ELSEVIER

European Journal of Pharmacology 352 (1998) 143–149

ejp

5-HT_3 receptors are not involved in conditioned taste aversions induced by 5-hydroxytryptamine, ipecacuanha or cisplatin

John A. Rudd *, Man P. Ngan, Man K. Wai

Department of Pharmacology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin NT, Hong Kong, China

Received 29 January 1998; revised 6 May 1998; accepted 8 May 1998

Abstract

We have used the rat to examine the involvement of the 5-HT_3 receptor in the mechanism(s) of conditioned taste aversion induced by 5-hydroxytryptamine (5-HT) and selected emetic drugs. 5-HT, ipecacuanha and cisplatin all induced conditioned taste aversion at doses known to induce emesis in other species but the responses were resistant to treatment with the 5-HT_3 receptor antagonists ondansetron and granisetron. Further, *m*-chlorophenylbiguanide, a selective and potent 5-HT_3 receptor agonist, failed to induce a conditioned taste aversion. The data provide strong evidence that the 5-HT_3 receptor is not involved in conditioned taste aversion mechanisms in the rat. Results are discussed in terms of the usefulness of the rat conditioned taste aversion paradigm to anti-emetic research.

Keywords: 5-HT_3 receptor; Conditioned taste aversion; (Rat)

1. Introduction

We have been recently interested in the development of animal models to accurately mimic the severe nausea and vomiting response induced by cisplatin in man (Naylor and Rudd, 1996; Rudd et al., 1994, 1996). Whilst it is technically simple to assess the effect of a drug on the vomiting response, it is considered more problematic to assess its effect on nausea (Fox, 1992). However, conditioned taste aversion induced by some toxins in the rat is considered to reflect the activation of pathways that are analogous to those involved in nausea and/or vomiting in other species (Fox, 1992; Grant, 1987). We have therefore focused an interest to the use of the conditioned taste aversion paradigm in the rat, a species that does not vomit, to assess the mechanisms involved in nausea and the role of the (5-hydroxytryptamine$_3$) 5-HT_3 receptor.

The basic conditioned taste aversion paradigm involves pairing a novel gustatory cue (the conditioned stimulus) with the administration of a toxic or emetic substance (the unconditioned stimulus). Toxic substances are hypothesized to produce a sensation of nausea or vomiting that causes the animal to avoid the ingestion of the gustatory cue on a subsequent test-day. The test-day can involve presenting the animal with a choice of water and the gustatory cue (e.g., saccharin solution) to record the relative preference for each solution as an index of conditioned taste aversion: the test usually commences 24–48 h after the injection of the toxin (Mele et al., 1992).

The cisplatin-induced conditioned taste aversion model has recently been used to investigate the role of the 5-HT_3 receptor in the mediation of the response (Mele et al., 1992). However, the 5-HT_3 receptor antagonists, ondansetron and zacopride, whilst highly effective to prevent emesis in animal models (Andrews et al., 1988; Smith et al., 1989; Stables et al., 1987), are ineffective to prevent the cisplatin-induced conditioned taste aversion in the rat (Mele et al., 1992). The failure of the 5-HT_3 receptor antagonists to prevent the cisplatin-induced conditioned taste aversion may suggest that other unspecified mechanisms are likely to be involved.

An alternative explanation is possible when we consider that, in the clinic, the nausea and emesis induced by cisplatin is characterized by 'acute' (the first 24 h) and 'delayed' (post-24 h) phases (Butcher, 1993; Martin, 1996). The 'acute', but not the 'delayed' phase is almost completely prevented by the use of 5-HT_3 receptor antagonists (Kris et al., 1992; Morrow et al., 1995). It seems pertinent to realize that the standard conditioned taste aversion

* Corresponding author. Tel.: +852-2609-6789; fax: +852-2603-5139; e-mail: jar@cuhk.edu.hk

0014-2999/98/$19.00

preference test in the rat is usually conducted at a time corresponding to the delayed phase of emesis in man. Under these circumstances, therefore, it would be extremely unlikely that a single injection of a 5-HT_3 receptor antagonist would be able to prevent the cisplatin-induced conditioned taste aversion.

In the present studies, we attempt to re-evaluate the role of the 5-HT_3 receptor in the mechanism of drug-induced conditioned taste aversion. To achieve this, we selected three relatively short-acting emetogens to use as unconditioned stimuli. The emetogens selected included 5-HT, the selective 5-HT_3 receptor agonist, *m*-chlorophenylbiguanide and ipecacuanha. Importantly, these agents can be considered suitable to use as unconditioned stimuli since the emesis is known to be completely prevented by pretreatment with a single injection of 5-HT_3 receptor antagonists (Costall et al., 1990; Kamato et al., 1993; Miller and Nonaka, 1992; Torii et al., 1991). For comparative purposes, we also re-examined the role of the 5-HT_3 receptor in mediating conditioned taste aversion induced by cisplatin.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats (350–450 g), obtained from the Chinese University of Hong Kong, were housed individually at 21 ± 2°C with 40–60% relative humidity and were fed a dry pellet diet (Rodent Diet,

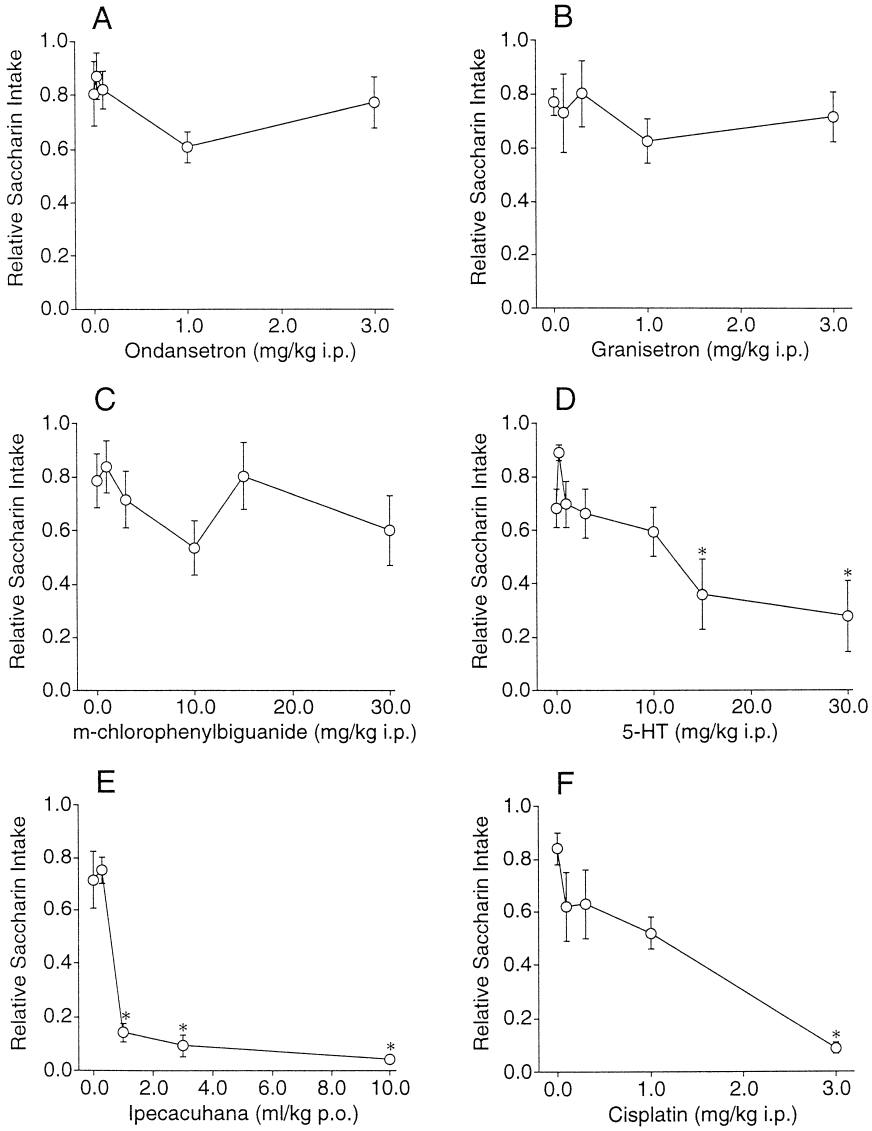

Fig. 1. The potential of ondansetron (0.1–3 mg/kg i.p. (A)), granisetron (0.1–3 mg/kg i.p. (B)), *m*-chlorophenylbiguanide (1–30 mg/kg i.p. (C)), 5-HT (0.3–30 mg/kg i.p. (D)), ipecacuanha (0.3–10 ml/kg p.o. (E)) and cisplatin (0.3–3 mg/kg i.p. (F)) to induce a conditioned taste aversion in the rat. Data represent the mean ± S.E.M. of three to eight determinations. Significant differences between the relative saccharin intake of vehicle/sham treated animals and drug treated animals are indicated as $* P < 0.05$ (ANOVA with post-hoc Bonferroni *t*-test).

Ridley Agriculture Products, Australia). Water was freely available prior to the start of the training. A 12-h artificial light cycle (lights on between 0600 to 1800 h) was used throughout the study.

2.2. Conditioning protocol

All training and testing were conducted in the rat homecage following a similar protocol as described by Mele et al. (1992). There was an initial 10-day training period where a single water bottle was presented for only 30 min/day (commencing at 1000 h) to each rat. On day 11, the conditioning day, a novel saccharin solution (0.1% w/v) was substituted for water. All vehicle and drug administrations were given after the removal of the saccharin solution (see Section 2.3). On day 12, the rats were presented with a single bottle of water for 30 min. On day 13, the preference test was conducted where one bottle of water and one bottle of saccharin solution was simultaneously presented for 30 min. The relative saccharin intake on day 13 (volume of saccharin solution intake divided by the volume of total fluid intake) was used as the index of conditioned taste aversion. Rats that lost $>10\%$ of their original starting body weight during the course of the experiment, or that failed to drink the saccharin solution on day 11, were excluded from data analysis.

2.3. Drug treatments

Ondansetron, granisetron, 5-HT, *m*-chlorophenylbiguanide, ipecacuanha and cisplatin were evaluated to examine their conditioned taste aversion-inducing potential.

Ondansetron or granisetron or vehicle was administered immediately after the removal of the saccharin solution. 5-HT, *m*-chlorophenylbiguanide, ipecacuanha and cisplatin or respective vehicles were administered 40 min after the removal of the saccharin solution.

To evaluate the drug interactions, each rat received two drug administrations (drug or vehicle) at the appropriate times after drinking. In some experiments, granisetron was administered immediately after and at 6 h post-saccharin removal.

Ondansetron (Glaxo Wellcome), granisetron (SmithKline Beecham), 5-HT (Sigma) and *m*-chlorophenylbiguanide (Research Biochemical International) were dissolved in saline (0.9% w/v) and injected intraperitoneally (i.p.) in a volume of 1 ml/kg. Cisplatin (David Bull Laboratories) was formulated in 0.1% w/v mannitol (in saline 0.9% w/v) and was injected i.p. in a volume of 3 ml/kg. Ipecacuanha (Thornton and Ross) was formulated according to the British Pharmacopoeia (1993).

2.4. Data analysis

Relative saccharin solution intake during the choice-test on day 13 was analyzed by a one-way analysis of variance (ANOVA) followed by a post-hoc Bonferroni *t*-test. Differences were considered statistically significant if $P < 0.05$.

3. Results

3.1. Drinking performance of rats during the study

At the beginning of the training period the rats consumed approximately 15 ml of water in the 30-min presentation period. The volume of water consumed gradually increased and by day 8 had stabilized to approximately 23 ml. On the drug/vehicle injection day (day 13), the animals consumed approximately 20 ml of the novel saccharin solution.

3.2. Conditioned taste aversion-inducing potential of 5-HT$_3$ receptor antagonists and emetogens

Ondansetron (0.1–3 mg/kg i.p.; Fig. 1A), granisetron (0.1–3 mg/kg i.p.; Fig. 1B) and *m*-chlorophenylbiguanide (0–30 mg/kg i.p.; Fig. 1C) failed to induce a conditioned taste aversion ($P > 0.05$). However, 5-HT produced a weak conditioned taste aversion at 15 and 30 mg/kg i.p. (the maximum reduction of relative saccharin intake was 61.9%; $P < 0.05$; Fig. 1D) but was associated with immobility (i.e., rats were unable to stand) that lasted for approximately 120 min.

The conditioned taste aversion potential of ipecacuanha was assessed by comparison with a sham administration of the drug. Using this protocol, ipecacuanha was found to be effective to induce a conditioned taste aversion ($P < 0.05$)

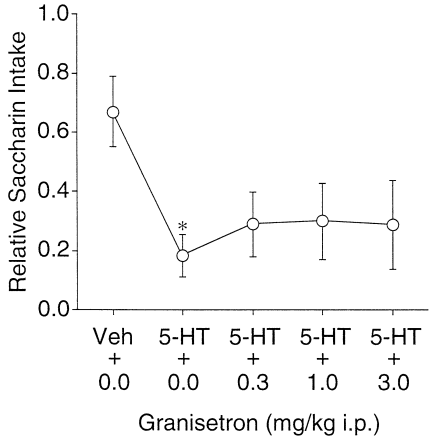

Fig. 2. Failure of granisetron (0.3–3 mg/kg i.p.) to reverse the conditioned taste aversion induced by 5-HT (15 mg/kg i.p.) in the rat. Data represent the mean ± S.E.M. of six to seven determinations. Granisetron or vehicle was administered as a 40-min pretreatment prior to the administration of 5-HT. Significant differences between the relative saccharin intake of 5-HT vehicle (Veh) + granisetron vehicle (0.0 mg/kg) treated animals and 5-HT + granisetron treated animals are indicated as * $P < 0.05$ (ANOVA with post-hoc Bonferroni *t*-test).

at doses as low as 1 ml/kg p.o. (the maximum reduction of saccharin intake was 94.4%; Fig. 1E). Cisplatin also produced a dose-dependent conditioned taste aversion (the maximum reduction of saccharin intake was 89.3%) that was statistically significant at 3 mg/kg i.p. ($P < 0.05$; Fig. 1F).

3.3. Failure of granisetron to reverse the 5-HT-induced conditioned taste aversion

A dose of 5-HT, 15 mg/kg i.p., was selected to induce a conditioned taste aversion for the reversal studies. However, this dose did not induce conditioned taste aversion in some experiments and we were therefore unable to test the effect of ondansetron. However, in one experiment, 5-HT produced a significant 73.1% reduction of relative saccharin intake ($P < 0.05$) but this was not antagonized by pretreatment with granisetron (0.3–3 mg/kg i.p.; Fig. 2).

3.4. Failure of ondansetron and granisetron to reverse ipecacuanha-induced conditioned taste aversion

Ipecacuanha 3 ml/kg p.o. was selected as a reliable dose to produce a conditioned taste aversion and reduced the relative saccharin intake by approximately 73% (range: 55.3 to 91.5%; $P < 0.05$). However, both ondansetron (0.3–3 mg/kg i.p.) and granisetron (0.3–3 mg/kg i.p.), administered as single injections, failed to reverse the ipecacuanha-induced conditioned taste aversion ($P > 0.05$; Fig. 3). This prompted an evaluation of the potential of two injections of granisetron (0.3–3 mg/kg i.p.) to reverse the ipecacuanha-induced conditioned taste aversion. The injections of granisetron were administered 40 min prior to and 6 h following the oral administration of ipecacuanha

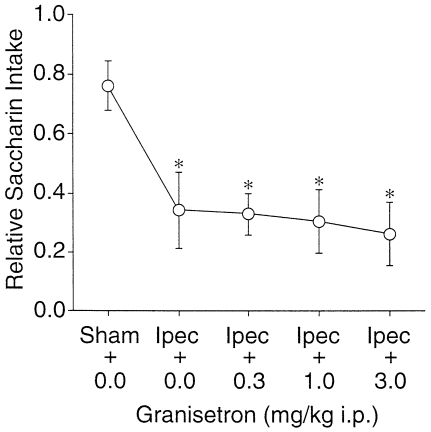

Fig. 4. Failure of a repeated administration of granisetron (0.3–3 mg/kg i.p.) to reverse the conditioned taste aversion induced by ipecacuanha (3 ml/kg p.o.) in the rat. Data represent the mean ± S.E.M. of four to eight determinations. Granisetron or vehicle was administered 40 min prior to and 6 h post the administration of ipecacuanha (Ipec). Significant differences between the relative saccharin intake of Ipec sham (sham) + granisetron vehicle (0.0 mg/kg) treated animals and Ipec + granisetron treated animals are indicated as $* P < 0.05$ (ANOVA with post-hoc Bonferroni *t*-test).

but similarly failed to reverse the conditioned taste aversion ($P > 0.05$; Fig. 4).

3.5. Failure of ondansetron and granisetron to reverse the cisplatin-induced conditioned taste aversion

A dose of cisplatin, 3 mg/kg i.p., was selected for the reversal studies and produced 70.3 to 93.7% reductions in the relative saccharin intake ($P < 0.05$) that were not reversed by either ondansetron (0.3–3 mg/kg i.p., $P >$

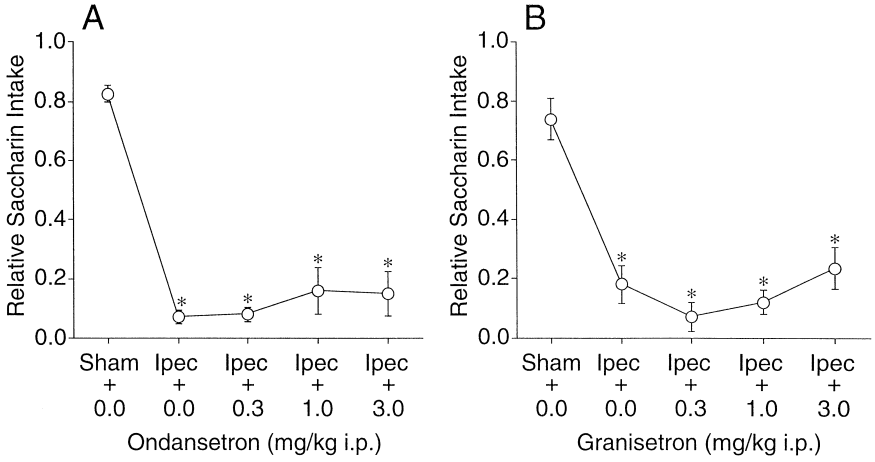

Fig. 3. Failure of a single administration of ondansetron (0.3–3 mg/kg i.p.) or granisetron (0.3–3 mg/kg i.p.) to reverse the conditioned taste aversion induced by ipecacuanha (3 ml/kg p.o.) in the rat. Data represent the mean ± S.E.M. of four to eight determinations. Ondansetron, granisetron or vehicle was administered as a 40-min pretreatment prior to the administration of ipecacuanha (Ipec). Significant differences between the relative saccharin intake of Ipec sham (sham) + ondansetron or granisetron vehicle (0.0 mg/kg) treated animals and Ipec + ondansetron or granisetron treated animals are indicated as $* P < 0.05$ (ANOVA with post-hoc Bonferroni *t*-test).

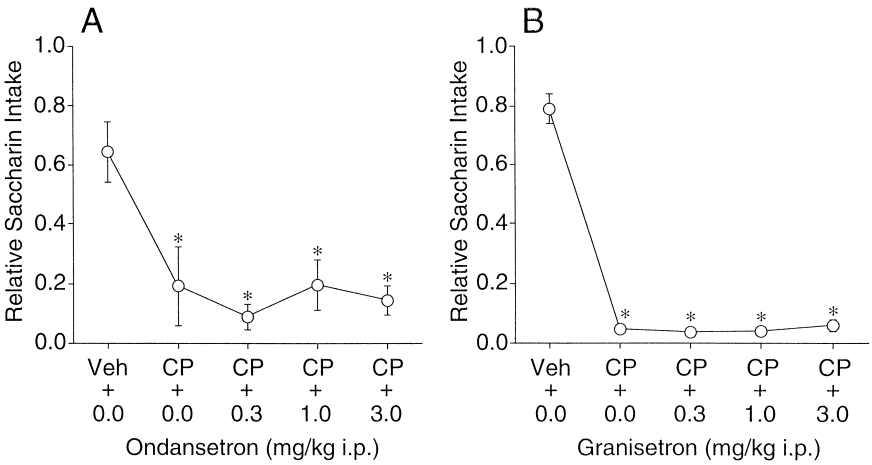

Fig. 5. Failure of a single administration of ondansetron (0.3–3 mg/kg i.p.) or granisetron (0.3–3 mg/kg i.p.) to reverse the conditioned taste aversion induced by cisplatin (3 mg/kg i.p.) in the rat. Data represent the mean ± S.E.M. of four to eight determinations. Ondansetron, granisetron or vehicle was administered as a 40-min pretreatment prior to the administration of cisplatin (CP). Significant differences between the relative saccharin intake of CP vehicle (Veh) + ondansetron or granisetron vehicle (0.0 mg/kg) treated animals and CP + ondansetron or granisetron treated animals are indicated as $* P < 0.05$ (ANOVA with post-hoc Bonferroni *t*-test).

0.05; Fig. 5A) or granisetron (0.3–3 mg/kg i.p., $P > 0.05$; Fig. 5B).

4. Discussion

We have utilized the rat to investigate the conditioned taste aversion-inducing potential of 5-HT, *m*-chlorophenylbiguanide, ipecacuanha and the chemotherapeutic drug, cisplatin. 5-HT, *m*-chlorophenylbiguanide and ipecacuanha are known to induce relatively short-lasting emesis (the duration of action ranges from 10 to 120 min) that can be completely prevented by the use of selective 5-HT_3 receptor antagonists (see Section 1 for references). In the species that possess the vomiting reflex, it is likely that the sites of anti-emetic action of the 5-HT_3 receptor antagonists are on the afferent vagus nerves and in the area postrema and nucleus tractus solitarius of the brainstem (Higgins et al., 1989; Kamato et al., 1993; Miller and Nonaka, 1992). The 5-HT_3 receptor is also located on the vagus nerves and brainstem areas of the rat that are important to the mechanisms of conditioned taste aversion (Fox, 1992; Kilpatrick et al., 1989; Sutton et al., 1988; Ossenkopp and Giugno, 1990).

The importance of the present studies has been to reveal that, like cisplatin, 5-HT and ipecacuanha are capable of inducing conditioned taste aversion in the rat. The results initially confirmed the hypothesis that emetic drugs are capable of inducing conditioned taste aversion behaviour in the rat. However, the mechanism of the 5-HT- and ipecacuanha-induced conditioned taste aversion was expected to involve an activation of 5-HT_3 receptors but we were surprised that ondansetron and granisetron, at doses which block the 5-HT_3 receptor in the rat (Butler et al., 1988; Sanger and Nelson, 1989), were ineffective to antagonize the aversions. However, caution should be exercised when interpreting the mechanism of 5-HT to induce conditioned taste aversion since the additional action to cause immobility may contribute to the response. Nevertheless, we are confident that the 5-HT_3 receptor is not involved in the mechanism(s) of conditioned taste aversion since even a double administration of granisetron was without effect to modify the ipecacuanha-induced conditioned taste aversion. Moreover, *m*-chlorophenylbiguanide, a potent agonist to depolarize the rat vagus nerve (Kilpatrick et al., 1990), was also ineffective to induce a conditioned taste aversion.

Clearly, the mechanism of 5-HT and ipecacuanha to induce conditioned taste aversion in the rat is different from the mechanism to induce emesis in other species. Whilst it is possible that the mechanism of 5-HT to induce a conditioned taste aversion may relate to the activation of 5-HT receptors other than the 5-HT_3 receptor subtype, the mechanism of ipecacuanha to induce conditioned taste aversion may be more complex. For example, an analysis of the mechanism of emetic action of ipecacuanha reveals an interaction with the peripheral vagal system, the area postrema and nucleus tractus solitarius and the gastrointestinal tract (Bhargava et al., 1961; Borison and Wang, 1953; Leslie and Reynolds, 1992). Such interactions may also be involved in the rat but the 5-HT_3 receptor is not likely to play a major role.

It may be pertinent that 5-HT was the only agent in the present studies that produced immobility following injection. This may relate to an ability to affect blood pressure and vascular resistance (Saxena and Villalón, 1990) and it is possible that this effect contributed towards the development of conditioned taste aversion. Certainly, the ears and feet of the rats that were immobile, following 5-HT administration, were of blue colour instead of the normal pink (Rudd, unpublished observations), to suggest a reduction of blood flow that was not seen with the other agents.

In the present studies, cisplatin also produced a conditioned taste aversion that was not prevented by either ondansetron or granisetron. The results are in close agreement with the data obtained by Mele et al. (1992) in the rat and validate the paradigm used throughout the present studies. However, it is interesting to note that cisplatin-induced conditioned taste aversion is antagonized by a single administration of the corticosteroid, dexamethasone, to complicate any future logical design of conditioned taste aversion experiments (Mele et al., 1992). For example, dexamethasone has a relatively short plasma half-life (Tsuei et al., 1979) and a single injection is ineffective to prevent nausea and emesis in man (Gralla et al., 1996) or emesis in animals (Rudd and Naylor, 1996, 1997) to contrast the action in the conditioned taste aversion paradigm (Mele et al., 1992). Thus dexamethasone has unexpected activity in the conditioned taste aversion paradigm to question the relevance of the rat model to the problem of nausea and emesis in man.

It is probable that the mechanism of drug-induced conditioned taste aversion in the rat involves brainstem areas known to be important to emesis in other species (Houpt et al., 1994; Yamamoto et al., 1992). However, only a few studies have examined the role of conditioned taste aversion learning in animals that are also capable of vomiting to attempt to delineate the respective behaviours. Studies in the cat have identified that the area postrema is important to both emesis and conditioned taste aversion induced by xylazine (Fox et al., 1990) but studies in the ferret have concluded that there is no definite relationship between drug-induced emesis and the acquisition of conditioned taste aversion (Rabin and Hunt, 1992). The apparent differences between the mechanisms of emesis and conditioned taste aversion existing in the cat and the ferret may preclude any assumption about the role of conditioned taste aversion in the rat.

In conclusion, we have provided evidence that the 5-HT_3 receptor is unlikely to be involved in the mechanisms of drug-induced conditioned taste aversion in the rat. In addition, the available evidence challenges the usefulness of the rat conditioned taste aversion paradigm to anti-emetic research. Certainly, in man the nausea and emesis induced by cisplatin and ipecacuanha is prevented by 5-HT_3 receptor antagonists (Minton, 1994; Yarker and McTavish, 1994). The mechanisms of the conditioned taste aversion induced by 5-HT, ipecacuanha and cisplatin are essentially unknown and not necessarily related to a potential to induce emesis.

Acknowledgements

The authors are grateful to SmithKline Beecham Pharmaceuticals for the generous gift of granisetron.

References

Andrews, P.L.R., Rapeport, W.G., Sanger, G.J., 1988. Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol. Sci. 9, 334–341.

Bhargava, K.P., Gupta, P.C., Chandra, O., 1961. Effect of ablation of the chemoreceptor trigger zone (CT zone) on the emetic response to intraventricular injections of apomorphine and emetine in the dog. J. Pharmacol. Exp. Ther. 134, 329–331.

Borison, H.L., Wang, S.C., 1953. Physiology and pharmacology of vomiting. Pharmacol. Rev. 5, 193–230.

Butcher, M.E., 1993. Global experience with ondansetron and future potential. Oncology 50, 191–197.

Butler, A., Hill, J.M., Ireland, S.J., Jordan, C.C., Tyers, M.B., 1988. Pharmacological properties of GR38032F, a novel antagonist at 5-HT_3 receptors. Br. J. Pharmacol. 94, 397–412.

Costall, B., Domeney, A.M., Naylor, R.J., Owera-Atepo, J.B., Rudd, J.A., Tattersall, F.D., 1990. Fluphenazine, ICS 205-930 and DL-fenfluramine differentially antagonize drug-induced emesis in the ferret. Neuropharmacology 29, 453–462.

Fox, R.A., 1992. Current status: animal models of nausea. In: Bianchi, A.L., Grélot, L., Miller, A.D., King, G.L. (Eds.), Mechanisms and Control of Emesis, Vol. 223. John Libbey Eurotext, Paris, pp. 341–278.

Fox, R.A., Corcoran, M., Brizzee, K.R., 1990. Conditioned taste aversion and motion sickness in cats and squirrel monkeys. Can. J. Physiol. Pharmacol. 68, 269–278.

Gralla, R.J., Rittenberg, C., Peralta, M., Lettow, L., Cronin, M., 1996. Cisplatin and emesis: aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 h after cisplatin. Oncology 53 (Suppl. 1), 86–91.

Grant, V.L., 1987. Do conditioned taste aversions result from activation of emetic mechanisms?. Psychopharmacology (Berl.) 93, 405–415.

Higgins, G.A., Kilpatrick, G.J., Bunce, K.T., Jones, B.J., Tyers, M.B., 1989. 5-HT_3 receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br. J. Pharmacol. 97, 247–255.

Houpt, T.A., Philopena, J.M., Wessel, T.C., Joh, T.H., Smith, G.P., 1994. Increased c-*fos* expression in nucleus of the solitary tract correlated with conditioned taste aversion to sucrose in rats. Neurosci. Lett. 172, 1–5.

Kamato, T., Ito, H., Nagakura, Y., Nishida, A., Yuki, H., Yamano, M., Miyata, K., 1993. Mechanisms of cisplatin- and *m*-chlorophenylbiguanide-induced emesis in ferrets. Eur. J. Pharmacol. 238, 369–376.

Kilpatrick, G.J., Jones, B.J., Tyers, M.B., 1989. Binding of the 5-HT_3 ligand, [^{3}H]GR65630, to rat area postrema, vagus nerve and the brains of several species. Eur. J. Pharmacol. 159, 157–164.

Kilpatrick, G.J., Butler, A., Burridge, J., Oxford, A.W., 1990. 1-(*m*-Chlorophenyl)-biguanide, a potent high affinity 5-HT_3 receptor agonist. Eur. J. Pharmacol. 182, 193–197.

Kris, M.G., Tyson, L.B., Clark, R.A., Gralla, R.J., 1992. Oral ondansetron for the control of delayed emesis after cisplatin: report of a phase II study and a review of completed trials to manage delayed emesis. Cancer 70, 1012–1016.

Leslie, R.A., Reynolds, D.J.M., 1992. Functional anatomy of the emetic circuitry in the brainstem. In: Bianchi, A.L., Grélot, L., Miller, A.D., King, G.L. (Eds.), Mechanisms and Control of Emesis, Vol. 223. John Libbey Eurotext, Paris, pp. 19–27.

Martin, M., 1996. The severity and pattern of emesis following different cytotoxic agents. Oncology 53 (Suppl. 1), 226–236.

Mele, P.C., McDonough, J.R., McLean, D.B., O'Halloran, K.P., 1992. Cisplatin-induced conditioned taste aversion: attenuation by dexamethasone but not zacopride or GR38032F. Eur. J. Pharmacol. 218, 229–236.

Miller, A.D., Nonaka, S., 1992. Mechanisms of vomiting induced by serotonin-3 receptor agonists in the cat: effect of vagotomy, splanch-

nicectomy or area postrema lesion. J. Pharmacol. Exp. Ther. 260, 509–517.

Minton, N.A., 1994. Volunteer models for predicting anti-emetic activity of 5-HT_3-receptor antagonists. Br. J. Clin. Pharmacol. 37, 525–530.

Morrow, G.R., Hickok, J.T., Rosenthal, S.N., 1995. Progress in reducing nausea and emesis: comparisons of ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban). Cancer 76, 343–357.

Naylor, R.J., Rudd, J.A., 1996. Mechanisms of chemotherapy/radiotherapy-induced emesis in animal models. Oncology 53 (Suppl. 1), 8–17.

Ossenkopp, K.P., Giugno, L., 1990. Nicotine-induced conditioned taste aversions are enhanced in rats with lesions of the area postrema. Pharmacol. Biochem. Behav. 36, 625–630.

Rabin, B.M., Hunt, W.A., 1992. Relationship between vomiting and taste aversion learning in the ferret: studies with ionizing radiation, lithium chloride, and amphetamine. Behav. Neural Biol. 58, 83–93.

Rudd, J.A., Naylor, R.J., 1996. An interaction of ondansetron and dexamethasone antagonizing cisplatin-induced acute and delayed emesis in the ferret. Br. J. Pharmacol. 118, 209–214.

Rudd, J.A., Naylor, R.J., 1997. The actions of ondansetron and dexamethasone to antagonize cisplatin-induced emesis in the ferret. Eur. J. Pharmacol. 322, 79–82.

Rudd, J.A., Jordan, C.C., Naylor, R.J., 1994. Profiles of emetic action of cisplatin in the ferret: a potential model of acute and delayed emesis. Eur. J. Pharmacol. 262, R1–R2.

Rudd, J.A., Bunce, K.T., Naylor, R.J., 1996. The interaction of dexamethasone with ondansetron on drug-induced emesis in the ferret. Neuropharmacology 35, 91–96.

Sanger, G.J., Nelson, D.R., 1989. Selective and functional 5-hydroxytryptamine$_3$ receptor antagonism by BRL 43694 (granisetron). Eur. J. Pharmacol. 159, 113–124.

Saxena, P.R., Villalón, C.M., 1990. Cardiovascular effects of serotonin agonists and antagonists. J. Cardiovasc. Pharmacol. 15, S17–S34, Suppl. 7.

Smith, W.L., Alphin, R.S., Jackson, C.B., Sancilio, L.F., 1989. The anti-emetic profile of zacopride. J. Pharm. Pharmacol. 41, 101–105.

Stables, R., Andrews, P.L.R., Bailey, H.E., Costall, B., Gunning, S.J., Hawthorn, J., Naylor, R.J., Tyers, M.B., 1987. Anti-emetic properties of the 5-HT_3-receptor antagonist, GR38032F. Cancer Treat. Rev. 14, 333–336.

Sutton, R.L., Fox, R.A., Daunton, N.G., 1988. Role of the area postrema in three putative measures of motion sickness in the rat. Behav. Neural. Biol. 50, 133–152.

Torii, Y., Saito, H., Matsuki, N., 1991. 5-Hydroxytryptamine is emetogenic in the house musk shrew, *Suncus murinus*. Naunyn-Schmiedeberg's Arch. Pharmacol. 344, 564–567.

Tsuei, S.E., Moore, R.E., Ashley, J.J., McBride, W.G., 1979. Disposition of synthetic glucocorticoids: 1. Pharmacokinetics of dexamethasone in healthy adults. J. Pharmacol. Biopharm. 7, 249–264.

Yamamoto, T., Shimura, T., Sako, N., Azuma, S., Bai, W.Z., Wakisaka, S., 1992. C-*fos* expression in the rat brain after intraperitoneal injection of lithium chloride. NeuroReport 3, 1049–1052.

Yarker, Y.E., McTavish, D., 1994. Granisetron: an update of its therapeutic use in nausea and vomiting induced by anti-neoplastic drugs. Drugs 48, 761–793.