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Pemirolast reduces cisplatin-induced kaolin intake in rats

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ABSTRACT

Emesis is the most feared side effect in patients who are undergoing cancer chemotherapy. In particular, cisplatin causes severe acute and delayed emesis. Although early vomiting is well controlled by 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonists, delayed-phase vomiting is not sufficiently controlled. Substance P is thought to be involved in the development of emesis, and tachykinin NK_1 receptor antagonists can inhibit delayed vomiting. We previously have reported that substance P is involved in the paclitaxel-induced hypersensitivity reaction in rats, and anti-allergic agent pemirolast reduces these reactions via inhibition of substance P release. In the present study, we investigated the effect of pemirolast on cisplatin-induced kaolin intake, which is an index of nausea/vomiting in the rat. Cisplatin (5 mg/kg, i.p.) induced kaolin intake and reduced normal feed intake from days 1 to 5 after injection. Cisplatin-induced kaolin intake was significantly reduced by co-administration of ondansetron (2 mg/kg, i.p.), a $5\text{-}HT_3$ receptor antagonist, and dexamethasone (2 mg/kg, i.p.) from days 1 to 5. Similarly, pemirolast (10 mg/kg, p.o.) and the tachykinin NK_1 receptor antagonist aprepitant (10 and 30 mg/kg, p.o.) significantly reduced cisplatin-induced kaolin intake on days 3 and 4. Moreover, pemirolast at the same dose significantly reversed the cisplatin-induced increase in the cerebrospinal fluid level of substance P in rats. These results suggest that substance P is involved in cisplatin-induced kaolin intake in rats, and pemirolast reduces kaolin intake by inhibition of substance P release.

1. Introduction

Cisplatin is a platinum-based chemotherapeutic agent that has been used widely for several malignancies. One of the most undesirable effects during treatment with cisplatin is severe emesis, which often limits its therapeutic use. Indeed, cisplatin is classified in the highest emetic risk group according to American Society of Clinical Oncology guidelines (American Society of Clinical Oncology et al., 2006). Cisplatin causes acute and delayed nausea and vomiting (Hainsworth and Hesketh, 1992; Martin, 1996). Serotonin (5-hydroxytryptamine, 5-HT) released from the enterochromaffin cells of the stomach and intestine by chemotherapy contributes to especially acute symptoms (Tyers and Freeman, 1992), and the first-generation $5\text{-}HT_3$ receptor antagonists prevent early but not delayed vomiting (Navari, 2009). Cisplatin also upregulates substance P mRNA and protein levels in the brain and gut of least shrew (Darmani et al., 2009; Dey et al., 2010), and tachykinin NK_1 receptor antagonists inhibit delayed emesis in ferrets and dogs (Gonsalves et al., 1996; Rudd et al., 1996; Singh et al., 1997; Tattersall et al., 2000; Watson et al., 1995). Therefore, substance P and 5-HT are thought to play an important role in cisplatin-induced emesis, and the tachykinin NK_1 receptor antagonist aprepitant is used clinically to control cisplatin-induced emesis.

Rats do not vomit. Instead, anticancer drugs induce kaolin ingestion behavior "pica" in rats, and it is evaluated as an index of nausea/vomiting (Takeda et al., 1993). Yamamoto et al. (2007) have reported that kaolin intake induced by anticancer drugs in rats is related to their clinical emetogenic potential. Moreover, pica is a good preclinical screen for drugs that are antiemetic. Dexamethasone, the $5\text{-}HT_3$ receptor antagonist ondansetron, and tachykinin NK_1 receptor antagonists GR205171 and HSP-117 have been reported to reduce cisplatin-induced kaolin consumption in rats (Malik et al., 2007; Saeki et al., 2001; Takeda et al., 1993). In addition, inhibition of cisplatin-induced kaolin consumption by tachykinin NK_1 receptor antagonists suggests that substance P is involved in cisplatin-induced kaolin intake.

We previously have reported that substance P plays an important role in the hypersensitivity reactions induced by the antineoplastic agent paclitaxel. Paclitaxel markedly increases substance P in plasma and bronchoalveolar lavage fluid in rats, and in plasma in patients

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with ovarian cancer (Itoh et al., 2004a; Sendo et al., 2004). Moreover, we have reported that the antiallergic agent pemirolast attenuates paclitaxel-induced pulmonary hypersensitivity reactions in rats through inhibition of substance P release (Itoh et al., 2004b). It also prevents paclitaxel-induced hypersensitivity reactions in patients with ovarian cancer (Yahata et al., 2006). These results suggest the involvement of substance P in the prophylactic effect of pemirolast. However, the effect of pemirolast on cisplatin-induced kaolin intake has not been studied, therefore, we investigated this in rats, along with the effects of cisplatin and pemirolast on substance P levels in cerebrospinal fluid (CSF).

2. Materials and methods

2.1. Animals

Male Wistar rats aged 6 weeks and weighing 160–250 g (Kyudo, Saga, Japan) were used. They were housed individually in a cage (225×338×140 mm) under a 12-h light/dark schedule (lights on at 07:00 h) and were given water, normal feed and kaolin ad libitum. All experiments were approved by the Experimental Animal Care and Use Committee of Kyushu University, in accordance with the National Institutes of Health guidelines.

2.2. Drugs

Cisplatin [cis-diamineplatinum (II) dichloride], ondansetron (ondansetron hydrochloride dihydrate) and dexamethasone (dexamethasone 21-phosphate disodium salt) were purchased From Sigma–Aldrich, Inc. (St. Louis, MO, USA) and dissolved in saline. Aprepitant (Emend®; Ono Pharmaceutical Co. Ltd, Osaka, Japan) was suspended in a vehicle of 10% ethanol:60% propylene glycol (Wako Pure Chemical Ltd., Osaka, Japan, respectively):30% water as described previously (Tattersall et al., 2000). Pemirolast (a generous gift from Mitsubishi Tanabe Pharma Factory Ltd., Osaka, Japan) was dissolved in distilled water.

2.3. Kaolin

Kaolin was prepared according to the method of Saito and Takano (2006), with minor modifications. Kaolin (Wako Pure Chemical Ltd.) was mixed with 7% gum arabic (Kanto Chemical Co., Tokyo, Japan) in distilled water to form a thick paste. The mixture was placed in a tube and partially dried in a dryer. The mixture was extruded from the tube, cut into a column of the same size as that for normal feed pellets, and dried completely in a dryer.

2.4. Experimental procedure

The mesh container of 30 g kaolin pellets was placed on the wire mesh floor of the cage, along with 70 g normal feed for 3 days before the experiment, and the animals were allowed to adapt to the presence of both containers. To measure the kaolin consumption during a 24-h period, the remaining kaolin in the container and kaolin spilled in the cage were collected, dried, and weighed at 16:00 h every day. The amount of normal feed intake was measured in the same manner as for kaolin intake. Fresh kaolin and normal feed pellets were placed in these containers. The rats with kaolin intake <1.0 g/day on the last of 3 days adaptation were used for drug tests.

The animals were injected i.p. with vehicle or cisplatin (2–10 mg/kg) at the same time as placement of the new pellets after adaptation (day 0). Ondansetron (2 mg/kg, i.p.) and dexamethasone (2 mg/kg, i.p.) were administered 10 min before and 24, 48, 72 and 96 h (five times in total) after administration of cisplatin. Aprepitant or pemirolast was administered 1 h or 30 min before and 24, 48, 72 and 96 h (five times in total) after administration of cisplatin. The doses and administration schedules of these drugs were chosen based on previous studies (Fujisaki et al., 2001; Miyazawa et al., 1997; Rudd et al., 2002; Saeki et al., 2001; Tattersall et al., 2000). To examine the effects of cisplatin, the amounts of kaolin and normal feed intake were measured during a 24-h period at the start of 16:00 h before and 24, 48, 72, 96 and 120 h (six times in total), after the administration of cisplatin. To examine the effects of ondansetron, dexamethasone, aprepitant and pemirolast, the amounts of kaolin and normal feed intake were measured before and 24, 48, 72, 96, 120, 144 and 168 h (eight times in total).

2.5. Measurement of substance P in CSF

Cisplatin (5 mg/kg, i.p.) or vehicle was administered on day 0. Pemirolast (10 mg/kg, p.o.) was administered 30 min before and 24, 48 and 72 h (four times in total) after administration of cisplatin. CSF was collected by cisternal puncture from rats anesthetized with sodium pentobarbital 1 h after the last administration of pemirolast. To avoid degradation of substance P, aprotinin (Wako Pure Chemical Ltd.), EDTA disodium salt (Dojindo Laboratories, Kumamoto, Japan) and 4% trifluoroacetic acid (Wako Pure Chemical Ltd.) were added to the CSF at final concentrations of 12.2 μL/mL, 1 mg/mL and 150 μL/mL, respectively. The content of substance P in the CSF was measured by EIA kit (Cayman Chemical Co., Ann Arbor, MI, USA).

2.6. Statistical analysis

Values were expressed as the mean ± S.E.M. Values were analyzed by one-way or two-way (with repeated measures) analysis of variance (ANOVA) followed by the Tukey–Kramer post hoc test (StatView; Abacus Concepts, Berkeley, CA, USA) to determine differences among the groups. A probability level of $P<0.05$ was accepted as statistically significant.

3. Results

3.1. Effects of cisplatin on intake of kaolin and normal feed, and body weight

For kaolin intake, repeated measures ANOVA revealed a significant drug effect [$F(3, 28)=10.176$, $P<0.001$], a significant time effect [$F(7, 196)=7.701$, $P<0.0001$], and a significant drug×time interaction [$F(21, 196)=4.137$, $P<0.0001$]. Cisplatin at a dose of 5 mg/kg significantly induced kaolin intake from days 1 to 7 after injection ($P<0.05$ or 0.01 by the Tukey–Kramer post hoc test; Fig. 1A). For normal feed intake, repeated measures ANOVA revealed a significant drug effect [$F(3, 28)=105.361$, $P<0.0001$], a significant time effect [$F(7, 196)=32.273$, $P<0.0001$], and a significant drug×time interaction [$F(21, 196)=18.411$, $P<0.0001$]. Cisplatin at the same dose significantly reduced normal feed intake from day 1 to 5 ($P<0.01$ by the Tukey–Kramer post hoc test; Fig. 1B) compared with vehicle. Cisplatin at a dose of 10 mg/kg markedly reduced normal feed intake ($P<0.01$ by the Tukey–Kramer post hoc test), without a significant increase in kaolin intake. For body weight, repeated measures ANOVA revealed a significant drug effect [$F(3, 28)=8.753$, $P<0.001$], a significant time effect [$F(7, 196)=35.870$, $P<0.0001$], and a significant drug×time interaction [$F(21, 196)=63.899$, $P<0.0001$]. Cisplatin at doses of 5 and 10 mg/kg significantly decreased body weight compared with vehicle ($P<0.05$ or 0.01 by the Tukey–Kramer post hoc test; Fig. 1C).

3.2. Effects of ondansetron and dexamethasone on cisplatin-induced increase of kaolin intake and decrease of normal feed intake

For kaolin intake, repeated measures ANOVA revealed a significant drug effect [$F(4, 41)=20.481$, $P<0.0001$], a significant time effect [$F(5, 205)=34.846$, $P<0.0001$], and a significant drug×time

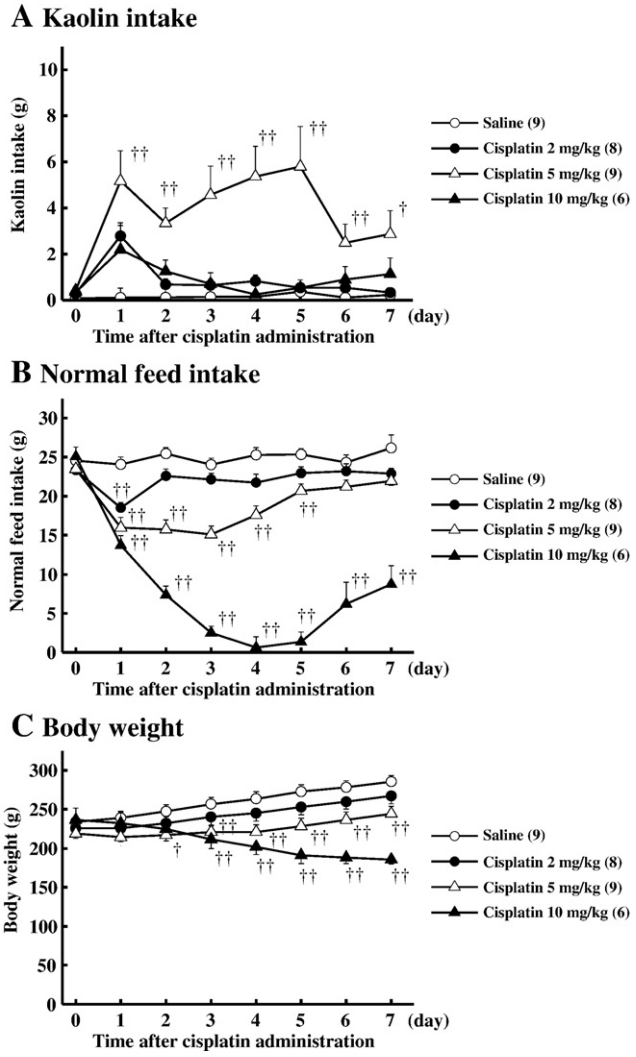

Fig. 1. Effects of cisplatin on intakes of kaolin (A) and normal feed (B), and body weight (C) in rats. Cisplatin (2–10 mg/kg, i.p.) or vehicle was administered on day 0. Data are expressed as mean ± S.E.M. The number of animals is shown in each parenthesis. †P<0.05, ††P<0.01 compared with vehicle (one-way ANOVA followed by Tukey–Kramer post hoc test).

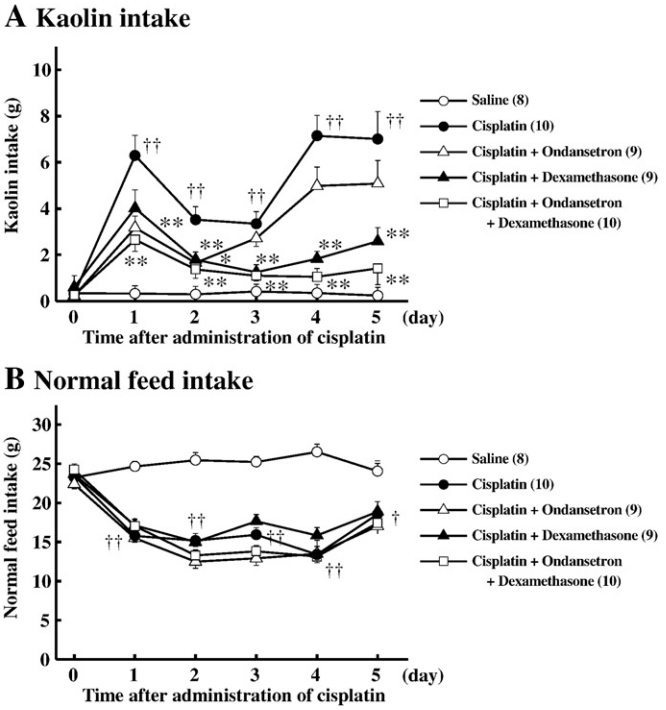

Fig. 2. Effects of ondansetron and dexamethasone on cisplatin-induced increase in kaolin intake (A) and decrease in normal feed intake (B) in rats. Cisplatin (5 mg/kg, i.p.) or vehicle was administered on day 0. Ondansetron (2 mg/kg, i.p.) and dexamethasone (2 mg/kg, i.p.) were administered 10 min before and 24, 48, 72 and 96 h after cisplatin. Data are expressed as mean ± S.E.M. The number of animals is shown in each parenthesis. †P<0.05, ††P<0.01 compared with vehicle, *P<0.05, **P<0.01 compared with cisplatin alone (one-way ANOVA followed by Tukey–Kramer post hoc test).

interaction [$F(20, 205) = 7.554$, P<0.0001]. Ondansetron (2 mg/kg, i.p., once daily for 5 days) significantly inhibited the cisplatin-induced increase in kaolin intake on days 1 and 2 (P<0.01 by the Tukey–Kramer post hoc test; Fig. 2A). Dexamethasone (2 mg/kg, i.p., once daily for 5 days) significantly inhibited the cisplatin-induced increase in kaolin intake from days 2 to 5 (P<0.05 or 0.01 by the Tukey–Kramer post hoc test; Fig. 2A). Moreover, co-administration of ondansetron and dexamethasone at the same doses significantly inhibited the cisplatin-induced increase in kaolin intake from days 1 to 5 (P<0.01 by the Tukey–Kramer post hoc test). For normal feed intake, repeated measures ANOVA revealed a significant drug effect [$F(4, 41) = 29.704$, P<0.0001], a significant time effect [$F(5, 205) = 61.870$, P<0.0001], and a significant drug × time interaction [$F(20, 205) = 7.903$, P<0.0001]. Ondansetron and dexamethasone had no effect on the cisplatin-induced decrease in normal feed intake (Fig. 2B).

3.3. Effects of aprepitant on cisplatin-induced increase of kaolin intake and decrease of normal feed intake

For kaolin intake, repeated measures ANOVA revealed a significant drug effect [$F(4, 37) = 10.821$, P<0.0001], a significant time effect [$F(5, 185) = 44.186$, P<0.0001], and a significant drug × time interaction [$F(20, 185) = 4.140$, P<0.0001]. Aprepitant (10 and 30 mg/kg, p.o., once daily for 5 days) significantly inhibited the cisplatin-induced increase in kaolin intake from days 2 to 4 (P<0.05 or 0.01 by the Tukey–Kramer post hoc test; Fig. 3A). For normal feed intake, repeated measures ANOVA revealed a significant drug effect [$F(4, 37) = 6.501$, P<0.001], a significant time effect [$F(5, 185) = 40.595$, P<0.0001], and a significant drug × time interaction [$F(20, 185) = 3.404$, P<0.0001]. Aprepitant had no effect on the cisplatin-induced decrease in normal feed intake (Fig. 3B).

3.4. Effects of pemirolast on cisplatin-induced increase of kaolin intake and decrease of normal feed intake

For kaolin intake, repeated measures ANOVA revealed a significant drug effect [$F(3, 33) = 16.547$, P<0.0001], a significant time effect [$F(5, 165) = 26.856$, P<0.0001], and a significant drug × time interaction [$F(15, 165) = 4.217$, P<0.0001]. Pemirolast (10 mg/kg, p.o., once daily for 5 days) significantly inhibited the cisplatin-induced increase in kaolin intake on days 3 and 4 (P<0.05 or 0.01 by the Tukey–Kramer post hoc test; Fig. 4A). For normal feed intake, repeated measures ANOVA revealed a significant drug effect [$F(3, 33) = 14.442$, P<0.0001], a significant time effect [$F(5, 165) = 31.129$, P<0.0001], and a significant drug × time interaction [$F(15, 165) = 4.794$, P<0.0001]. Pemirolast had no effect on the cisplatin-induced decrease in normal feed intake (Fig. 4B).

3.5. Effects of cisplatin and pemirolast on substance P levels in CSF

In rats treated with vehicle, substance P level in the CSF was 50.48 ± 1.79 pg/mL. Cisplatin (5 mg/kg, i.p.) significantly increased substance P levels in the CSF to 65.17 ± 3.00 pg/mL on day 3 after

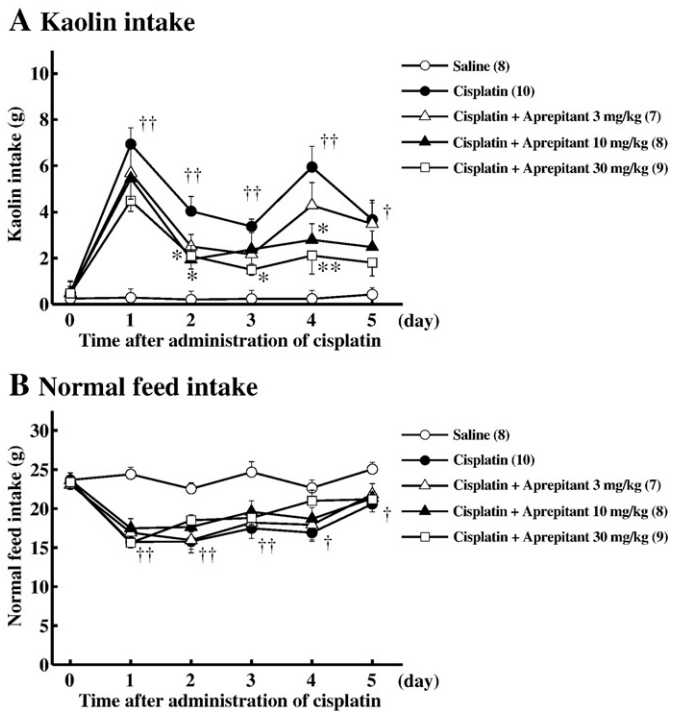

Fig. 3. Effects of aprepitant on cisplatin-induced increase in kaolin intake (A) and decrease in normal feed intake (B) in rats. Cisplatin (5 mg/kg, i.p.) or vehicle was administered on day 0. Aprepitant (3–30 mg/kg, p.o.) was administered 1 h before and 24, 48, 72 and 96 h after cisplatin. Data are expressed as mean ± S.E.M. The number of animals is shown in each parenthesis. †$P<0.05$, ††$P<0.01$ compared with vehicle, *$P<0.05$, **$P<0.01$ compared with cisplatin alone (one-way ANOVA followed by Tukey–Kramer post hoc test).

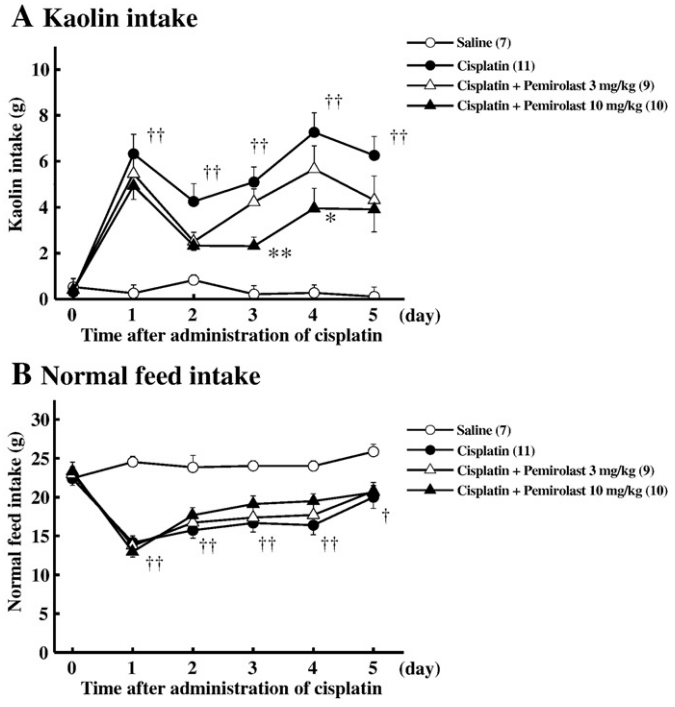

Fig. 4. Effects of pemirolast on cisplatin-induced increase in kaolin intake (A) and decrease in normal feed intake (B) in rats. Cisplatin (5 mg/kg, i.p.) or vehicle was administered on day 0. Pemirolast (3 and 10 mg/kg, p.o.) was administered 30 min before and 24, 48, 72 and 96 h after cisplatin. Data are expressed as mean ± S.E.M. The number of animals is shown in each parenthesis. †$P<0.05$, ††$P<0.01$ compared with vehicle, *$P<0.05$, **$P<0.01$ compared with cisplatin alone (one-way ANOVA followed by Tukey–Kramer post hoc test).

injection [$F(2, 19) = 6.762$, $P<0.01$ by one-way ANOVA; $P<0.01$ by the Tukey–Kramer post hoc test; Fig. 5]. Pemirolast (10 mg/kg, p.o., once daily for 4 days) significantly reversed the cisplatin-induced increase of substance P levels to vehicle levels in the CSF (substance P level of rats co-treated with cisplatin and pemirolast was 54.89 ± 3.15 pg/mL) ($P<0.05$ by the Tukey–Kramer post hoc test).

4. Discussion

A single administration of cisplatin (5 mg/kg, i.p.) induced kaolin intake and reduced normal feed intake from day 1 after injection, and these effects were weak on days 6 and 7. Thus, we confirmed an obvious kaolin intake until at least day 5. Cisplatin (10 mg/kg, i.p.) markedly reduced normal feed intake without significantly increasing kaolin intake and decreasing body weight. In addition, some rats had diarrhea and died. Therefore, cisplatin (5 mg/kg) was used in the subsequent experiments.

In the present study, the repeated administration of ondansetron significantly reduced the cisplatin-induced kaolin intake on days 1 and 2, and this effect disappeared from day 3. Thus, the inhibitory effect of ondansetron on the kaolin intake was observed only in the early phase, and this feature was similar to its clinical antiemetic efficacy (Cocquyt et al., 2001). The repeated administration of dexamethasone also reduced the cisplatin-induced kaolin intake from days 2 to 5. Moreover, co-administration of ondansetron and dexamethasone almost completely reduced the cisplatin-induced kaolin intake. These results support a previous study of the effects of ondansetron and dexamethasone on cisplatin-induced vomiting behavior in ferrets (Rudd and Naylor, 1996). On the other hand, ondansetron and dexamethasone had no effect on the cisplatin-induced decrease in normal feed intake, which suggests that these inhibitory effects on kaolin intake were not due to decreased appetite.

The repeated administration of aprepitant also reduced the cisplatin-induced kaolin intake from days 2 to 4, without affecting the cisplatin-induced decrease in normal feed intake. Similarly, pemirolast significantly reduced the cisplatin-induced kaolin intake on days 3 and 4, without affecting the cisplatin-induced decrease in normal feed intake. These results suggest that substance P is involved in the cisplatin-induced kaolin intake in rats. This hypothesis is supported by our measurements of substance P in the present study. In fact, cisplatin increased substance P levels in CSF, and pemirolast reversed this effect.

Substance-P-related emesis seems to be mediated via tachykinin NK_1 receptor in the medulla oblongata (the area postrema, nucleus tractus solitarius, and dorsal motor nucleus of the vagus) and on the

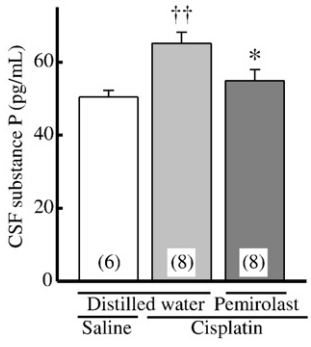

Fig. 5. Effects of cisplatin and pemirolast on substance P levels in CSF of rats. Cisplatin (5 mg/kg, i.p.) or vehicle was administered on day 0. Pemirolast (10 mg/kg, p.o.) was administered 30 min before and 24, 48 and 72 h after cisplatin. The CSF was collected from rats anesthetized with sodium pentobarbital 1 h after the last administration of pemirolast. Data are expressed as mean ± S.E.M. The number of animals is shown in each parenthesis. ††$P<0.01$ compared with vehicle, *$P<0.05$ compared with cisplatin alone (one-way ANOVA followed by Tukey–Kramer post hoc test).

abdominal vagal afferent nerve that projects to the medulla oblongata (Darmani et al., 2008; Minami et al., 1998, 2001; Saito et al., 2003). Only brain-penetrating tachykinin NK_1 agonists/antagonists have emetic/antiemetic effects (Darmani et al., 2008; Rupniak et al., 1997). Tattersall et al. (1996) also have reported that brain penetration is essential for the antiemetic action of systemically administered tachykinin NK_1 receptor antagonists. Furthermore, we found that cisplatin increased substance P levels in the CSF. The cisterna magna is connected to the fourth ventricle; therefore, the substance P levels in the CSF may reflect those in the anatomical structures involved in emesis, such as the area postrema and nucleus tractus solitarius. Taken together, the substance-P-related emesis induced by cisplatin may be mainly due to action on tachykinin NK_1 receptors in the central nervous system.

Pemirolast, an antiallergic agent, which possesses mast-cell-stabilizing activity, reduces the release of chemical mediators such as histamine by inhibition of calcium mobilization (Fujimiya et al., 1991; Yanagihara et al., 1988). Calcium mobilization also plays a critical role in substance P release (Rane et al., 1987; White, 1996). Therefore pemirolast is thought to inhibit the release of substance P by inhibition of calcium mobilization. The release of chemical mediators is thought to depend on calcium mobilization (Mazurek et al., 1980), and mast cell stabilizers may generally inhibit calcium mobilization. Therefore, other mast cell stabilizers are also expected to inhibit the release of substance P and reduce the cisplatin-induced kaolin intake.

Although pemirolast does not antagonize histamine H_1 receptors (Yanni et al., 1997), pemirolast inhibits the release of histamine (Minami et al., 2005). Anti-histaminergic drugs cannot prevent cisplatin-induced emesis in humans (Tsukuda et al., 1995) and pica in rats (Takeda et al., 1995). Therefore, pemirolast may reduce cisplatin-induced kaolin intake via non-histaminergic mechanisms.

Cisplatin is known to upregulate substance P at the mRNA and protein levels in the brain and gut of least shrew (Darmani et al., 2009; Dey et al., 2010). Cisplatin and other antineoplastic agents also increase serum level of substance P in humans (Higa et al., 2009; Yamada et al., 2007), and serum substance P penetrates the brain via the blood–brain barrier (Chappa et al., 2006; Freed et al., 2002). In this study, we found that cisplatin increased substance P levels in the CSF at 3 days after injection, and pemirolast reversed the cisplatin-induced increase of substance P. In ferrets and *Suncus murinus*, the ultrapotent capsaicin analog resiniferatoxin causes emesis by releasing substance P at a critical site in the emetic pathway; thought to be the nucleus tractus solitarius. Then, the depletion of substance P is responsible for the subsequent antiemetic effects (Andrews et al., 2000; Andrews and Bhandari, 1993). Thus substance P plays an important role in emesis. Pemirolast might reverse the cisplatin-induced increase of substance P in the CSF by inhibiting the release of substance P, and consequently, reduce kaolin intake.

In the present study, we found that pemirolast, as well as dexamethasone and aprepitant, reduced cisplatin-induced kaolin intake in the delayed phase. Although dexamethasone and aprepitant are currently used for the treatment of delayed emesis, the control of vomiting and nausea is still not complete. Also, dexamethasone must be used with caution because of its many side effects. Aprepitant is a substrate, moderate inhibitor and inducer of cytochrome P450 (CYP) 3A4 and CYP2C9, therefore, it is necessary to pay particular attention to drug interactions (Navari, 2004). On the other hand, pemirolast is a safe and inexpensive drug. Therefore, pemirolast might be clinically useful for prevention of delayed emesis.

5. Conclusions

This study shows that substance P is related to cisplatin-induced kaolin intake in rats, and pemirolast probably reduces kaolin intake by inhibition of substance P release.

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