_3$ receptors in fluvoxamine-induced vomiting. In another experiment, we examined the vomiting induced by a step-wise dose-up schedule of fluvoxamine and compared the results with those using a fixed high-dose schedule, to identify more effective dosing strategy to avoid vomiting.

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Materials and Methods

Animals

Suncus murinus of both sexes were purchased from Clea Japan (Tokyo) when they were 5 weeks old. Our previous result did not show any sex differences in emetic response to fluvoxamine. A maximum of 10 shrews per group were housed in a cage measuring $28 \times 43.5 \times 18$ cm for at least 7 days in a room that was maintained at 23–27 °C and 50–70% humidity, with lighting from 0700 to 1900 h. They had free access to water and food (CIEA305, Clea Japan) throughout the experiment. All studies were performed according to the guidelines of the Animal Care and Use Committee of Pharmaceutical Research Center, Meiji Seika Kaisha Ltd and the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society.

Drugs

Fluvoxamine (maleate; Meiji Seika, Tokyo, Japan), fluoxetine (hydrochloride; synthesized by Erregierre SpA, Italy) and serotonin (hydrochloride; Sigma, St Louis, MO) were used. Fluvoxamine and fluoxetine were dissolved in distilled water and administered orally. Serotonin was dissolved in saline and treated intraperitoneally.

Experimental procedures

To assess vomiting behaviour, the shrews were transferred to individual cages measuring $17 \times 24.5 \times 12.5$ cm. At the start of the first experiment, fluvoxamine $90\,mg\,kg^{-1}$ was administered orally as a pre-test. This dose was selected because it caused almost maximal and stable vomiting in *Suncus murinus* (43 of 45 animals, >95%) upon intermittent administration if the interval between administrations was at least 1 week (Fujiwara et al 2000). Seven days after the pre-test with fluvoxamine, daily treatment with $10\,mg\,kg^{-1}$ serotonin was continued for 6 consecutive days. On the day after the last treatment with serotonin, $90\,mg\,kg^{-1}$ fluvoxamine was administered again. Since the vomiting episodes elicited by $90\,mg\,kg^{-1}$ fluvoxamine or $10\,mg\,kg^{-1}$ serotonin were completed within 40 min after administration (Fujiwara et al 2000), vomiting was observed each day for 1 h after administration. In another experiment, fluvoxamine was administered at a fixed dose of $90\,mg\,kg^{-1}$ or in step-wise doses from 10 to $90\,mg\,kg^{-1}$ once a day for 5 consecutive days. The vomiting episodes were also observed each day for 1 h after administration.

Statistical analysis

The results are presented as the incidence of vomiting in which both the numbers of shrews that vomited and were tested are shown. Statistical analysis was performed by Fisher's exact test.

Results

Table 1 shows the incidence of vomiting induced by either fluvoxamine or repeated treatment with serotonin. Before the start of repeated treatment with serotonin, we confirmed that $90\,mg\,kg^{-1}$ fluvoxamine induced vomiting in all the shrews. The first treatment with $10\,mg\,kg^{-1}$ serotonin also induced vomiting in all the shrews, whereas the incidence of vomiting gradually decreased use-dependently to only 30% by the sixth treatment (the decrease in vomiting was significant, compared with the first treatment of serotonin, from the fourth treatment). Fluvoxamine, administered on the day after the last injection of serotonin, induced vomiting in 11 of 15 shrews. This frequency tended to be lower than that in the pre-test.

The results with the repeated administration of fluvoxamine using the fixed-dose and step-wise dose-up schedules are compared in Table 2. With the fixed-dose schedule, $90\,mg\,kg^{-1}$ fluvoxamine induced vomiting in 15 of 16 shrews on the first day. This frequency decreased with repeated administration and reached a steady, and significantly lower, level of approximately 50% (7 or 8 of 16) by the third administration. Similarly, $60\,mg\,kg^{-1}$ fluoxetine induced vomiting in *Suncus murinus* and the incidence of vomiting induced by fluoxetine also decreased with repeated administration (data not shown). On the other hand, with the step-wise dose-up schedule, fluvoxamine administered at 10 to $60\,mg\,kg^{-1}$ on the first to fourth days induced vomiting in none or only a few of the shrews. When fluvoxamine was administered at a final dose of $90\,mg\,kg^{-1}$, only 4 of 15 shrews vomited. This frequency was significantly lower than that with the first administration using the fixed-dose schedule. In addition, 7 of 15 shrews never vomited throughout this step-wise dose-up period, and this incidence was significantly lower than that in the fixed-dose schedule, under which all of shrews vomited.

Table 1 Vomiting induced by either fluvoxamine or serotonin in *Suncus murinus*.

Day	Fluvoxamine ($mg\,kg^{-1}$, p.o.)	Serotonin ($mg\,kg^{-1}$, i.p.)	Incidence of vomiting
−6 (pre)	90	—	15/15
1	—	10	15/15
2	—	10	12/15
3	—	10	12/15
4	—	10	10/15*
5	—	10	6/15**
6	—	10	5/15**
7	90	—	11/15†

The incidence of vomiting on each day is shown as the number of shrews that vomited/the number of shrews tested. *$P < 0.05$, **$P < 0.001$ vs the first treatment of serotonin (day 1) and †$P < 0.10$ vs pre-test with fluvoxamine, analysed by Fisher's exact test.

Table 2 Vomiting induced by repeated administration of fluvoxamine with fixed-dose and step-wise dose-up schedules in *Suncus murinus*.

Day	Fixed dose		Step-wise dose-up	
	Dose (mg kg^{-1}, p.o.)	Incidence of vomiting	Dose (mg kg^{-1}, p.o.)	Incidence of vomiting
1	90	15/16	10	2/15
2	90	12/16	20	0/15
3	90	8/16*	30	0/15
4	90	7/16**	60	3/15
5	90	8/16*	90	4/15***
1–5	—	16/16	—	8/15†

The incidence of vomiting on each day is shown as the number of shrews that vomited/the number of shrews tested. The values of the lowest line indicate the number of shrews that vomited at least once throughout the experiment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs the first administration of the fixed-dose schedule and †$P < 0.01$ vs corresponding value of the fixed-dose schedule, analysed by Fisher's exact test.

Discussion

Clinical studies have reported that the nausea or emesis induced by SSRIs generally decreases with prolonged treatment (Bergeron & Blier 1994). Our finding, that *Suncus murinus* developed tolerance to fluvoxamine- and fluoxetine-induced vomiting, is similar to the findings in these clinical studies. Although the mechanism of emesis induced by SSRIs remains unclear, research on tolerance against vomiting might give some insight into not only the mechanism of SSRI-induced vomiting but also a better treatment regimen with SSRIs.

The first finding in this study was that fluvoxamine-induced vomiting was partially inhibited in the shrews that had developed tolerance to serotonin. Torii et al (1991) reported that peripheral treatment with serotonin by itself via intraperitoneal, intravenous and subcutaneous routes elicited vomiting in *Suncus murinus*, probably through the stimulation of peripheral 5-HT$_3$ receptors, since serotonin does not penetrate the blood–brain barrier and a 5-HT$_3$ receptor agonist induced vomiting whereas a 5-HT$_3$ receptor antagonist inhibited serotonin-induced vomiting. Although SSRIs exert their beneficial effects in depression and anxiety disorders by elevating brain serotonin levels (Bel & Artigas 1992), it is reported that SSRIs including fluvoxamine and fluoxetine also increase plasma serotonin level (Ortiz & Artigas 1992). Fluvoxamine might therefore induce vomiting by elevating peripheral serotonin, resulting in the activation of 5-HT$_3$ receptors. Our findings support this hypothesis. Firstly, our previous study indicated that oral administration of granisetron, a 5-HT$_3$ receptor antagonist, slightly but dose-dependently decreased the incidence of fluvoxamine-induced vomiting by 30% up to 10 mg kg^{-1} in *Suncus murinus* (Fujiwara et al 2000). In addition, another 5-HT$_3$ receptor antagonist, ondansetron, prevented fluvoxamine-induced nausea in man (Bailey et al 1995). Furthermore, litoxetine, an SSRI with 5-HT$_3$ receptor-antagonist activity, did not elicit nausea or vomiting in man or ferrets (Angel et al 1993). In fact, 5-HT$_3$ receptor antagonists are clinically used to treat emesis induced by cancer chemotherapeutic agents such as cisplatin (Roila et al 1997). Furthermore, *Suncus murinus* have been reported to develop tolerance to the emesis induced by serotonin if the treatment interval is shorter than 7 days (Selve et al 1994). The tolerance to serotonin-induced vomiting was also observed in this study. The result obtained in this study, that fluvoxamine-induced vomiting was partially inhibited in shrews that showed tolerance to serotonin, further supports the involvement of peripheral 5-HT$_3$ receptors in fluvoxamine-induced vomiting. However, the decrease in incidence of fluvoxamine-induced vomiting with granisetron and repeated treatment with serotonin was only partial. Consequently, we cannot exclude the possibility that fluvoxamine may induce emesis through some other mechanism(s). For example, cisplatin was reported to induce emesis by inducing the release of serotonin not only in the gastrointestinal tract but also in the brain (Endo et al 2000).

Another finding in this study was that the step-wise dose-up schedule with fluvoxamine dramatically lowered the incidence of vomiting compared with the fixed-dose schedule. The finding that low doses of fluvoxamine hardly induce vomiting is consistent with the clinical finding that the nausea induced by another SSRI, paroxetine, is dose-related (Robbe & O'Hanlon 1995). Furthermore, almost half of the shrews under the step-wise dose-up schedule never vomited and the others showed only a low incidence of vomiting. It is unclear why the step-wise dose-up schedule was more effective in suppressing vomiting than the fixed dose. However, vomiting induced by orally treated substances results in an excretion of the substance. Therefore, one possible explanation is that the blood concentration of fluvoxamine might not reach a level high enough to develop tolerance to vomiting in the fixed-dose schedule, due to the high incidence of vomiting. These results suggest that a careful dosing strategy, starting with a low dose, may be effective for avoiding the nausea and emesis associated with the clinical use of fluvoxamine. This may also be applicable to other SSRIs.

In conclusion, we examined fluvoxamine-induced vomiting in *Suncus murinus*. Fluvoxamine-induced vomiting was partially inhibited in the shrews that had developed tolerance to serotonin. In addition, the step-wise dose-up schedule with fluvoxamine dramatically lowered the incidence of vomiting compared with the fixed-dose schedule. These results suggest that fluvoxamine might induce vomiting, at least partially, by activating peripheral 5-HT_3 receptors and that a careful dosing strategy starting with a low dose might be effective for avoiding emesis associated with the clinical use of fluvoxamine.

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