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Male/Female Differences in Drug-induced Emesis and Motion Sickness in *Suncus murinus*

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Emesis Motion sickness Male/female difference Cisplatin Veratrine Tropisetron Copper sulfate Nicotine Serotonin

EMESIS is a defensive reflex to expel ingested toxic substances from the stomach, but not all mammals have this capability, and the presence of species-dependent differences is well known (5,12). Non-human primates and the carnivores, such as dogs, cats and ferrets, have been used as experimental animal models for emesis (12). We have shown that *Suncus murinus*, a species of insectivore, has a capability of vomiting in response to various emetic stimuli including motion (10,11, 16,22-26). The animal is small in size and a useful experimental model for emesis and motion sickness.

Clinical studies have shown a higher incidence of nausea and vomiting in female patients during cancer chemotherapy (4,17,21) and post-anesthesia (15). Women suffer more frequently than men from post-operative nausea and vomiting, and the severity of vomiting is also higher in women (7). It has been postulated that hormonal factors relating to the menstrual cycle may exaggerate nausea and vomiting, but there is no substantive evidence for this theory. A sex-dependent difference in emesis and motion sickness in animals has not been formally investigated. In humans psychological factors may be

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very important for the initiation of nausea and vomiting (3), and hence the effects of an emetic challenge may not directly correlate with a sex difference in the sensitivity of the emetic system itself.

In the present study, emetic responses to various stimuli were compared between male and female adult *Suncus murinus*.

MATERIALS AND METHODS

Healthy adult *Suncus murinus* (4–7 month-old, 50–80 g (male) and 30–50 g (female) body weight) were used throughout the experiments. The animals were housed in a temperature controlled room at 24 ± 1°C, lighted between 0800 and 2000. They were allowed free access to pellet chow and tap water. The detailed protocols used for the observation of emetic responses and motion sickness were reported previously (10,22,25). These animals had never received any drug or experimental motion stimulus before, and to avoid possible involvement of the residual effect, each animal underwent only one experiment.

Emetogenic drugs used were cisplatin (IP, cis-platinum-(II)diamine dichlorides, Sigma), nicotine tartrate (SC, Wako), veratrine (SC, Sigma), serotonin creatinine sulfate (IP, Sigma) and copper sulfate (PO, Wako). The antiemetic effect of tropisetron, a selective 5-HT_3 receptor antagonist, (SC, ICS 205-930, Sandoz) against cisplatin- and serotonin-induced emesis was also compared. Tropisetron was injected 30 min prior to the administration of 20 mg/kg cisplatin (IP) or 10 mg/kg serotonin (IP). The dose was changed with the fixed ratio of two to estimate ED_{50} or ID_{50} values from small numbers of samples (Brownlee's up-and-down method, 6). At least 10 animals were used to determine each value. Student's *t*-test, χ^2-test and Fisher's exact probability test were used to test statistical significance.

Since female *Suncus murinus* do not have an apparent ovarian cycle and are induced ovulators, it was not necessary to ensure that animals were tested at the same stage of the ovarian cycle.

Cisplatin was dissolved in warmed (about 50°C) saline whose pH was adjusted to 4.0 using 0.1N HCl. The solution

TABLE 1

COMPARISON OF DRUG-INDUCED EMESIS BETWEEN MALE AND FEMALE *SUNCUS*

	Dose (mg/kg)	No. of *Suncus* Vomiting/Tested	No. of Vomiting Episodes	Latency (min)	ED_{50} (mg/kg)
Cisplatin (IP)					
Male	40	4/4	16.3 ± 2.7	38.2 ± 8.6	12.6
	20	3/4	11.0 ± 2.0	53.7 ± 14.7	
	10	2/5	(6, 9)	(40, 62)	
	5	0/4	—	—	
Female	40	4/4	13.2 ± 3.7	44.3 ± 11.3	13.1
	20	4/5	9.0 ± 1.5	40.0 ± 2.0	
	10	2/6	(5, 10)	(47, 64)	
	5	0/4	—	—	
Veratrine (SC)					
Male	0.5	4/4	15.3 ± 7.7	7.0 ± 1.6*	0.31
	0.25	1/5	(16)	(8)	
Female	0.5	5/5	3.4 ± 1.7	15.6 ± 2.4	0.35
	0.25	0/5	—	—	
Nicotine (SC)					
Male	2.5	5/5	9.4 ± 3.9	4.4 ± 1.0	1.77
	1.25	0/5	—	—	
Female	5.0	4/4	15.8 ± 7.0	4.7 ± 1.5	2.03
	2.5	4/5	12.0 ± 2.5	6.8 ± 0.8	
	1.25	0/4	—	—	
Copper Sulfate (PO)					
Male	80	4/4	8.3 ± 2.5	9.8 ± 1.7	32.5
	40	4/5	5.5 ± 2.3	9.0 ± 1.9	
	20	0/4	—	—	
Female	80	4/4	5.2 ± 1.8	8.8 ± 2.9	32.5
	40	4/5	7.5 ± 1.4	9.0 ± 5.5	
	20	0/4	—	—	
Serotonin (IP)					
Male	5.0	4/4	7.2 ± 2.3	0.5 ± 0.1	2.7
	2.5	2/5	(7, 4)	(0.2, 0.3)	
	1.25	0/4	—	—	
Female	10	4/4	6.4 ± 1.8	0.4 ± 0.1	4.7
	5.0	3/5	5.7 ± 1.7	0.8 ± 0.4	
	2.5	0/4	—	—	

Values for the number of vomiting episodes and the latency are means ± SEM, but actual values are indicated in the parentheses if the number of vomiting animals was less than three.

*$p < 0.05$, significantly different from the corresponding female value by Student's *t*-test.

TABLE 2

COMPARISON OF INHIBITORY EFFECTS OF TROPISETRON ON CISPLATIN- AND SEROTONIN-INDUCED EMESIS BETWEEN MALE AND FEMALE *SUNCUS*

	Dose (μg/kg)	No. of *Suncus* Vomiting/Tested	No. of Vomiting Episodes	Latency (min)	ED_{50} (μg/kg)
Cisplatin (20 mg/kg, IP)					
Male	25	0/3	—	—	5.8
	12.5	0/5*	—	—	
	6.25	2/5	(5, 13)	(58, 41)	
	3.13	3/3	5.7 ± 2.1	56.3 ± 11.0	
Female	50	0/3	—	—	21
	25	2/4	(3, 6)	(71, 73)	
	12.5	3/4	5.3 ± 3.4	72.3 ± 12.2	
	6.25	2/2	(2, 14)	(48, 59)	
Serotonin (10 mg/kg, SC)					
Male	10	0/3	—	—	4.7
	5	2/5	(8, 8)	(1, 2)	
	2.5	2/2	(4, 23)	(3, 1)	
Female	10	0/3	—	—	4.7
	5	2/5	(21, 10)	(1, 2)	
	2.5	3/3	9.7 ± 4.8	2.3 ± 1.3	

Values for the number of vomiting episodes and the latency are means ± SEM, but actual values are indicated in the parentheses if the number of vomiting animals was less than three. Tropisetron was injected 30 min prior to the administration of cisplatin or serotonin.

*$p < 0.05$, significantly different from female by Fisher's exact probability test.

was cooled to 37°C just before the administration. All other drugs were dissolved in saline alone. Except for copper sulfate, the doses of drugs were expressed as the weight of base. The concentration of drug solution, except for cisplatin, was adjusted so that the injection volume would be 0.1 ml/50 g body weight. In the case of cisplatin the injection volume was 0.5 ml/50 g body weight.

RESULTS

Cisplatin caused dose-dependent emesis in both sexes (Table 1). The calculated ED_{50} value was 13 mg/kg for both male and female *Suncus*. At a dose of 20 mg/kg, the number of vomiting episodes and latency between male and female were similar. Therefore, there was no apparent sex-dependent difference in cisplatin-induced emesis. Similar results were obtained when nicotine and copper sulfate were used as emetic stimuli. The ED_{50} values were virtually the same between the two sexes, as were the numbers of vomiting episodes when animals were tested at the ED_{100}.

Although ED_{50} values for veratrine were almost identical between male and female animals, the latency in male *Suncus* was significantly shorter than that in female *Suncus* at a dose of 0.5 mg/kg. The number of vomiting episodes was higher in males but this was not statistically significant. Serotonin also caused dose-dependent emesis in both sexes, but the estimated ED_{50} value in males was smaller than in females.

Tropisetron blocked both cisplatin- and serotonin-induced emesis dose-dependently (Table 2). There was no apparent difference in sensitivity between male and female animals when 10 mg/kg serotonin was used as an emetic stimulus. However, the ID_{50} value for tropiseton against cisplatin in males (5.8 μg/kg) was about one fourth of the ID_{50} in females (21 μg/kg). Tropisetron at a higher dose of 12.5 μg/kg was also more effective against cisplatin in males.

Reciprocal shaking (horizontal oscillation 40 mm and duration 5 min) at various frequencies was applied to the animals to evaluate the emetogenic effects of experimental motion stimuli. As shown in Table 3, only one male *Suncus* vomited at 0.5 Hz and no females vomited at this frequency. When the frequency was increased to 1 Hz, 94% of male and 74% of female animals vomited. The number of vomiting episodes was greater in males, and the latency was significantly shorter than in females. At a frequency of 2 Hz, ratio of vomiting animals was decreased both in male and female *Suncus*. No statistically significant sex-dependent difference was observed at 2 Hz.

DISCUSSION

In the present study, there was no apparent sex-dependent difference in cisplatin-induced emesis in *Suncus murinus*. Cis-

TABLE 3

SEX-DEPENDENT DIFFERENCES IN MOTION-INDUCED EMESIS OF *SUNCUS*

	No. of *Suncus* Vomiting/Tested	No. of Vomiting Episodes	Latency (s)
0.5 Hz			
Male	1/10	2	23
Female	0/10	—	—
1.0 Hz			
Male	60/64†	8.0 ± 0.6*	94.2 ± 7.2*
Female	28/38	5.8 ± 0.5	148.2 ± 14.9
2.0 Hz			
Male	12/16	6.1 ± 1.8	115.4 ± 17.0
Female	9/16	4.8 ± 0.6	147.0 ± 21.5

Values are means ± SEM. Motion Stimulus: amplitude 40 mm, duration 5 min.

*$p < 0.01$ vs female, by Student's *t*-test.

†$p < 0.01$ vs female by χ^2-test.

platin is one of the potent anti-cancer drugs but also causes frequent nausea and vomiting (2). The mechanism of cisplatin-induced emesis is considered to be as follows. Cisplatin is converted to cis-diaqodiammineplatinum (II) (19) and releases serotonin from the enterochromaffin cells through the production of free radicals (24). The locally released serotonin stimulates 5-HT_3 receptors on the vagal afferents and causes emesis (1,2,16). There was also no apparent sex-related difference in nicotine or copper sulfate-induced emesis in *Suncus murinus*. Copper sulfate- but not nicotine-induced emesis was blocked by surgical vagotomy (Matsuki et al. unpublished). Therefore, these two drugs seem to cause emesis through different mechanisms but still produce the similar effects on both male and female animals. The exact mechanism for veratrine-induced emesis is still controversial (12). The numbers of vomiting animals were similar but only the latency was shorter in male animals, suggesting that the difference seems to be very small. However, male animals were clearly more sensitive to serotonin. A dose of 5.0 mg/kg was enough to induce emesis in all male animals but 10 mg/kg was necessary for female. Therefore, except for serotonin, there was no clear sex-dependent difference in responses to emetogenic drugs in *Suncus*.

Tropisetron, a selective 5-HT_3 receptor antagonist, blocked both cisplatin- and serotonin-induced emesis dose-dependently. There was no apparent sex-dependent difference in the effect of tropisetron when the same dose (10 mg/kg) of serotonin was used as an emetic stimulus. However, sex-dependent difference in the effect of tropisetron was observed against cisplatin-induced emesis. The ID_{50} value for tropisetron to block cisplatin-induced emesis in males was 5.8 μg/kg, and when tropisetron at doses higher than 12.5 μg/kg was used, no animals vomited. The ID_{50} value in females was 21 μg/kg, and doses of 50 μg/kg or higher tropisetron were necessary to block cisplatin-induced emesis completely. Therefore, tropisetron was more effective against cisplatin-induced emesis in male animals. However, it should be remembered that there was no apparent difference in the magnitude of the emetic response to cisplatin in the two sexes. Taken together, these results can be explained if cisplatin released more serotonin in female animals. Higher doses of tropisetron would therefore be necessary to block the cisplatin-induced emesis if the concentration of serotonin at the active site (vagal afferent terminals) was higher in females. Further experiments, e.g. measurement of released serotonin, levels of sex hormones, are necessary to clarify the cause of sex-dependent differences in susceptibilities to 5-HT_3 antagonists.

There is a great species-dependent difference in emetic responses (5), and the present data in *Suncus* cannot be immediately applicable to other species. However, it is important to clarify the sex-dependent difference besides the species-dependent difference. As far as the authors can determine, the sex-dependent difference in experimental animals has not been formally tested. Only a small number of papers concerning human data have been reported. Female patients suffer more frequent and more severe nausea and vomiting during cancer chemotherapy (4,17,21), post-anesthesia (15) and post-operation (7). Antiemetic drugs including 5-HT_3 receptor antagonists are generally less effective in female patients against cancer chemotherapy-induced emesis (17,20), which is in agreement with the present results. However, it is not clear whether the present results represent characteristics of male/female difference in humans. These kind of experiments should be performed in various animal species.

In the present study, male *Suncus murinus* was significantly more sensitive to experimental motion stimuli than in females. Male animals had more emetic episodes at 1 Hz. A higher frequency of 2 Hz was less effective for induction of motion sickness in both sexes, which disagrees with our previous data (26) which reported a tendency for the higher shaking frequencies to result in a greater incidence of emesis. However, we consider the present data to be more reliable because the previous study was based on a small number of animals.

A sex-dependent difference in motion sickness in humans is controversial. Initial study in humans suggested that females are more susceptible to motion sickness (see 18). Vomiting incidence was also greater in female passengers at sea (13). In airline experience, airsickness incidence in adult female passengers was approximately five times that observed in adult males (see 9). However, several investigators have shown no difference (8,9,14,27).

In conclusion, except for serotonin, there was no significant sex-dependent difference in emetic response to emetogenic drugs in *Suncus murinus*. However, the 5-HT_3 receptor antagonist, tropisetron, was less effective in preventing cisplatin-induced emesis in female animals than in males. Male animals were more susceptible to motion sickness.

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REFERENCES

1. Andrews, P. L. R.; Rapeport, W. G.; Sanger, G. J.: Neuropharmacology of emesis induced by anti-cancer therapy. Trend Pharmacol. Sci. 9:334–341; 1988.
2. Andrews, P. L. R.; Davis, C. J.: The mechanism of emesis induced by anti-cancer therapies. In: Andrews, P. L. R.; Sanger, G. J. eds. Emesis in Anti-Cancer Therapy. London: Chapman & Hall Medical; 1993:113–161.
3. Andrykowski, M. A.: Psychological aspects of nausea and vomiting. In: Bianchi, A. L.; Grelot, L.; Miller, A. D.; King, G. L., eds. Mechanisms and control of emesis. Colloque INSERM: John Libbey Eurotext Ltd.; 1992:313–322.
4. Becouarn, Y.; Nguyen, B. B.; David, M.; Lakdja, F.; Brunet, R.; Chauvergne, J.: Improved control of cisplatin-induced emesis with a combination of high doses of methylprednisolone and metoclopramide: a single-blind randomized trial. Eur. J. Cancer Clin. Oncol. 22:1421–1424; 1986.
5. Borison, H. L.; Borison, R.; McCarthy, L.: Phylogenic and neurologic aspects of the vomiting process. J. Clin. Pharmacol. 21:23S–29S; 1981.
6. Brownlee, K. A.; Hodges, J. R., Jr.; Rosenblatt, M.: The up-and-down method with small samples. J. Am. Stat. Assoc. 48:262–277: 1953.
7. Cookson, R. F.: Mechanisms and treatment of post-operative nausea and vomiting. In: Davis, C. J.; Lake-Bakaar, G. V.; Grahame-Smith, D. G. eds. Nausea and Vomiting: Mechanisms and Treatment. Berlin: Springer-Verlag; 1986:130–150.
8. Cowings, P. S.: Autogenic-feedback training: A treatment for motion and space sickness. In: Crampton, G. H. ed. Motion and Space Sickness. Boca Raton: CRC Press; 1990:353–372.
9. Guignard, J. C.; McCauley, M. E.: The accelerative stimulus for motion sickness. In: Crampton, G. H. ed. Motion and Space Sickness. Boca Raton: CRC press; 1990:123–152.
10. Kaji, T.; Saito, H.; Ueno, S.; Matsuki, N.: Comparison of various

motion stimuli on motion sickness and acquisition of adaptation in *Suncus murinus*. Experimental Animals 39:75–79; 1990.
11. Kaji, T.; Saito, H.; Ueno, S.; Yasuhara, T.; Nakajima, T.; Matsuki, N.: Role of histamine in motion sickness of *Suncus murinus*. Aviat. Space and Environ. Med. 62:1054–1058; 1991.
12. King, G. L.: Animal models in the study of vomiting. Can. J. Physiol. Pharmacol. 68:260–268; 1990.
13. Lawther, A.; Griffin, M. J.: A survey of the occurrence of motion sickness amongst passengers at sea. Aviat. Space Environ. Med. 59:399–406; 1988.
14. Levy, G. D.; Rapaport, M. H.: Transderm scopolamine efficacy related to time of application prior to the onset of motion. Aviat. Space Environ. Med. 56:591–593; 1985.
15. Mataruski, M. R.; Keis, N. A.; Smouse, D. J.; Workman, M. L.: Effects of steroids on postoperative nausea and vomiting. Nurse. Anesth. 1:183–188; 1990.
16. Matsuki, N.; Torii, Y.; Ueno, S.; Saito, H.: *Suncus murinus* as an experimental animal model for emesis and motion sickness. In: Bianchi, A. L.; Grelot, L.; Miller, A. D.; King, G. L., eds. Mechanisms and control of emesis. Colloque INSERM: John Libbey Eurotext Ltd.; 1992:323–329.
17. Mellink, W. A.; Blijham, G. H.; Van-Deyk, W. A.: Amitriptyline plus fluphenazine to prevent chemotherapy-induced emesis in cancer patients: a double-blind randomized cross-over study. Eur. J. Cancer Clin. Oncol. 20:1147–1150; 1984.
18. Money, K. E.: Motion sickness. Physiol. Rev. 50: 1–39; 1970.
19. Mutoh, M.; Imanishi, H.; Torii, Y.; Tamura, M.; Saito, H.; Matsuki, N.: Cisplatin-induced emesis in *Suncus murinus*. Japan. J. Pharmacol. 58:321–234; 1992.
20. Roila, F.; Tonato, M.; Basurto, C.; Picciafuoco, M.; Bracarda, S.; Donati, D.; Malacarne, P.; Monici, L.; DiCostanzo, F.; Patoia, L.: Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with methylprednisolone versus metoclopramide combined with dexamethasone and diphenhydramine. J. Clin. Oncol. 7:1693–1700; 1989.
21. Roila, F.; Boschetti, E.; Tonato, M.; Basurto, C.; Bracarda, S.; Picciafuoco, M.; Patoia, L.; Santi, E.; Penza, O.; Ballatori, E.; Favero, A.: Predictive factors of delayed emesis in cisplatin-treated patients and antiemetic activity and tolerability of metoclopramide or dexamethasone. Am. J. Clin. Oncol. 14:238–242; 1991.
22. Torii, Y.; Saito, H.; Matsuki, N.: Selective blockade of cytotoxic drug-induced emesis by 5-HT_3 receptor antagonists in *Suncus murinus*. Japan. J. Pharmacol. 55:107–113; 1991.
23. Torii, Y.; Saito, H.; Matsuki, N.: 5-Hydroxytryptamine is emetogenic in *Suncus murinus*. Naunyn-Schmiedeberg's Arch Pharmacol. 344:564–567; 1991.
24. Torii, Y.; Mutoh, M.; Saito, H.; Matsuki, N.: Involvement of free radicals in cisplatin-induced emesis in *Suncus murinus*. Eur. J. Pharmacol. 248:131–135; 1993.
25. Ueno, S.; Matsuki, N.; Saito, H.: *Suncus murinus*: A new experimental model in emesis research. Life Sci. 41:513–518; 1987.
26. Ueno, S.; Matsuki, N.; Saito, H.: *Suncus murinus* as a new experimental animal model for motion sickness. Life Sci. 43:413–420; 1988.
27. Yardle, L.: Motion sickness susceptibility and the utilization of visual and otolithic information for orientation. Eur. Arch. Otorhinolaryngol. 247:300–304; 1990.