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The anti-emetic activity of GK-128 in *Suncus murinus*

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Abstract

In *Suncus murinus*, various emetic responses and the anti-emetic activity of a new 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist, GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo[*f*]thiochromen-1-one monohydrochloride hemihydrate), were investigated. Cancer chemotherapeutic agents, cisplatin and cyclophosphamide, dose-dependently induced emesis of long-lasting duration. The 5-HT$_3$ receptor agonist, 2-methyl-5-HT, and copper sulfate also induced emesis of short duration. However, another 5-HT$_3$ receptor agonist, *m*-chlorophenylbiguanide, was not consistently emetic. GK-128 inhibited the emetic responses induced by chemotherapeutic agents and 2-methyl-5-HT with similar potency. The anti-emetic action of GK-128 was more potent than that of ondansetron, Y-25130, granisetron and metoclopramide. The order of potency of these drugs, except granisetron, was consistent with that of their 5-HT$_3$ receptor binding affinity in rat cortex. GK-128 failed to inhibit copper sulfate-induced emesis. These data suggest that GK-128 has a potent inhibitory effect on emesis via the 5-HT$_3$ receptor, and that the 5-HT$_3$ receptor involved in emesis in *Suncus murinus* may be different from the classically defined 5-HT$_3$ receptor in other animals such as rats, dogs and ferrets.

Keywords: 5-HT$_3$ receptor; GK-128; Emesis; (*Suncus murinus*)

1. Introduction

Nausea and vomiting are common side effects of cancer chemotherapy (Laszlo and Lucas, 1981). These serious discomforts reduce the patient's quality of life and often cause refusal of potentially curative cycles of chemotherapy (Trizzi and Laszlo, 1987). Cisplatin is one of the most effective of all chemotherapeutic agents, but is also one of the most emetogenic (Longo et al., 1982). Many researchers have focused on the control of nausea and vomitting associated with the use of highly emetogenic agents such as cisplatin.

Nearly 9 years ago it was reported that several 5-HT$_3$ receptor antagonists were very effective in preventing acute cisplatin-induced emesis in ferrets and dogs, and in reducing the nausea and vomiting in humans (Costall et al., 1986; Miner and Sanger, 1986; Haga et al., 1993; Kamato et al., 1991; King and Sanger, 1989; Leo et al., 1992). Cisplatin is known to cause damage to the small intestine and to release 5-HT from enterochromaffin cells (Schworer et al., 1991; Fukui et al., 1993). Cubeddu and co-workers (Cubeddu et al., 1992; Cubeddu and Hoffmann, 1993) reported that chemotherapeutic drugs induced acute nausea and emesis in parallel with a marked increase in serotonin release in cancer patients.

Suncus murinus (a house musk shrew) is a species of insectivore considered to be closer to primates than rodents, lagomorphs or carnivores in the phylogenetic system (Colbert, 1958). In *Suncus murinus*, Mutoh et al. (1992) reported that cisplatin-induced emesis was completely prevented by abdominal vagotomy without splanchnicectomy; a combination of atropine and hexamethonium did not block the emesis. Similar results were reported for the emesis induced by 5-HT in *Suncus murinus* (Torii et al., 1991a). These results indicate that cisplatin evokes emesis via the stimulation of vagal afferent nerves in which 5-HT$_3$ receptors exist (Kilpatrick et al., 1989), at least, in *Suncus murinus*.

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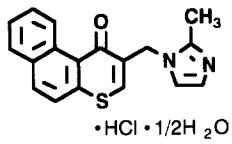

Fig. 1. Chemical structure of GK-128.

In the present study, we investigated the features of drug-induced emesis and the inhibitory effect of a new 5-HT_3 receptor antagonist, GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo[*f*]thiochromen-1-one monohydrochloride hemihydrate) (Fig. 1) on the emesis in *Suncus murinus*. GK-128, synthesized at the Taisho Research Center, is a potent and selective 5-HT_3 receptor antagonist in vitro and in vivo (Ito et al., 1993).

2. Materials and methods

2.1. Animals

Male and female *Suncus murinus* (Nihon Clea, Tokyo, Japan), weighing 50–70 g (male) and 30–50 g (female) were used. The animals were housed with free access to pellet chow, supplied by Nihon Clea (Tokyo, Japan), and water in a room kept at 22–24°C, under a 12-h light-dark cycle. The experiments were carried out at a room temperature of 22–24°C.

2.2. Emesis induced by cancer chemotherapeutic agents, 5-HT_3 receptor agonists and copper sulfate

A chronic juglar catheter was inserted for i.v. drug administration according to the method of Torii et al. (1991b) with a slight modification. The *Suncus murinus* were anaesthetized with ether, and a polyethylene catheter filled with 500 U/ml of sodium heparin was inserted into the jugular vein. The other end of the catheter was then taken out of the dorsal portion of the neck. The animals were used 3 days after the operation and the features of their emetic episodes were observed after the administration of emetogenic agents. The latency to the first emetic episode and the number of emetic episodes were recorded. On the basis of preliminary results, the observation periods after the administration of emetogenic agents were fixed as follows: 120 min for cancer chemotherapeutic agents, and 60 min for 5-HT_3 receptor agonists and copper sulfate, respectively.

2.3. Inhibitory effects on cisplatin-induced emesis

Test drugs were given 30 (i.v. and i.p.) or 45 (p.o.) min before the administration of cisplatin (30 mg/kg i.v.). In the study of the duration of anti-emetic action, test drugs were administered i.p. for 3, 4 and 6 h.

2.4. Effects of GK-128 on cyclophosphamide-, 2-methyl-5-HT- and copper sulfate-induced emesis

GK-128 was administered i.p. 30 min before the administration of cyclophosphamide (300 mg/kg i.v.), 2-methyl-5-HT (10 mg/kg i.v.), and copper sulfate (30 mg/kg p.o.).

2.5. Drugs used

GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo-[*f*]thiochromen-1-one monohydrochloride hemihy-

Table 1
Emetic responses in *suncus murinus*

Emetics [a]	Dose (mg/kg)	No. of animals emesis/tested	Latency to first emetic episodes (min) [b]	No. of emetic episodes
Cisplatin	5 i.v.	0/3	> 120	0
(120 min)	10	1/4	98.8 ± 21.3	1.0 ± 1.0
	20	4/4	20.0 ± 2.9	12.3 ± 4.4
	30	16/16	39.5 ± 6.0	13.1 ± 2.3
Cyclophosphamide	200 i.v.	2/4	64.8 ± 31.9	1.3 ± 0.8
(120 min)	300	8/8	7.5 ± 2.7	13.8 ± 2.6
	400	3/3	4.7 ± 1.5	30.3 ± 4.5
2-Methyl-5-HT	2.5 i.v.	0/3	> 60	0
(60 min)	5	1/3	40.3 ± 19.7	1.0 ± 1.0
	10	9/10	1.5 ± 1.5	4.2 ± 1.4
	30	4/4	< 1	4.3 ± 1.7
m-Chlorophenylbiguanide	5 i.v.	2/2	< 1	1.0
(60 min)	10	2/2	< 1	1.0
	10 i.p.	3/3	< 1	1.0
Copper sulfate	10 p.o.	3/4	19.0 ± 13.7	2.5 ± 1.2
(60 min)	30	11/11	4.5 ± 0.9	6.8 ± 1.3
	100	5/5	3.8 ± 0.9	12.8 ± 2.6

Values for the number of emetic episodes and the latency are means ± S.E.M. [a] Observation period in parentheses. [b] If an animal did not vomit, the latency period was taken as equal to the observation period.

drate), ondansetron (GR38032F; (±)-1,2,3,9-tetrahydro-3-[(methylimidazole-1-yl)methyl]-9-methyl-4*H*-carbazol-4-one hydrochloride), Y-25130 {(±)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-o × o-3,4-dihydro-2*H*-1, 4-benzoxazine-8-carboxamide hydrochloride}, granisetron (BRL43694; *N*-endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methyl-indazole-3-carboxamide hydrochloride) and *m*-chlorophenylbiguanide were synthesized at the Taisho Research Center (Taisho Pharmaceutical Co., Ohmiya, Saitama, Japan). Cisplatin (Sigma Chemical Co., St. Louis, MO., USA), 2-methyl-5-hydroxytryptamine and metoclopramide hydrochloride (Research Biochemicals, Natick, MA., USA), cyclophosphamide (Shionogi Chemical Co., Osaka, Japan) and copper sulfate ($CuSO_4$ $5H_2O$) (Kokusan Chemical Works, Tokyo, Japan) were of the highest grade available commercially.

All drugs except GK-128 and cisplatin were dissolved in 0.9% saline. GK-128 was dissolved in 5.5% glucose solution. Cisplatin was dissolved in 50% polyethylene glycol 400/0.9% saline.

2.6. Statistical analysis

The statistical significance of the differences between means was calculated using the multiple comparison of Dunnett's (1964) or Scheffe's (1959) test. The half-effective dose (ED_{50}) was calculated using the Litchfield and Wilcoxon method (1949).

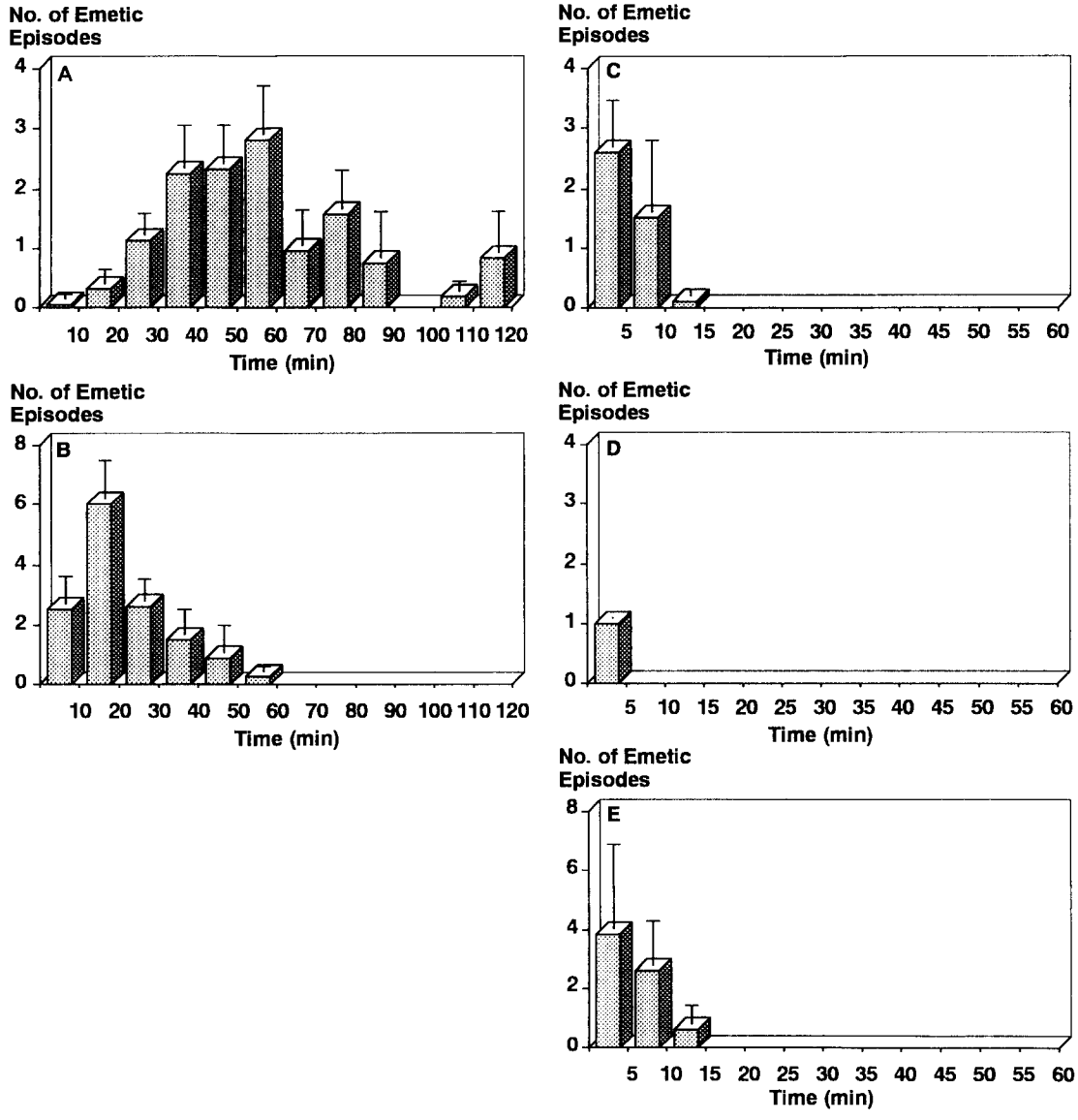

Fig. 2. Patterns of emesis induced by cisplatin (A: 30 mg/kg i.v.), cyclophosphamide (B: 300 mg/kg i.v.), 2-methyl-5-HT (C: 10 mg/kg i.v.), *m*-chlorophenylbiguanide (D: 10 mg/kg i.p.) and copper sulfate (E: 30 mg/kg p.o.). The ordinate indicates the average number of emetic episodes per 5- or 10-min period. The abscissa indicates time (min) after administration of emetics. Vertical bars represent the S.E.M. The number of animals was 3–16.

3. Results

3.1. Emetic responses to cancer chemotherapeutic agents, 5-HT_3 receptor agonists and copper sulfate

The profile of emetic episodes induced by cisplatin, cyclophosphamide, 2-methyl-5-HT, *m*-chlorophenylbiguanide and copper sulfate is summarized in Table 1 and Fig. 2.

3.1.1. Cancer chemotherapeutic agents

Cisplatin (5–30 mg/kg i.v.) dose-dependently evoked emesis in *Suncus murinus*. Maximal episodes appeared between 30–60 min after administration. These episodes lasted for about 120 min. Cyclophosphamide also induced an intense emetic response. The latency to the first emesis induced by cyclophosphamide was shorter than that for cisplatin. The maximal response of cyclophosphamide-induced emesis was observed within 20 min, and the episodes disappeared after 60 min.

3.1.2. 5-HT_3 receptor agonists

2-Methyl-5-HT (2.5–30 mg/kg i.v.), a 5-HT_3 receptor agonist, also induced an emetic response dose-dependently. The episodes displayed a maximal response within 5 min of administration and disappeared within 15 min. In contrast, another 5-HT_3 receptor agonist, *m*-chlorophenylbiguanide, evoked only one emetic episode at a dose up to 10 mg/kg i.v. and i.p. There was no second episode. Both 2-methyl-5-HT and *m*-chlorophenylbiguanide evoked the first emesis within 1 min. The number of emetic episodes induced by 2-methyl-5-HT was fewer than the number induced by cisplatin.

3.1.3. Copper sulfate

Oral administration of copper sulfate (10–100 mg/kg p.o.) evoked emesis dose-dependently. The maximal response was reached within 5 min and disappeared within 15 min.

Table 2
Effect of GK-128 on cisplatin-induced emesis in *suncus murinus*

GK-128 (mg/kg)	No. of animals emesis/tested	Latency to first emetic episodes (min) [a]	No. of emetic episodes
0 (p.o.)	6/6	42.8±13.5	13.5±4.6
0.03	6/6	46.8± 4.7	10.5±2.5
0.3	4/6	79.2±14.0	2.3±0.8
3	1/5	111.0± 9.0 [c]	0.6±0.6 [b]
30	1/5	96.4±23.6 [b]	0.2±0.2 [c]
0 (i.p.)	6/6	42.8± 7.4	15.7±3.8
0.003	6/7	46.6±12.5	10.6±3.8
0.03	7/7	43.0± 6.1	7.3±2.0
0.3	6/7	65.3±12.0	4.6±1.5
3	0/7	>120 [c]	0 [c]
0 (i.v.)	5/5	28.0± 6.3	11.2±2.4
0.003	6/6	46.8± 2.7	8.5±2.2
0.03	6/6	40.5± 3.5	9.3±1.3
0.3	1/5	109.2±10.8 [c]	1.2±1.2 [b]
3	0/6	>120 [c]	0 [c]

Values for the number of emetic episodes and the latency are means ±S.E.M. [a] If an animal did not vomit, the latency period was taken as equal to the observation period (120 min). [b] $P < 0.05$, [c] $P < 0.01$: significantly different from vehicle control (shown as 0 for doses).

3.2. Inhibitory effects on cisplatin-induced emesis

Considering the dose-dependency of cisplatin-induced emesis (Table 1 and Fig. 2), we used a dosage of 30 mg/kg (i.v.) to evaluate the anti-emetic effects of 5-HT_3 receptor antagonists in *Suncus murinus*. Orally administered GK-128 (0.03–30 mg/kg) prolonged the latency to the first emetic episode and decreased the number of emetic episodes induced by cisplatin dose-dependently (Table 2). The i.p. and i.v. administration of GK-128 (0.003–3 mg/kg) also inhibited the cisplatin-induced emesis in a dose-dependent manner. ID_{50} values (95% confidence limits) for GK-128 calculated from the inhibitory effects on the number of

Table 3
Effects of 5-HT_3 receptor antagonists on cisplatin-induced emesis in *suncus murinus*

	ID_{50} (μg/kg) [a]			ID_{90} (μg/kg)
	p.o.	i.p.	i.v.	i.v.
GK-128	79.9 (49.3–129.6)	18.8 (11.4–31.3)	36.1 (20.6–63.4)	677.1 (422.9–1238.8)
Ondansetron	89.9 (53.3–151.5)	61.5 (42.9–88.3)	164.5 (114.0–237.6)	1171.9 (820.6–1866.8)
Y-25130	N.T.	152.9 (104.4–224.1)	341.7 (240.4–485.7)	1334.1 (928.4–2151.2)
Granisetron	842.6 (495.5–1432.7)	N.T.	2132.5 (1355.3–3355.4)	6640.6 (4564.3–11341.8)
Metoclopramide	378.2 (227.8–627.8)	410.0 (245.7–684.2)	>3000	

[a] 95% confidence limits in parentheses. N.T.: not tested.

Table 4
Duration of anti-emetic effects of GK-128 and ondansetron on the cisplatin-induced emesis in *suncus murinus*

Drugs	Treatment time (h)	No. of animals emesis/ tested	Latency to first emetic episodes (min) [a]	No. of emetic episodes
Vehicle	(4)	6/6	35.8± 2.3	9.3±3.7
GK-128	3	0/4	>120 [c]	0 [b]
	4	1/4	104.5±15.5	0.8±0.8 [b]
	6	1/4	99.5±20.5	0.8±0.8 [b]
Ondansetron	3	0/4	>120 [c]	0 [b]
	4	2/5	100.6±13.4 [b]	1.0±0.6 [b]
	6	2/3	84.7±18.4	6.0±3.0

Values for the number of emetic episodes and the latency are means±S.E.M. [a] If an animal did not vomit, the latency period was taken as equal to the observation period (120 min). [b] $P < 0.05$, [c] $P < 0.01$: significantly different from vehicle control (shown as 0 for doses).

emetic episodes were 79.9 (49.3–129.6; p.o.), 18.8 (11.4–31.3; i.p.) and 36.1 (20.6–63.4; i.v.) μg/kg, respectively. Ondansetron, Y-25130, granisetron and metoclopramide (i.v., i.p. and/or p.o.) also inhibited the cisplatin-induced emesis in a dose-dependent manner. The ID_{50} and ID_{90} values are shown in Table 3. In view of the ID_{50} values, the potency of agents administered by the i.p. route was greater than that of the same administered by the i.v. route. The inhibitory effect of GK-128 (3 mg/kg i.p.) on the cisplatin-induced emesis continued for 6 h after administration, but that of ondansetron (3 mg/kg i.p.) disappeared within 6 h (Table 4).

Table 5
Effect of GK-128 on cyclophosphamide-, 2-methyl-5-HT- and copper sulfate-induced emesis in *suncus murinus*

Emetics [a]	GK-128 (mg/kg i.p.)	No. of animals emesis/ tested	Latency to first emetic episodes (min) [b]	No. of emetic episodes
Cyclophosphamide (120 min)	0	5/5	4.0± 1.2	15.2±3.4
	0.003	4/5	28.2±10.4	7.2±3.6
	0.03	5/5	20.2± 6.6	7.2±2.2
	0.3	5/5	10.4± 5.0	8.2±2.3
	3	3/5	28.0±13.1	2.4±1.1 [c]
2-Methyl-5-HT (60 min)	0	9/10	1.5± 1.5	4.2±1.4
	0.003	3/4	3.8± 3.8	3.0±2.3
	0.03	4/5	3.0± 3.0	1.0±0.3
	0.3	3/5	7.0± 3.3	0.6±0.2
	3	1/5	12.4± 2.6 [c]	0.2±0.2 [c]
Copper sulfate (60 min)	0	11/11	4.5± 0.9	6.8±1.3
	0.003	6/6	5.3± 0.5	7.8±1.4
	0.03	6/6	2.5± 0.5	6.3±1.6
	0.3	6/6	5.3± 0.3	5.8±1.2
	3	5/6	12.8± 4.3	5.8±1.9

Values for the number of emetic episodes and the latency are means±S.E.M. [a] Observation period in parentheses. [b] If an animal did not vomit, the latency period was taken as equal to the observation period. [c] $P < 0.05$: significantly different from vehicle control (shown as 0 for doses).

3.3. Effects of GK-128 on cyclophosphamide-, 2-methyl-5-HT- and copper sulfate-induced emesis

GK-128 (0.003–3 mg/kg i.p.) prolonged the latency to the first emetic episode and decreased the number of emetic episodes induced by 2-methyl-5-HT (10 mg/kg i.v.) in a dose-dependent manner (Table 5). The ID_{50} value of GK-128 was 8.8 (4.6–16.8) μg/kg. GK-128 (0.003–3 mg/kg i.p.) also afforded protection against cyclophosphamide (300 mg/kg i.v.)-induced emesis, but no clear dose-response relationship was seen (Table 5). GK-128 did not affect the emesis induced by copper sulfate (30 mg/kg p.o.) at a dose up to 3 mg/kg (i.p.) (Table 5).

4. Discussion

We investigated the potential of various emetogenic agents to induce emesis and the anti-emetic activity of GK-128 in *Suncus murinus*. Cisplatin, cyclophosphamide, 2-methyl-5-HT and copper sulfate induced dose-dependent emesis. Cisplatin induced long-lasting emesis with a long latency. The latency and the duration of cyclophosphamide-induced emesis were shorter than those of cisplatin. 2-Methyl-5-HT, one of the 5-HT_3 receptor agonists, evoked transient emesis with a shorter latency than the two above-mentioned cancer chemotherapeutic agents. Another 5-HT_3 receptor agonist, *m*-chlorophenylbiguanide, induced only one emetic episode within 1 min of administration, in spite of its reported greater potency at the 5-HT_3 receptor in the rat (Kilpatrick et al., 1990). Copper sulfate also induced emesis with a short latency and transient duration.

This is the first report demonstrating the anti-emetic activity of orally administered 5-HT_3 receptor antagonists in *Suncus murinus*, although several studies which used ferrets (Leo et al., 1992) and dogs (Smith et al., 1989) have already been reported. A new 5-HT_3 receptor antagonist, GK-128 (i.v., i.p. and p.o.), showed potent inhibitory effects on cancer chemotherapy agent- and 5-HT_3 receptor agonist-induced emesis with a similar potency. The anti-emetic action of GK-128 was more potent than that of ondansetron, Y-25130, granisetron and metoclopramide in *Suncus murinus*. GK-128 showed a dose-dependent inhibitory effect, but statistical significance was found only at higher doses of GK-128, probably because the data showed some variance. In the investigation of the duration of the anti-emetic effect, the significant inhibition of GK-128 lasted for 6 h after administration, but that of ondansetron disappeared, suggesting that GK-128 has a long-lasting anti-emetic action. GK-128 did not inhibit copper sulfate-induced emesis in *Suncus murinus*.

Torii et al. (1991b) also reported the same result with regard to ondansetron in *Suncus murinus*. Copper sulfate-induced emesis was not considered to involve 5-HT_3 receptors in this species.

Recently, several findings have suggested the possibility of a species-dependent heterogeneity in the 5-HT_3 receptor. Butler et al. (1990) reported that the affinity of 5-HT_3 receptor agonists and antagonists in guinea-pig was lower than that in other species. In a binding study, Wong et al. (1993a) reported that *m*-chlorophenylbiguanide exhibited a 25-, 93- and 2000-fold higher affinity in rat cortex than in NG 108-15 cells, rabbit ileum and guinea-pig ileum, respectively. The species-dependent difference in the 5-HT_3 receptor does not necessarily extend to the 5-HT_3 receptor subtypes. However, there are some indications of receptor heterogeneity within a single species and a single tissue. Bonhaus et al. (1993) showed the heterogenous populations of 5-HT_3 receptors in mouse ileum and cortex. Moreover, the densities of sites labelled by different 5-HT_3 radioligands vary, even in the same tissue (Wong et al., 1993b), which also suggests the intra-species heterogeneity of 5-HT_3 receptors. Further, Gebauer et al. (1993) reported that the release of 5-HT from enterochromaffin cells of guinea-pig isolated small intestine was inhibited by granisetron but not by ondansetron.

In this study with *Suncus murinus*, the potency of granisetron was lower than that of ondansetron on cisplatin-induced emesis. Torii et al. (1991b) also reported a low potency of granisetron on the same emesis in *Suncus murinus*. However, most studies with dogs and ferrets show opposite results (Haga et al., 1993; Kamato et al., 1991). In our binding study, GK-128 inhibited specific [^{3}H]GR65630 binding with a K_i value of 0.58 nM in rat cortical membrane. The value for granisetron, ondansetron, Y-25130 and metoclopramide was 0.16, 1.56, 1.39 and 233.3 nM, respectively (Ito et al., 1993). The order of potency of the anti-emetic effect of these agents, except granisetron, was consistent with that of their 5-HT_3 receptor binding affinity in rat cortex. The anti-emetic effect of granisetron was less than its relative 5-HT_3 receptor binding affinity in rat cortex. Further, there were clear differences between the features of emesis induced by 5-HT_3 receptor agonists, 2-methyl-5-HT and *m*-chlorophenylbiguanide, in *Suncus murinus*. 2-Methyl-5-HT induced emesis dose-dependently with a duration of about 15 min. In contrast, *m*-chlorophenylbiguanide caused only one emesis within 1 min after administration. In contrast, Kamato et al. (1993) reported that *m*-chlorophenylbiguanide caused emesis dose-dependently, though 5-HT and 2-methyl-5-HT evoked only retches without emesis in ferrets.

Ravenscroft et al. (1992) reported that 5-HT rarely induced emesis when injected i.v., and that phenylbiguanide injected i.v. inhibited emesis induced by loperamide or radiation in ferrets. In the present study, emesis was induced by 2-methyl-5-HT given intravenously in *Suncus murinus*, and *m*-chlorophenylbiguanide evoked only one emetic episode regardless of the administration route. In the ferret, the emetic responses to 5-HT_3 receptor agonists or cisplatin were abolished by the combination of abdominal vagotomy and splanchnicectomy (Ravenscroft et al., 1992; Kamato et al., 1993). However, Mutoh and co-workers demonstrated that the emetic responses to 5-HT or cisplatin were completely prevented by abdominal vagotomy without splanchnicectomy in *Suncus murinus* (Mutoh et al., 1992; Torii et al., 1991a). Preziosi et al. (1992) showed the intrinsic emetic effects of 5-HT_3 receptor antagonists in the pigeon. In *Suncus murinus*, however, it has been reported that some 5-HT_3 receptor antagonists induce emesis only at the high dose of 64 mg/kg (s.c.) (Torii et al., 1991). The emetic effects of 5-HT_3 receptor antagonists used in this study were not observed at the dose of 3 mg/kg.

It is well known that 5-HT or 5-HT_3 receptor agonists injected intravenously in other species result in the activation of the Bezold-Jarisch reflex (Fozard and Host, 1982). We have confirmed that the injection of 2-methyl-5-HT and *m*-chlorophenylbiguanide also elicits bradycardia in *Suncus murinus* (unpublished data). According to our data, *m*-chlorophenylbiguanide exhibited a 10-fold higher potency than 2-methyl-5-HT in causing bradycardia, and GK-128 completely abolished the response to 2-methyl-5-HT.

These results suggest that the 5-HT_3 receptors involved in emesis in *Sincus murinus* may be different from the 5-HT_3 receptors in other species, and, possibly, that they may be different from the 5-HT_3 receptors relevant to blood pressure control in *Suncus murinus*.

In conclusion, we investigated the emetic responses induced by various emetogenic agents, and the anti-emetic activity of GK-128 in *Suncus murinus*, which is phylogenetically closer to primates than other experimental animals, such as ferrets and dogs. Cancer chemotherapeutic agent-induced emesis was more severe than the emesis induced by other agents. In *Suncus murinus*, cancer chemotherapeutic agent- and 2-methyl-5-HT-induced emesis was potently inhibited by a new 5-HT_3 receptor antagonist, GK-128, with a similar potency. These results suggest that GK-128 is a useful drug in the treatment of the nausea and vomiting of patients undergoing cancer chemotherapy. Further, two results, the low potency of granisetron against cisplatin-induced emesis and that of the emetogenic effect of *m*-chlorophenylbiguanide, suggest that the 5-HT_3 receptors involved in emesis in *Suncus murinus* may be different from the 5-HT_3 receptors in other animals such as rats, dogs and ferrets.

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