博 士 論 文

Physiological study of the effects of cisplatin-induced conditioned sweet taste aversion on feeding and drinking behavior in rats

（シスプラチン誘発条件付け甘味嫌悪がラットの摂食・飲水行動に与える影響に関する生理学的研究）

令和 7 年 3 月申請

北海道大学

大学院歯学院口腔医学専攻

魏 紫茉

Abstract

We investigated the rejection behavior of a saccharin-sweet diet in rats following the acquisition of conditioned taste aversion (CTA) to 0.1% saccharin solution. Male Sprague-Dawley rats (7 weeks old) underwent 22 hours and 40 minutes of food deprivation and 21 hours and 40 minutes of water deprivation. Diet intake, fluid intake, and body weight changes were measured. To induce nausea, emetine dihydrochloride (5.54 mg/kg, 1% BW, i.p.) or cisplatin dihydrochloride (3 mg/kg, 1% BW, i.p.) was used as the unconditioned stimulus. Control group rats received saline (1% BW, i.p.) instead of emetine or cisplatin. In some cisplatin-conditioned rats, the effects of ondansetron (a 5-HT_3 receptor antagonist, 0.1 mg/kg, 0.1% BW, i.p.) were tested 30 minutes prior to the conditioned stimulus or on the day of testing. Sweet diet intake was assessed on five test days after a recovery day (tests 1–5). Pre-administration of ondansetron prevented the reduction in sweet diet intake in the cisplatin group. In contrast, sweet diet intake increased on tests 3–5 in the control group compared to the conditioning days. These findings suggest that feeding inhibition is mediated by neural circuits activated through 5-HT_3 receptors.

1. Introduction

Conditioned taste aversion (CTA) is a phenomenon that occurs when an animal tastes toxic or spoiled food and associates it with symptoms of nausea, vomiting, and illness caused by the harmful substances. CTA helps prevent the body from being re-exposed to the toxin, reducing the possibility of consuming similarly flavored foods in the future to avoid further poisoning. Unlike classical conditioning, represented by Pavlovian conditioned reflexes, CTA is a single-trial learning process and is established with only one conditioning session

When rats experience sweet solution intake and nausea induction at the same time, they develop a conditioned taste aversion and reduce their next intake of sweet solution. When rats are reared as laboratory animals, solid feed for rats is used, but this feed does not contain sweetening ingredients, and rats do not experience sweet taste throughout their lives under normal rearing. When such rats ingest sweetened solution for the first time, they initially show fear of the novel taste and ingest the sweetened solution with carefully tasting whether it is safe or not.

Since sweet taste is innately perceived as an energy source and pleasant information, sweet taste preference eventually instinctively becomes dominant, followed by a gradual increase in sweet solution intake. Since Garcia proposed the concept of CTA, many researchers have conducted animal experiments using rats and mice to elucidate the neural mechanisms of conditioned taste aversion or avoidance(1–14). When rats acquire CTA by conditioning with a pair of sweet taste and nausea induction, they avoid the next intake of saccharin, despite being thirsty due to water deprivation (15–19). Most of them compare the intake of sweetened solutions at a certain time (15-30 minutes) after forcing experimental animals deprived of water for a considerable period of time. In other words, this is tantamount to assessing how much water of an unpleasant taste the

experimental animals will consume even against thirst. Our question here is how much rats that have acquired a CTA for sweetness will consume an unpleasant sweet-tasting diet, even against hunger. Hunger sensation is a physiological motivation that triggers feeding behavior and is an important emotion essential for life maintenance. We hypothesized and tested in this study that acquisition of a conditioned aversion memory for a specific taste would lead to avoidance of ingestion of food.

Emetogenic drug-induced nausea (visceral discomfort) was used as an unconditioned stimulus to induce CTA to saccharin. In this study, emetine, which induces acute nausea, and cisplatin, an antineoplastic drug that induces acute and delayed nausea, were used. Emetine is one of the alkaloids contained in the root of Ipecac (Carapichea ipecacuanha), which is native to Brazil. In humans, emetine potently induces nausea and vomiting immediately after ingestion. Taking advantage of this effect, Ipecac syrup, which is used as first aid for infants who accidentally ingest cigarettes, was sold as a household remedy (20,21). However, due to recent advances in emergency medicine, Ipecac syrup was discontinued in the U.S. in November 2003, and in Japan, Tsumura's product was discontinued in 2012. CTA for emetine-induced saccharin solution was reported by our previous study(15,22).

Cisplatin-induced nausea and vomiting is one of the side effects of antineoplastic drugs, and antiemetic therapy is often given in parallel with cancer chemotherapy (23,24). Severe nausea and vomiting caused by the side effects of anticancer drugs not only reduce the quality of life, but also decrease the effectiveness of chemotherapy treatment due to reduced food intake caused by anorexia and a decrease in physical strength and natural healing power. In such cases, ondansetron or tropisetron, inhibitors of serotonin type 3 (5-HT_3) receptors, are often prescribed as antiemetic agents.

The symptoms of nausea and vomiting produced by cisplatin can be divided into acute (occurring in the first 24 h) and delayed (occurring 24–120 h post the start of chemotherapy) phases(25,26). The acute phase is very sensitive to the antagonistic effects of 5-HT_3 receptor antagonists(27). Therefore, 5-HT_3 receptor antagonists are often used as antiemetics in the clinic. Ondansetron is a 5-HT_3 receptor antagonist. As an antiemetic agent, it is effective and well tolerated in the prevention and treatment of emesis caused by cancer chemotherapy, radiation therapy and postoperative nausea and vomiting (28–32). However, the ability of 5-HT_3 receptor antagonists to reverse cisplatin-induced conditioned taste aversion is not well defined.

The present study was conducted to test the hypothesis that feeding behavior is suppressed by emetine- and cisplatin-induced conditioned taste aversion memory and that the mechanism involves neural information mediated by 5-HT_3 receptors. The ultimate goal of this study is to examine and discuss whether the central mechanism of CTA is associated with the pathogenesis of eating disorders.

2. Methods

2.1. Animals

Thirty-nine male Sprague-Dawley rats were used for the experiments. Their body weight was 180-220g at the beginning of every experiment period. Rats were individually kept in cages and the light/dark cycle was 12h. All animals were handled according to the Hokkaido University Animal Experiment Guidelines. Rats were feed by normal diet or self-made sweet diet. Sweet diet was prepared by mixing regular solid diet with an equal amount of 0.2% saccharin solution. The normal diet was also processed in the same way to match the texture.

2.2. Measuring sweet diet intake after obtaining CTA

We used modified CTA protocol as shown. Fig.1. We added the food deprivation to the protocol. The experiment was run for 12 days. Throughout of the experiment, rats were acclimated to a total of 20 h 40 min of water deprivation and 22 h 40 min of food deprivation per day.

An additional 1 h feeding, and 3 h drinking period began at 12:20 p.m. were given to rats for adequate food and water intake. The CTA conditioning with 0.1% saccharin solution was started at 10:00 a.m on experiment day 6 (the conditioning day). The unconditioned stimulus of emetine hydrochloride (5.54 mg/kg, 1% BW, i.p., n = 6) or cisplatin dihydrochloride (3mg/kg, 1% BW, i.p., n = 9) were applied at 10:20 a.m. In the control group of rats, saline (1% BW, i.p., n = 6) was used instead of emetine or cisplatin. On the day 7 for recorvery, rats drank distilled water instead of saccharin solution. On the test day 1 to 5 (experiment day 8‑12) , the rats were fed sweet diet instead of the normal diet for 20 min from every 10:00 a.m. The amount of sweet diet intake during this period was measured. The rats' body weight, fluid intake and normal diet intake were also measured on each experimental day.

Some cisplatin-conditioned groups received ondansetron (0.1 mg/kg, 0.1% BW, i.p.), a 5-HT_3 receptor antagonist, 30 min before the conditioned stimulus (n=6) or just before the start of the test (n = 5). In addition, some cisplatin conditioned groups were also tested on normal feed during the 20 min of tests 1-5 (n = 5).

2.3. Statistical analysis

The mean consumption of sweet diet was analyzed with a one-way analysis of variance. The comparisons of each test days with conditioning day were performed with the Dunnett's multiple test. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed with StatPlus (version 7.8.11).

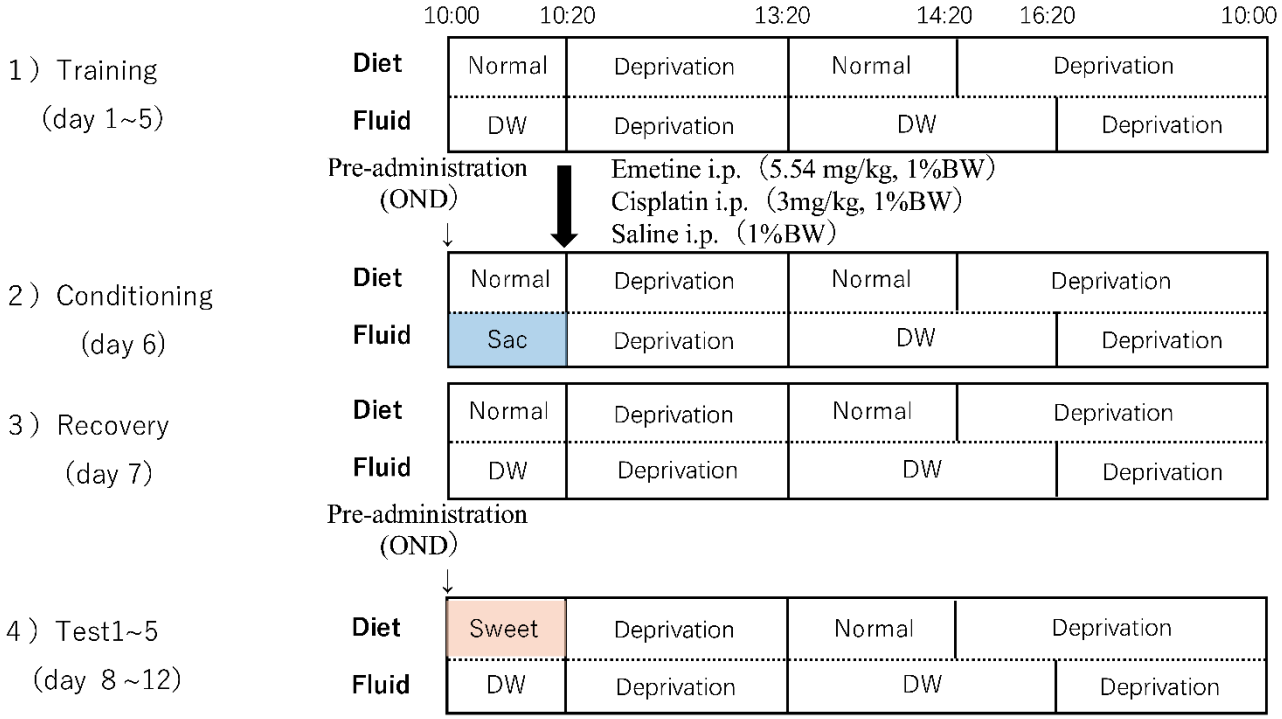

Fig.1. Modified CTA protocol with food deprivation and water deprivation schedule. 0.1% saccharin solution as conditioned stimulus; Emetine or cisplatin induced nausea as unconditioned stimulus. Saline injection as control group. Normal diet: homemade non-saccharin diet; Sweet diet: homemade diet containing 0.2% saccharin; Sac: saccharin solution; DW: distilled water. saccharin diet; Sac: saccharin solution; DW: distilled water.

3. Results

Fig.2 shows the changes of body weight between groups in conditioning day and every test day. The cisplatin-treated group showed a significant decrease compared to the saline-treated group on test 1-5 ($F(5,65) = 8.326$, $P < 0.05$) (Fig. 2B). While there was no significant weight loss in other groups.

Fig. 3 shows the amount of fluid intake per body weight (Fig. 3.1) and the fluid intake ratio (Fig. 3.2) in conditioning day and every test day. The cisplatin-treated group showed a significant decrease in fluid intake per body weight compared to the saline-treated group on test 1 and 4 ($F(5,65) = 2.654$, $P < 0.05$) (Fig. 3.1B).

Fig. 4 shows the amount of diet intake per body weight (Fig. 4.1) and the diet intake ratio (Fig. 4.2) in conditioning day and every test day. The emetine-treated group showed a significant decrease in sweet diet intake ratio on test 1-5 compared to saline-treated group ($F(5,50) = 5.159$, $P < 0.05$) (Fig. 4.2A), and showed a significant decrease in sweet diet intake ratio and sweet diet intake per body weight in the test 1-4 as compared to the conditioning day ($F(5,30) = 9.737$, $P < 0.05$ and $F(5,30) = 7.497$, $P < 0.05$) (Fig. 4.1A and Fig. 4.2A) . The cisplatin-treated group showed a significant decrease in sweet diet intake ratio and sweet diet intake per body weight in the test 1and 2 as

compared to the conditioning day ($F(5,48) = 2.55$, $P < 0.05$ and $F(5,48) = 4.639$, $P < 0.05$) (Fig. 4.1B and Fig. 4.2B). We also found that the amount of normal diet intake was not significantly reduced in test 1-5 (Fig. 4.1C and Fig. 4.2C). Pre-administration of ondansetron abolished the decrease in sweet diet intake in the cisplatin group (Fig. 4.1D and E, Fig. 4.2D and E). In the control group, sweet diet consumption was rather increased in the test 3-5 compared to conditioning days (Fig. 4.1A and Fig 4.2A).

4. Discussion

The emetine-induced CTA group showed no weight loss during the experimental period, while the cisplatin-induced CTA group showed significant weight loss compared to the conditioning day. It was found that ondansetron treatment prevented weight loss in the cisplatin-treated group. In addition, rats that acquired CTA to the sweet taste of saccharin showed suppressed feeding behavior even in the fasting state. Furthermore, it was suggested that this feeding inhibition may be mediated by 5-HT_3 receptors. These results suggest that CTA may alter feeding behavior and provide useful information for further research on the central mechanism of eating disorders.

Previous studies have demonstrated that after avoiding the conditioning of a specific flavor, the drinking of a specific flavor solution is suppressed even in a state of thirst(15–18,33,34). Emetine- and cisplatin-induced CTA to saccharin solution has been also demonstrated in our previous study in rats (22). The present study demonstrates a decrease in specific flavored diet after the development of CTA.

Ondansetron, 5-HT_3 receptor antagonist, is widely used for the prevention and treatment of nausea and emesis caused by the cancer chemotherapy, the radiation therapy and the postoperative nausea and vomiting. Previous studies have shown that ondansetron is effective in preventing vomiting in animal models (35–39) . This highlights the close involvement of 5-HT_3 receptors in the mechanisms of nausea and vomiting. The antiemetic effect of these antagonists is believed to target the afferent vagal nerve, as well as regions in the brainstem of the area postrema and the nucleus tractus solitarius (40–42). Although rats are non-vomiting animals, 5-HT_3 receptors are also present in both the vagal nerve and the brainstem (43–45), making them valuable models for studying CTA. In humans, 5-HT_3 receptor antagonists effectively prevent nausea and vomiting induced by emetic substances such as ipecacuanha and cisplatin (46,47), which is similar with our findings in the present study. Therefore, we propose that the central mechanisms involved in CTA could be linked to eating disorders, such as anorexia nervosa.

Although previous papers have shown the unlikely involvement of 5-HT_3 receptors in the mechanism that induces CTA in rats (16,17), 5-HT_3 receptor antagonist injections did not reverse the reduction in saccharin solution intake in the conditioned taste aversion state induced by cisplatin (17). It has been shown that advance injection of ondansetron reduces toxicant-induced aversion (48) and antagonizes cisplatin-induced kaolin ingestion (49–51).This difference could stem from differences in the mechanisms of eating and drinking behaviors. Cannon and Washburn, for example, proposed that hunger arises from "hunger pains" caused by the friction of an empty stomach's walls rubbing against each other (52). This was demonstrated that the destruction of a

longitudinal pathway connecting the paraventricular hypothalamus and hindbrain regions was responsible for hypothalamic hyperphagia (53,54). Thirst, in contrast, is triggered by signals from the hypothalamic drinking center, which responds to elevated blood osmolality levels in animals with nervous systems, including humans.

In this study, we used saccharin solution as the conditioned stimulus, and although we obtained the desired results, there are some limitations because the conditioned stimulus is different from the measurement data for evaluating the acquisition of CTA. Moreover, the homemade sweet diet in this study is not purely sweet, so we have to take into account that the sweetened feed used in this experiment tasted of sweetness mixed with regular feed. Although there are some previous studies on the taste sensation of rats (55–61), we are not sure that the ratio of the homemade diet we used in this study was appropriate for the rats. Despite these limitations, we hope to contribute to the study of the central mechanisms of CTA and the etiology of eating disorders by further consideration based on the results of this study.

5. Acknowledgments

The Grants-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology in Japan (22K09900), The Akiyama Life Science Foundation, and JST SPRING (JPMJSP2119).

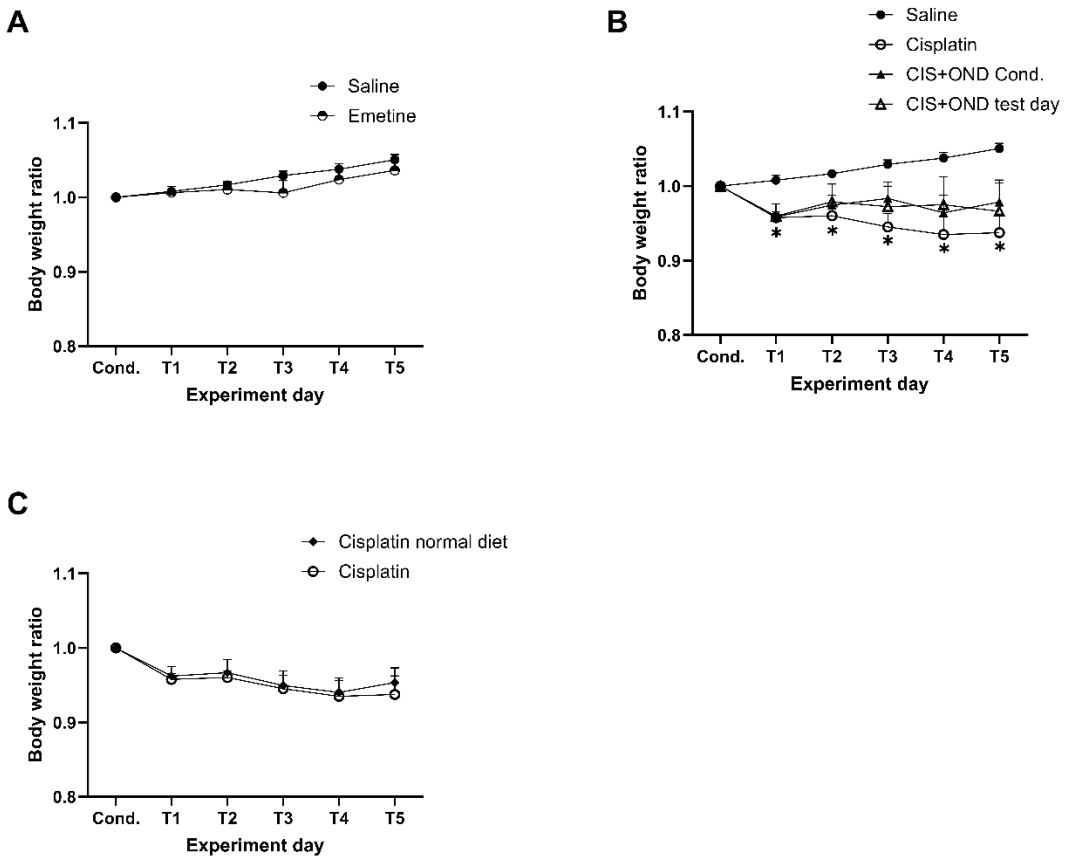

Fig. 2 Temporal change of body weight. Body weight in the group of saline injection and emetine hydrochloride on conditioning day (A), saline injection, cisplatin dihydrochloride on conditioning day and pre-administration of ondansetron on conditioning day (CIS+OND Cond.) or on test days (CIS+OND test day) in cisplatin treated group, (B), cisplatin dihydrochloride injection on conditioning day and cisplatin dihydrochloride injection on conditioning day but give normal diet on test day (C). *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

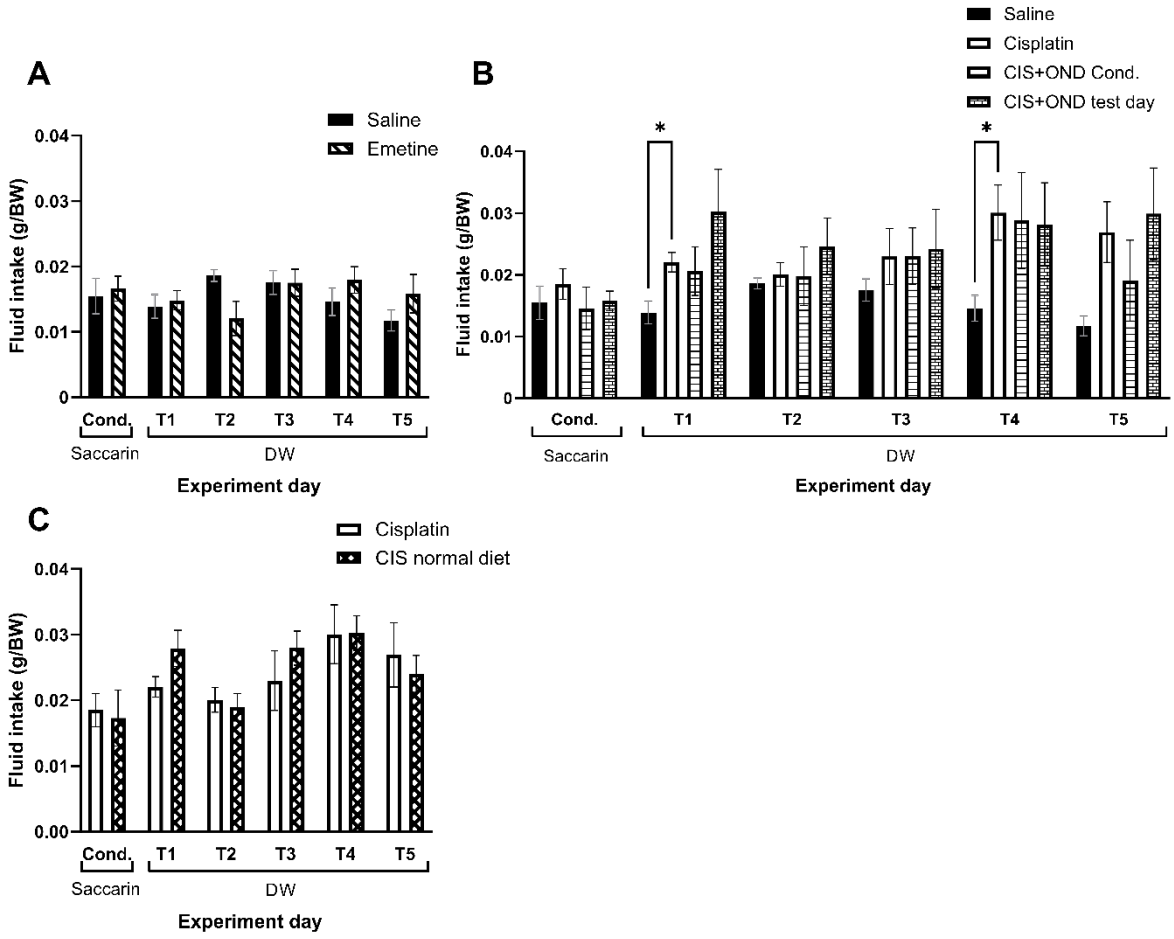

Fig. 3.1 Temporal change of fluid intake per body weight. Fluid intake in the group of saline injection and emetine hydrochloride on conditioning day (A), saline injection, cisplatin dihydrochloride on conditioning day and pre-administration of ondansetron on conditioning day (CIS+OND Cond.) or on test days (CIS+OND test day) in cisplatin treated group (B), cisplatin dihydrochloride injection on conditioning day and cisplatin dihydrochloride injection on conditioning day but give normal diet on test day (C). *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

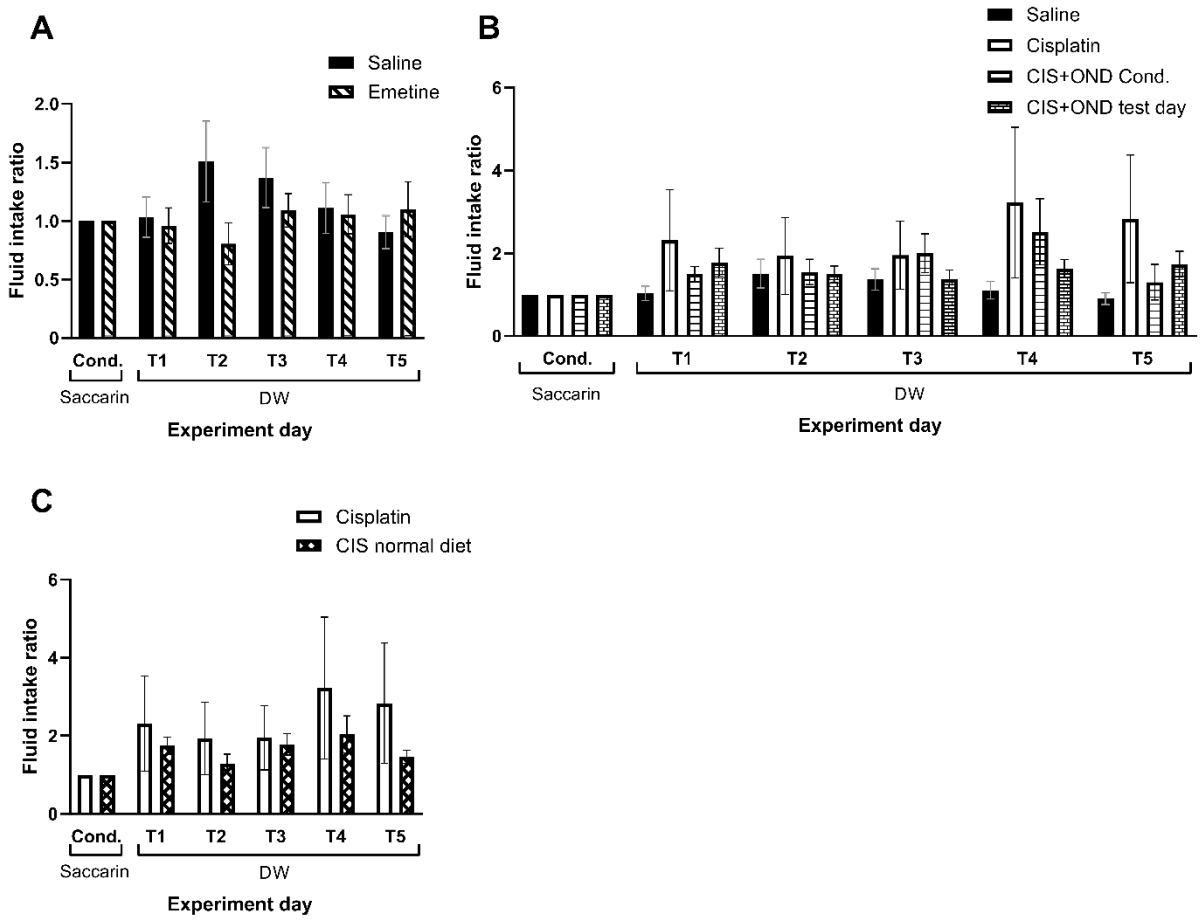

Fig. 3.2 Temporal change of fluid intake ratio. Fluid intake in the group of saline injection and emetine hydrochloride on conditioning day (A), saline injection, cisplatin dihydrochloride on conditioning day and pre-administration of ondansetron on conditioning day (CIS+OND Cond.) or on test days (CIS+OND test day) in cisplatin treated group (B), cisplatin dihydrochloride injection on conditioning day and cisplatin dihydrochloride injection on conditioning day but give normal diet on test day (C).*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

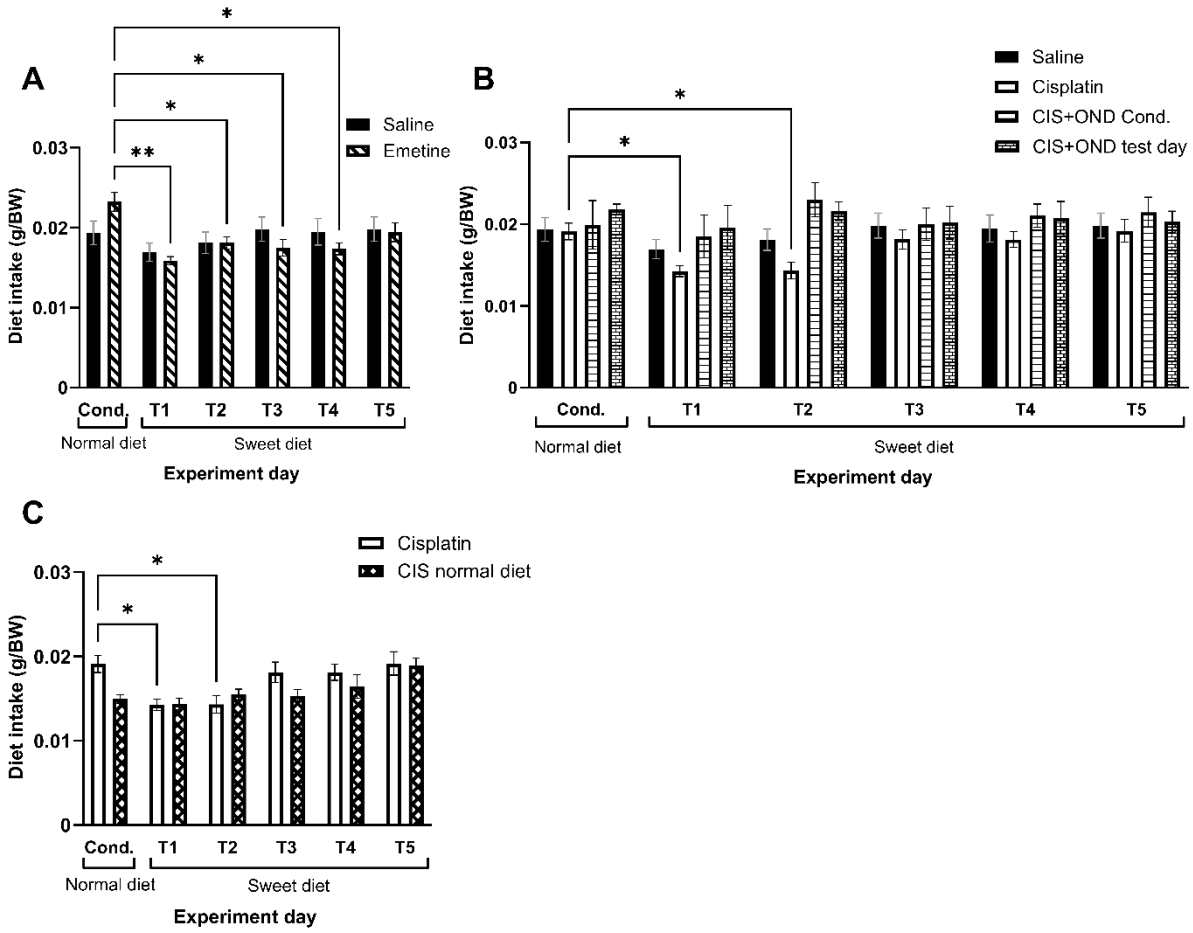

Fig. 4.1 Temporal change of diet intake per body weight Diet intake in the group of saline injection and emetine hydrochloride on conditioning day (A), saline injection, cisplatin dihydrochloride on conditioning day and pre-administration of ondansetron on conditioning day (CIS+OND Cond.) or on test days (CIS+OND test day) in cisplatin treated group (B), cisplatin dihydrochloride injection on conditioning day and cisplatin dihydrochloride injection on conditioning day but give normal diet on test day (C). *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

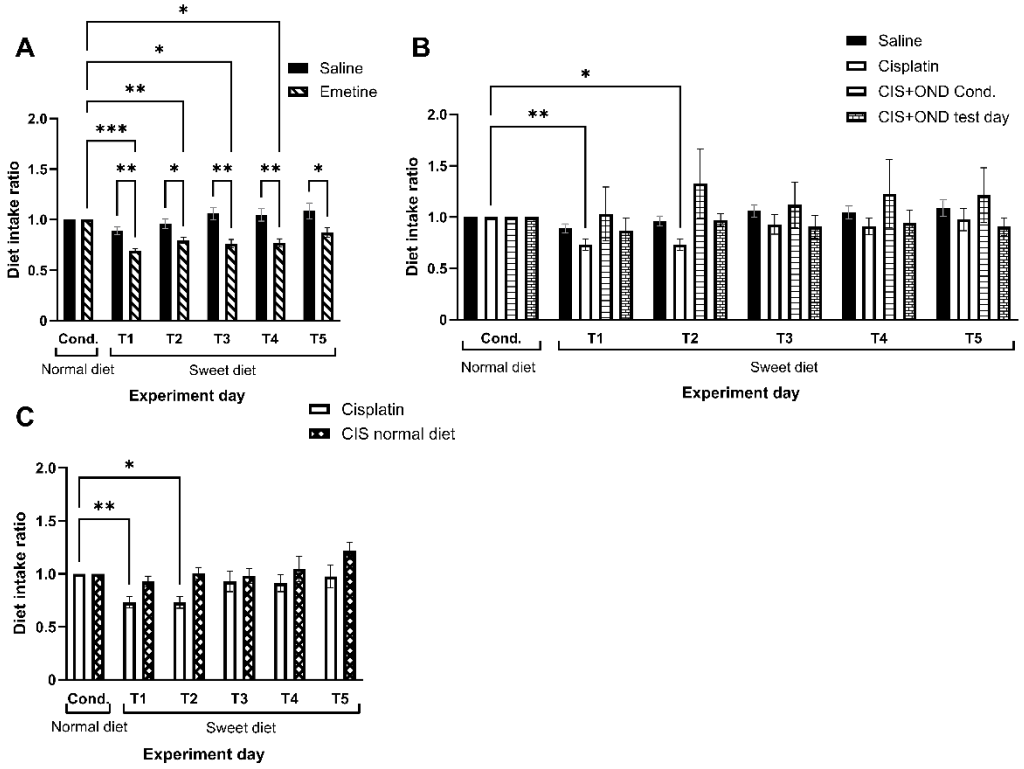

Fig. 4.2 Temporal change of diet intake ratio. Diet intake in the group of saline injection and emetine hydrochloride on conditioning day (A), saline injection, cisplatin dihydrochloride on conditioning day and pre-administration of ondansetron on conditioning day (CIS+OND Cond.) or on test days (CIS+OND test day) in cisplatin treated group (B), cisplatin dihydrochloride injection on conditioning day and cisplatin dihydrochloride injection on conditioning day but give normal diet on test day (C). *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

References

1. Garcia J, Kimeldorf DJ, Koelling RA. Conditioned Aversion to Saccharin Resulting from Exposure to Gamma Radiation. Science. 1955 Jul 22;122(3160):157–8.
2. Garcia J, Hankins WG, Rusiniak KW. Behavioral Regulation of the Milieu Interne in Man and Rat: Food preferences set by delayed visceral effects facilitate memory research and predator control. Science. 1974 Sep 6;185(4154):824–31.
3. Yamamoto T, Azuma S, Kawamura Y. Significance of cortical-amygdalar-hypothalamic connections in retention of conditioned taste aversion in rats. Exp Neurol. 1981 Dec;74(3):758–68.
4. Yamamoto T, Matsuo R, Kiyomitsu Y, Kitamura R. Taste responses of cortical neurons in freely ingesting rats. J Neurophysiol. 1989 Jun 1;61(6):1244–58.
5. Kalivas PW, Duffy P. D1 receptors modulate glutamate transmission in the ventral tegmental area. J Neurosci Off J Soc Neurosci. 1995 Jul;15(7 Pt 2):5379–88.
6. Yamamoto T, Fujimoto Y, Shimura T, Sakai N. Conditioned taste aversion in rats with excitotoxic brain lesions. Neurosci Res. 1995 Mar;22(1):31–49.
7. Bermudez-Rattoni F, McGaugh JL. Insular cortex and amygdala lesions differentially affect acquisition on inhibitory avoidance and conditioned taste aversion. Brain Res. 1991 May;549(1):165–70.
8. Roth SR, Schwartz M, Teitelbaum P. Failure of recovered lateral hypothalamic rats to learn specific food aversions. J Comp Physiol Psychol. 1973;83(2):184–97.
9. Miller JS, Nonneman AJ, Kelly KS, Neisewander JL, Isaac WL. Disruption of neophobia, conditioned odor aversion, and conditioned taste aversion in rats with hippocampal lesions. Behav Neural Biol. 1986 Mar;45(2):240–53.
10. Jay Braun J, Slick TB, Lorden JF. Involvement of gustatory neocortex in the learning of taste aversions. Physiol Behav. 1972 Oct;9(4):637–41.
11. Burešová O, Bureš J. Cortical and subcortical components of the conditioned saccharin aversion. Physiol Behav. 1973 Oct;11(4):435–9.
12. Desmedt A, Hazvi S, Dudai Y. Differential Pattern of cAMP Response Element-Binding Protein Activation in the Rat Brain after Conditioned Aversion as a Function of the Associative Process Engaged: Taste versus Context Association. J Neurosci. 2003 Jul 9;23(14):6102–10.
13. Ma L, Wang DD, Zhang TY, Yu H, Wang Y, Huang SH, et al. Region-Specific Involvement of BDNF Secretion and Synthesis in Conditioned Taste Aversion Memory Formation. J Neurosci. 2011 Feb 9;31(6):2079–90.
14. Yasoshima Y, Scott TR, Yamamoto T. Memory-dependent c-Fos expression in the nucleus accumbens and extended amygdala following the expression of a conditioned taste aversive in the rat. Neuroscience. 2006;141(1):35–45.
15. Su S, Fujita M, Wei Z, Huang H, Yoshizawa T, Inui T, et al. Effects of area postrema lesions and bilateral subdiaphragmatic afferent vagotomy on emetine-induced conditioned taste avoidance in rats. Physiol Behav. 2021 Nov;241:113565.
16. Mele PC, McDonough JR, McLean DB, O'Halloran KP. Cisplatin-induced conditioned taste aversion: attenuation by dexamethasone but not zacopride or GR38032F. Eur J Pharmacol. 1992 Aug;218(2–3):229–36.
17. Rudd JA, Ngan MP, Wai MK. 5-HT3 receptors are not involved in conditioned taste aversions induced by 5-hydroxytryptamine, ipecacuanha or cisplatin. Eur J Pharmacol. 1998 Jul;352(2–3):143–9.

18. Nissenbaum JW, Sclafani A. Qualitative differences in polysaccharide and sugar tastes in the rat: A two-carbohydrate taste model. Neurosci Biobehav Rev. 1987 Jun;11(2):187–96.
19. Inui T, Shimura T, Yamamoto T. The role of the ventral pallidum GABAergic system in conditioned taste aversion: Effects of microinjections of a GABAA receptor antagonist on taste palatability of a conditioned stimulus. Brain Res. 2007 Aug;1164:117–24.
20. Höjer J, Troutman WG, Hoppu K, Erdman A, Benson BE, Mégarbane B, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. Clin Toxicol. 2013 Mar;51(3):134–9.
21. Hasegawa M, Sasaki T, Sadakane K, Tabuchi M, Takeda Y, Kimura M, et al. Studies for the Emetic Mechanisms of Ipecac Syrup (TJN-119) and Its Active Components in Ferrets: Involvement of 5-Hydroxytryptamine Receptors. Jpn J Pharmacol. 2002;89(2):113–9.
22. Su S, Wei Z, Huang H, Yoshizawa T, Inui T, Funahashi M. Conditioned nausea induced by cisplatin and emetine identified by a taste reactivity test in rats. Physiol Behav. 2023 Oct;269:114278.
23. Kosmas C, Tsavaris NB, Malamos NA, Vadiaka M, Koufos C. Phase II Study of Paclitaxel, Ifosfamide, and Cisplatin as Second-Line Treatment in Relapsed Small-Cell Lung Cancer. J Clin Oncol. 2001 Jan 1;19(1):119–26.
24. Oun R, Moussa YE, Wheate NJ. The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans. 2018;47(19):6645–53.
25. Kris MG, Gralla RJ, Clark RA, Tyson LB, O'Connell JP, Wertheim MS, et al. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. J Clin Oncol. 1985 Oct;3(10):1379–84.
26. Martin M. The Severity and Pattern of Emesis following Different Cytotoxic Agents. Oncology. 1996;53(1):26–31.
27. Kris MG, Roila F, De Mulder PHM, Marty M. Delayed emesis following anticancer chemotherapy. Support Care Cancer. 1998 Apr 27;6(3):228–32.
28. Csáki C, Ferencz T, Koós R, Schuler D, Borsi J. [Use of ondansetron, a 5-HT3 receptor antagonist, as a new type of antiemetic in pediatric oncology]. Orv Hetil. 1993 Jun 20;134(25):1363–7.
29. Karim F, Roerig SC, Saphier D. Role of 5-hydroxytryptamine3 (5-HT3) antagonists in the prevention of emesis caused by anticancer therapy. Biochem Pharmacol. 1996 Sep;52(5):685–92.
30. Perez EA. Use of dexamethasone with 5-HT3-receptor antagonists for chemotherapy-induced nausea and vomiting. Cancer J Sci Am. 1998;4(2):72–7.
31. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2011 Nov 1;29(31):4189–98.
32. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010 May;21:v232–43.
33. Sato T, Hirai Y, Su S, Zimo W, Yasuura N, Inui T, et al. Involvement of the area postrema and the nucleus tractus solitarius in the emetogenic action of emetine in rats. J Oral Biosci. 2020 Dec;62(4):310–4.
34. Shi J. Evaluating the various phases of cisplatin-induced emesis in rats. Oncol Lett. 2014 Nov;8(5):2017–22.
35. Andrews PLR, Rapeport WG, Sanger GJ. Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol Sci. 1988 Sep;9(9):334–41.

36. Smith WL, Alphin RS, Jackson CB, Sancilio LF. The Antiemetic Profile of Zacopride. J Pharm Pharmacol. 2011 Apr 12;41(2):101–5.
37. Stables R, Andrews PLR, Bailey HE, Costall B, Gunning SJ, Hawthorn J, et al. Antiemetic properties of the 5HT3-receptor antagonist, gr38032f. Cancer Treat Rev. 1987 Dec;14(3–4):333–6.
38. Sanger GJ. New antiemetic drugs. Can J Physiol Pharmacol. 1990 Feb 1;68(2):314–24.
39. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. Br J Pharmacol. 1986 Jul;88(3):497–9.
40. Higgins GA, Kilpatrick GJ, Bunce KT, Jones BJ, Tyers MB. 5-HT $_3$ receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br J Pharmacol. 1989 May;97(1):247–55.
41. Kamato T, Ito H, Nagakura Y, Nishida A, Yuki H, Yamano M, et al. Mechanisms of cisplatin- and m-chlorophenylbiguinide-induced emesis in ferrets. Eur J Pharmacol. 1993 Jul;238(2–3):369–76.
42. Miller AD, Nonaka S. Mechanisms of vomiting induced by serotonin-3 receptor agonists in the cat: effect of vagotomy, splanchnicectomy or area postrema lesion. J Pharmacol Exp Ther. 1992 Feb;260(2):509–17.
43. Kilpatrick GJ, Jones BJ, Tyers MB. Binding of the 5-HT3 ligand, [3H]GR65630, to rat area postrema, vagus nerve and the brains of several species. Eur J Pharmacol. 1989 Jan;159(2):157–64.
44. Sutton RL, Fox RA, Daunton NG. Role of the area postrema in three putative measures of motion sickness in the rat. Behav Neural Biol. 1988 Sep;50(2):133–52.
45. Ossenkopp KP, Giugno L. Nicotine-induced conditioned taste aversions are enhanced in rats with lesions of the area postrema. Pharmacol Biochem Behav. 1990 Jul;36(3):625–30.
46. Minton N. Volunteer models for predicting antiemetic activity of 5-HT3-receptor antagonists. Br J Clin Pharmacol. 1994 Jun;37(6):525–30.
47. Yarker YE, McTavish D. Granisetron: An Update of its Therapeutic Use in Nausea and Vomiting Induced by Antineoplastic Therapy. Drugs. 1994 Nov;48(5):761–93.
48. Balleine B, Gerner C, Dickinson A. Instrumental outcome devaluation is attenuated by the anti-emetic ondansetron. Q J Exp Psychol B. 1995 Aug;48(3):235–51.
49. Saeki M, Sakai M, Saito R, Kubota H, Ariumi H, Takano Y, et al. Effects of HSP-117, a Novel Tachykinin NK-Receptor Antagonist, on Cisplatin-Induced Pica as a New Evaluation of Delayed Emesis in Rats. Jpn J Pharmacol. 2001;86(3):359–62.
50. Takeda N, Hasegawa S, Morita M, Matsunaga T. Pica in rats is analogous to emesis: An animal model in emesis research. Pharmacol Biochem Behav. 1993 Aug;45(4):817–21.
51. Rudd JA, Yamamoto K, Yamatodani A, Takeda N. Differential action of ondansetron and dexamethasone to modify cisplatin-induced acute and delayed kaolin consumption (“pica”) in rats. Eur J Pharmacol. 2002 Nov;454(1):47–52.
52. Cannon WB, Washburn AL. An Explanation of Hunger [1]. Obes Res. 1993 Nov;1(6):494–500.
53. Kirchgessner AL, Sclafani A. PVN-hindbrain pathway involved in the hypothalamic hyperphagia-obesity syndrome. Physiol Behav. 1988 Jan;42(6):517–28.
54. Gold RM, Jones AP, Sawchenko PE, Kapatos G. Paraventricular area: Critical focus of a longitudinal neurocircuitry mediating food intake. Physiol Behav. 1977 Jun;18(6):1111–9.
55. Xu H, Staszewski L, Tang H, Adler E, Zoller M, Li X. Different functional roles of T1R subunits in the heteromeric taste receptors. Proc Natl Acad Sci. 2004 Sep 28;101(39):14258–63.
56. Bachmanov AA. Positional Cloning of the Mouse Saccharin Preference (Sac) Locus. Chem Senses. 2001 Sep 1;26(7):925–33.

57. Hoon MA, Adler E, Lindemeier J, Battey JF, Ryba NJP, Zuker CS. Putative Mammalian Taste Receptors. Cell. 1999 Feb;96(4):541–51.
58. Max M, Shanker YG, Huang L, Rong M, Liu Z, Campagne F, et al. Tas1r3, encoding a new candidate taste receptor, is allelic to the sweet responsiveness locus Sac. Nat Genet. 2001 May;28(1):58–63.
59. Montmayeur JP, Liberles SD, Matsunami H, Buck LB. A candidate taste receptor gene near a sweet taste locus. Nat Neurosci. 2001 May;4(5):492–8.
60. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJP, Zuker CS. Mammalian Sweet Taste Receptors. Cell. 2001 Aug;106(3):381–90.
61. Sainz E, Korley JN, Battey JF, Sullivan SL. Identification of a novel member of the T1R family of putative taste receptors. J Neurochem. 2001 May;77(3):896–903.