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GR205171 blocks apomorphine and amphetamine-induced conditioned taste aversions

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Abstract

The tachykinin NK_1 receptor antagonist, GR205171 ([2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-(2*S*-phenyl-piperidin-3*S*-yl)-amine), is a potent inhibitor of emesis induced by a wide variety of emetogens. This is in contrast to 5-HT_3 (5-hydroxytryptamine$_3$) receptor antagonists, such as ondansetron, which have a more restricted antiemetic profile. The present study evaluated the efficacy of GR205171, in comparison with ondansetron to block the acquisition of a conditioned taste aversion induced by either apomorphine (0.25 mg kg^{-1} s.c.) or by amphetamine (0.5 mg kg^{-1} s.c.) in rats. Pretreatment with GR205171 (0.1–1.0 mg kg^{-1} s.c.) and ondansetron (0.001–0.1 mg kg^{-1} s.c.) produced a dose-dependent blockade of conditioned taste aversions evoked by apomorphine. In contrast, the acquisition of conditioned taste aversions induced by amphetamine was inhibited by GR205171 (0.3–0.5 mg kg^{-1} s.c.), but only attenuated by ondansetron (0.001–0.1 mg kg^{-1} s.c.). These results suggest that tachykinin NK_1 receptor antagonists may have potential in the treatment of drug-induced conditioned aversive behaviour and nausea.

Keywords: Tachykinin NK_1 receptor antagonist; Aversion; Apomorphine; Amphetamine

1. Introduction

Conditioned taste aversion is a well-established procedure for measuring the aversive properties of a variety of agents in rats and involves the pairing of a drug injection (unconditional stimulus) with a particular flavour (conditional stimulus). A wide range of psychotropic drugs from different pharmacological classes are capable of acting as the unconditional stimulus (Cappell and Le Blanc, 1975). Psychoactive drugs such as apomorphine and amphetamine paradoxically produce both positive reinforcing and aversive properties over a similar dose range, as demonstrated in the conditioned place preference and conditioned taste aversion paradigms, respectively (van der Kooy et al., 1983; Reicher and Holman, 1977). There is strong evidence that forebrain dopamine systems are critical for drug reward (Wise, 1982). However, there is controversy concerning the neural systems recruited in the conditioned taste aversion phenomenon although it has previously been hypothesised that the neural pathways that mediate emesis are involved in conditioned taste aversion learning (Garcia et al., 1985).

The substrates for the sites of action by which apomorphine produces its aversive effects remain unclear but appear to be centrally mediated (Kiefer et al., 1981; Martin, 1979; Pratt and Stolerman, 1984). The ability of both the dopamine receptor antagonist, pimozide, and also lesions of central dopamine neurons by 6-hydroxydopamine to significantly attenuate amphetamine-induced conditioned taste aversions (Grupp, 1977; Wagner et al., 1981) indicate that dopamine plays a role in mediating conditioned taste aversions to amphetamine. Furthermore, the area postrema, a structure on the peripheral side of the blood–brain barrier, may contribute to the acquisition of amphetamine-conditioned taste aversions along with a central dopaminergic component (Carr and White, 1986; Rabin and Hunt, 1989). Conversely, lesioning the area postrema fails to affect conditioned taste aversions induced by apomorphine in rats (van der Kooy et al., 1983).

Tachykinin NK_1 receptor antagonists have a wide variety of potential clinical uses, with one of the most important being their effectiveness in preventing emesis induced by a broad spectrum of emetogens, (Bountra et al., 1993; Gardner et al., 1995, 1996). High levels of binding of

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radiolabelled substance P (the endogenous ligand at the NK_1 receptor) have been shown in the nucleus of the solitary tract and dorsal motor nucleus of the vagus of the rat and ferret, and NK_1 receptor-mediated responses have been recorded electrophysiologically in these structures (Maubach et al., 1995; Maubach and Jones, 1997). These are brainstem structures which may be important in apomorphine-induced conditioned taste aversions and which have already been implicated in conditioned taste aversions evoked by amphetamine (Carr and White, 1986). Therefore, one aim of the present study was to investigate the ability of a novel non-peptide tachykinin NK_1 receptor antagonist, GR205171 ([2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-(2*S*-phenyl-piperidin-3*S*-yl)-amine), to prevent apomorphine- and amphetamine-induced conditioned taste aversions. GR205171 is a highly selective and potent NK_1 receptor antagonist with a $pK_i = 9.5$ in rat cortex (Gardner et al., 1996). Like NK_1 antagonists, 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonists have been shown to be effective in preventing emesis induced by chemotherapeutic agents, such as cisplatin, in both humans and animals (Sanger, 1991). However, they are relatively ineffective against apomorphine-induced emesis (Andrews and Bhandari, 1993) and cisplatin-induced conditioned taste aversions (Mele et al., 1992). The aim of the present study was therefore to compare the abilities of the tachykinin NK_1 receptor antagonist, GR205171, and the 5-HT_3 receptor antagonist, ondansetron, to prevent the acquisition of conditioned taste aversions induced by apomorphine and amphetamine. Part of this work has appeared in abstract form (McAllister and Pratt, 1996).

2. Materials and methods

2.1. Animals

Male Lister Hooded rats (Charles River) weighing between 250 and 300 g at the start of the experiment were used. Animals were housed individually in a temperature regulated room with a 12-h light–dark cycle (lights on 0600) and allowed food ad libitum.

2.2. Conditioning procedure

Rats were water deprived 23 h daily for 1 week before any flavoured solutions were presented and on all days between flavour presentation. Two conditioning trials of a counterbalance design were carried out. One of two flavoured solutions (sodium chloride 0.9% or sodium saccharin 0.1%) was presented for 15 min every other day. The flavours were presented alternately and the position of the bottles was adapted to control for the influence of position preference. Immediately after removal of the flavours, the animals were injected with drug (apomorphine or amphetamine) or the appropriate vehicle. For half the rats, one particular flavour was paired twice with the drug injection and the other flavour was paired twice with vehicle. These flavour–injection pairings were reversed in the remaining rats, ensuring that the inherent palatability of the flavours were balanced out.

After the two conditioning trials, a two-stimulus test was carried out over 2 days. In this test, the drug-paired and vehicle-paired flavoured solutions were presented simultaneously for 15 min and on the following day, the positions of the two flavours were reversed. The mean fluid consumption of each flavour was measured for each rat during the 2 test days. This procedure is adopted to control for any position preference (Pratt and Stolerman, 1984).

2.3. Drug treatments

Different groups of rats were pretreated with ondansetron (0.001–0.1 mg kg^{-1} s.c.), GR205171 (0.1–1.0 mg kg^{-1} s.c.) or vehicle 30 and 15 min prior to flavour presentation, respectively. The efficacy of these drugs in attenuating conditioned taste aversions evoked by apomorphine (0.25 mg kg^{-1} s.c.) and amphetamine (0.5 mg kg^{-1} s.c.) was assessed during the two-stimulus test. The possibility that ondansetron and GR205171 could produce conditioned taste aversions when administered alone was also examined. In these experiments, the compounds were administered immediately after flavour presentation during the conditioning trials and their ability to induce conditioned taste aversions were assessed during the two-stimulus test, as outlined in Section 2.2. Apomorphine hydrochloride (Sigma) was dissolved in a solution of ascorbic acid (0.2 mg ml^{-1}) in distilled water. D-Amphetamine sulphate (Sigma) and ondansetron hydrochloride (Glaxo Wellcome) were dissolved in 0.9% saline. The GR205171 (Glaxo Wellcome) was dissolved in distilled water.

2.4. Statistical analysis

The results from the two-stimulus test were analysed in two ways. The ability of individual treatment groups to produce a conditioned taste aversion was assessed by comparing the drug-paired flavour intake with the vehicle-paired flavour intake using a paired *t*-test. In order to quantify the ability of each of the antagonists to block drug-induced conditioned taste aversions, results from the two-stimulus test were analysed as follows. For each rat from each of the treatment groups, the amount of flavour consumed, which was paired with the drug injections, was calculated as a percentage of the total fluid intake. These percentage scores were subjected to arc-sine transformations to normalise their distributions (Winer, 1971) and analysed by one-way analysis of variance (ANOVA) followed by student Newman–Keuls test for comparisons between groups. Statistical significance was defined when

$P < 0.05$. Total fluid intake during the conditioning trials and the two-stimulus test was analysed by ANOVA.

3. Results

3.1. Effect of pretreatment with GR205171 on conditioned taste aversions induced by apomorphine and amphetamine

Pretreatment with GR205171 (0.1 mg kg^{-1}) did not prevent apomorphine or amphetamine-induced conditioned taste aversions. At a dose of 0.2 mg kg^{-1}, GR205171 significantly attenuated conditioned taste aversions evoked by apomorphine. However, at a dose of 0.3 mg kg^{-1}, GR205171 prevented the acquisition of conditioned taste aversions induced by both apomorphine (Table 1; Fig. 1) and amphetamine (Table 2; Fig. 2). The total fluid consumption during each stage of the procedure was the same and was not affected by drug treatment. Thus, the total fluid consumption of both flavours during the two-stimulus test days (when the rats have access to both solutions simultaneously) was approximately equal to the mean fluid intake recorded during each flavour–injection pairing day during the two conditioning trials, when only one particular flavour associated with the appropriate drug or vehicle injection was presented (Figs. 1 and 2).

The blocking effect of GR205171 upon conditioned tasted aversions produced by apomorphine was dose-related. Thus, analysis of variance of the data from the two-stimulus test indicated that there were differences between apomorphine-treated groups; $F(3,26) = 122.30$, $P < 0.05$. Post-hoc Newman–Keuls tests revealed that a dose of 0.1 mg kg^{-1} had no effect on the percentage of drug-paired fluid intake as compared with the control (effect of apomorphine alone), but at doses of 0.2–1.0 mg kg^{-1}, the percentage of the drug-paired fluid intake of GR205171 was significantly different from control (Table 1).

The tachykinin NK_1 receptor antagonist, GR205171, also blocked amphetamine-induced conditioned taste aversions in a dose-dependent manner. Analysis of variance of results from the two-stimulus choice test showed that there was a significant difference between treatment groups,

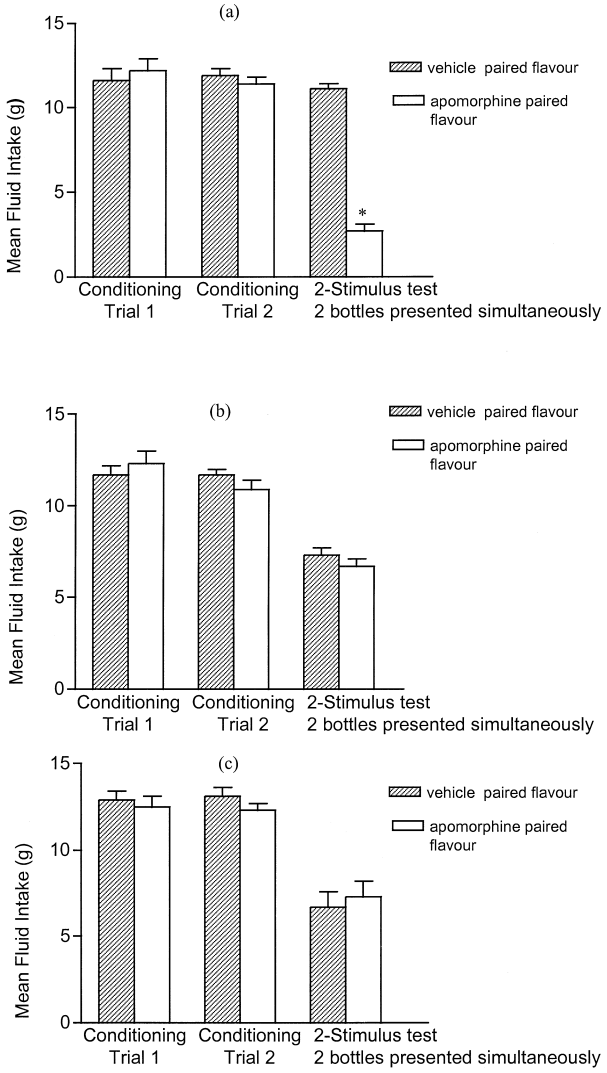

Fig. 1. Blockade of apomorphine-induced conditioned taste aversions by GR205171 and ondansetron. Representative experiments showing conditioned taste aversions induced by apomorphine in three groups of rats ($n = 8$ group^{-1}). Conditioning trials 1 and 2 represent the mean fluid intake during the conditioning sessions, where the rats have access to only one flavour paired with the appropriate drug injection. During the two-stimulus test, the rats have access to both flavours simultaneously. (a) Apomorphine (0.25 mg kg^{-1} s.c.) induces conditioned taste aversions which were blocked following pretreatment with (b) GR205171 (0.3 mg kg^{-1} s.c.) and (c) ondansetron (0.1 mg kg^{-1} s.c). Note that the total fluid intake was similar in the two-stimulus test and in the conditioning trials. $*$ $P < 0.05$, as compared to respective vehicle-paired flavour intake (paired *t*-test), indicates conditioned taste aversions.

Table 1
Effect of 5-HT_3 receptor- and NK_1 receptor-antagonists on the development of apomorphine-induced conditioned taste aversions in rats

Pretreatment (mg kg^{-1})	Treatment (mg kg^{-1})	*n*	Drug-paired flavour intake (Mean% ± SEM)
Saline	apomorphine (0.25)	8	27.3 ± 0.5
Ondansetron (0.001)	apomorphine (0.25)	7	33.1 ± 1.1[a]
Ondansetron (0.01)	apomorphine (0.25)	7	35.1 ± 1.1[a]
Ondansetron (0.1)	apomorphine (0.25)	8	46.8 ± 4.1[a]
Saline	ondansetron (0.1)	8	46.4 ± 2.1[a]
Saline	apomorphine (0.25)	16	26.2 ± 1.1
GR205171 (0.1)	apomorphine (0.25)	8	25.7 ± 0.9
GR205171 (0.2)	apomorphine (0.25)	8	35.4 ± 0.8[a]
GR205171 (0.3)	apomorphine (0.25)	8	43.9 ± 1.0[a]
GR205171 (1.0)	apomorphine (0.25)	8	44.8 ± 1.3[a]
Saline	GR205171 (0.3)	6	46.1 ± 0.8[a]
Saline	GR205171 (1.0)	8	45.4 ± 1.2[a]

[a] $P < 0.05$ as compared to saline + apomorphine group.
ANOVA followed by Newman–Keuls test.

Table 2
Effect of 5-HT_3 receptor- and NK_1 receptor-antagonists on the development of amphetamine-induced conditioned taste aversions in rats

Pretreatment (mg kg^{-1})	Treatment (mg kg^{-1})	n	Drug-paired flavour intake (Mean% ± SEM)
Saline	amphetamine (0.5)	8	26.5 ± 0.9
Ondansetron (0.001)	amphetamine (0.5)	8	27.6 ± 1.7
Ondansetron (0.01)	amphetamine (0.5)	8	34.4 ± 1.9[a]
Ondansetron (0.1)	amphetamine (0.5)	8	35.4 ± 2.0[a]
Saline	amphetamine (0.5)	8	26.7 ± 2.5
GR205171 (0.1)	amphetamine (0.5)	8	28.0 ± 1.8
GR205171 (0.3)	amphetamine (0.5)	8	45.5 ± 1.7[a]
GR205171 (0.5)	amphetamine (0.5)	8	43.9 ± 1.3[a]

[a] $P < 0.05$ as compared to saline + amphetamine group.
ANOVA followed by Newman–Keuls test.

$F(3,28) = 28.9$, $P < 0.05$. Pretreatment with GR205171 (0.1 mg kg^{-1}) had no significant effect on the percentage of drug-paired fluid intake as compared to the amphetamine control; but at the higher doses of 0.3 and 0.5 mg kg^{-1}, drug-paired fluid consumption was significantly different from the control such that rats showed neither a preference or an aversion (Fig. 2; Table 2).

GR205171 (0.3 and 0.1 mg kg^{-1}) alone did not induce conditioned taste aversions (Table 1; Fig. 3), as the mean fluid intake of each flavour recorded during the two-stimulus test was approximately the same, indicating that the rats showed neither an aversion or preference for the two different solutions. Similarly, the mean total fluid intake during the conditioning trials and the two-stimulus test was similar (Fig. 3). Animals that had both flavours paired with vehicle injections also showed no preference or aversion for either flavour (Fig. 3), indicating that there was no inherent preference for either flavour in the vehicle-treated control rats.

3.2. Effect of pretreatment with ondansetron on conditioned taste aversions produced by apomorphine and amphetamine

The results for pretreatment with ondansetron are summarised in Tables 1 and 2 and show that ondansetron blocked apomorphine-induced conditioned taste aversions and attenuated amphetamine-induced conditioned taste aversions. In addition, ondansetron did not affect total fluid intake during the conditioning trials and during the two-stimulus test (Figs. 1 and 2).

Analysis of variance of the arc-sine transformed percentages of drug-paired fluid intake recorded during the two-stimulus test, for experiments concerned with the effect of ondansetron on apomorphine-conditioned taste aversions showed a difference between groups; $F(2,21) = 11.38$, $P < 0.05$. Ondansetron appeared to block conditioned taste aversions evoked by apomorphine in a dose-dependent manner. The two lower doses of 0.001 and 0.01 mg kg^{-1} significantly attenuated, but did not block conditioned taste aversions evoked by apomorphine. At the highest dose of ondansetron tested (0.1 mg kg^{-1}), the percentage of drug-paired fluid intake was significantly different as compared with the control group receiving apomorphine alone (Table 1). At this dose, ondansetron (0.1 mg kg^{-1}) blocked apomorphine-induced conditioned

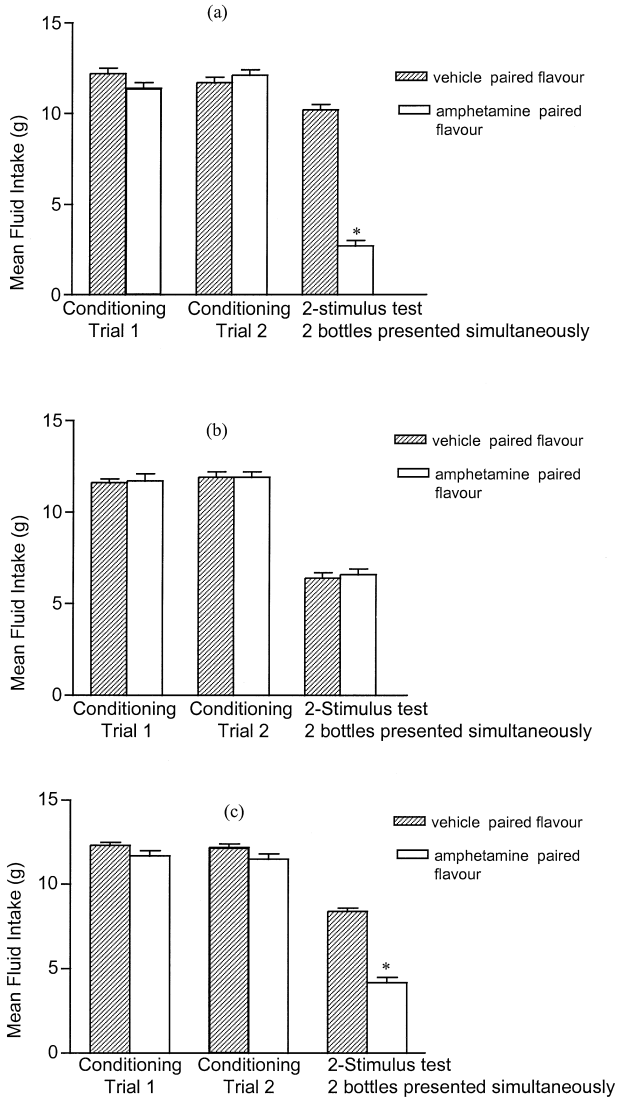

Fig. 2. Effect of GR205171 and ondansetron on amphetamine-induced conditioned taste aversions. Representative experiments showing conditioned taste aversions induced by amphetamine in three groups of rats ($n = 8$ group^{-1}). Conditioning trials 1 and 2 represent the mean fluid intake during the conditioning sessions, where the rats have access to only one flavour paired with the appropriate drug injection. During the two-stimulus test, the rats have access to both flavours simultaneously. (a) Amphetamine (0.5 mg kg^{-1} s.c.) induces conditioned taste aversions which were blocked following pretreatment with (b) GR205171 (0.3 mg kg^{-1} s.c.) and were significantly attenuated following pretreatment with (c) ondansetron (0.1 mg kg^{-1} s.c.). Note that the total fluid intake was similar in the two-stimulus test and in the conditioning trials. * $P < 0.05$, as compared to respective vehicle-paired flavour intake (paired t-test), indicates conditioned taste aversions.

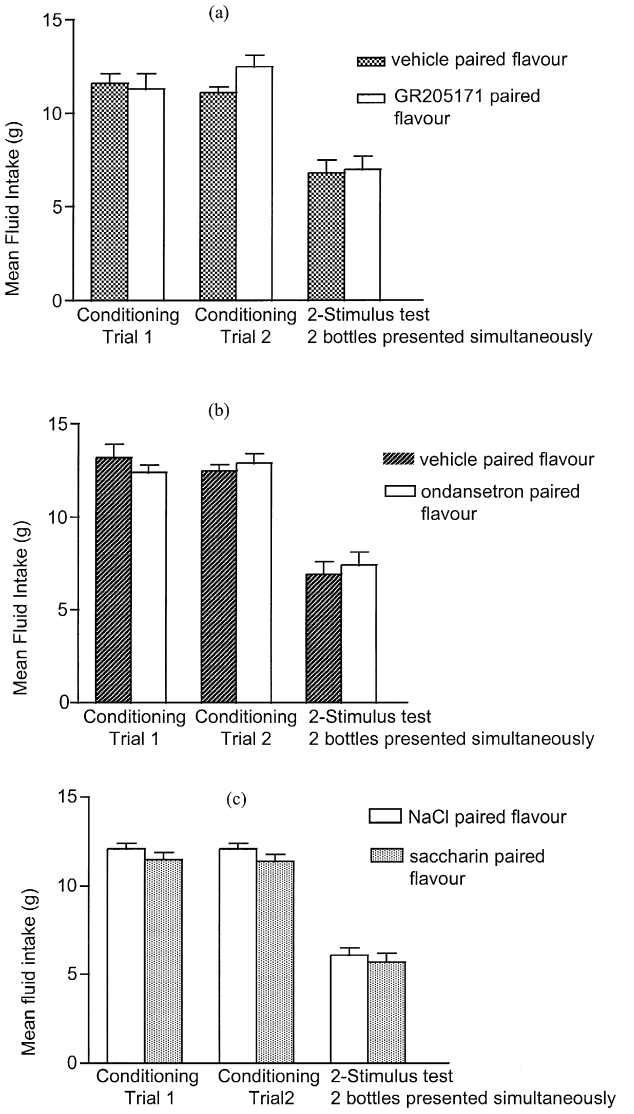

Fig. 3. Inability of GR205171 and ondansetron to induce conditioned taste aversions. Experiments showing the inability of (a) GR205171 (0.3 mg kg^{-1} s.c), (b) ondansetron (0.1 mg kg^{-1} s.c) and vehicle (c) to evoke conditioned taste aversions in different groups of rats ($n = 8$ $group^{-1}$). Conditioning trials 1 and 2 represent the mean fluid intake during the conditioning sessions, where the rats have access to only one flavour paired with the appropriate drug injection. During the two-stimulus test, the rats have access to both flavours simultaneously. Results from the two-stimulus test show that doses of 0.3 mg kg^{-1} GR205171 and 0.1 mg kg^{-1} ondansetron alone did not evoke conditioned taste aversions as the rats drank approximately the same amount of the drug- and vehicle-paired solutions. Note that the total fluid intake was similar in the two-stimulus test and in the conditioning trials. Similarly, rats that had both flavours paired with vehicle injections (c) drank the same amount of each of the two flavoured solutions, indicating that there was no inherent preference or aversion for either flavour.

taste aversions as the rats drank equal amounts of the two flavours during the two-stimulus choice test (Fig. 1).

Ondansetron (0.01–0.1 mg kg^{-1}) attenuated conditioned taste aversions induced by amphetamine. Results of the drug-paired fluid intake during the two-stimulus test were analysed by one-way ANOVA and showed that there was a difference between treatment groups $F(3,28) = 7.6$, $P < 0.05$. Pretreatment with ondansetron at doses of 0.01 mg kg^{-1} and 0.1 mg kg^{-1} (Table 2; Fig. 2) significantly attenuated the conditioned taste aversions as compared to the amphetamine control; however, the lower dose of 0.001 mg kg^{-1} ondansetron had no effect on amphetamine-conditioned taste aversions. These results indicate that ondansetron is more effective in preventing the acquisition of a conditioned taste aversion induced by apomorphine than a conditioned taste aversion evoked by amphetamine.

Ondansetron (0.001–0.1 mg kg^{-1} s.c.) alone does not induce conditioned taste aversions (Table 1; Fig. 3). The drug-paired and vehicle-paired fluid consumption during the two-stimulus test days indicated that there was neither an aversion or preference for either flavour as the rats were drinking approximately the same amount of each solution. Similarly, total fluid intake was similar in the conditioning trials and in the two-stimulus test (Fig. 3).

4. Discussion

The present study indicates that the tachykinin NK_1 receptor antagonist, GR205171, is effective in preventing the acquisition of a conditioned taste aversion to both apomorphine and amphetamine. Both these psychotropic drugs can paradoxically produce both aversive and positive reinforcing properties as demonstrated in the conditioned taste aversion and conditioned place preference paradigms, respectively (van der Kooy et al., 1983; Reicher and Holman, 1977). Apomorphine (0.25 mg kg^{-1}) and amphetamine (0.5 mg kg^{-1}) also produced conditioned taste aversions of a similar magnitude (Figs. 1 and 2). In comparison, the 5-HT_3 receptor antagonist, ondansetron, showed a dose-dependent blockade of apomorphine-induced conditioned taste aversions, but only attenuated conditioned taste aversions evoked by amphetamine. Conversely, GR205171 (0.3–1.0 mg kg^{-1}) and ondansetron (0.001–0.1 mg kg^{-1}), when administered alone, do not induce conditioned taste aversions. These results suggest that NK_1 and 5-HT_3 receptors are involved in psychotropic drug-induced conditioned taste aversions, but the anatomical sites of action and neural pathways involved in these effects remain to be elucidated.

The present results show that at doses of 0.3 and 1.0 mg kg^{-1}, GR205171 blocks conditioned taste aversions evoked by apomorphine (0.25 mg kg^{-1}). It has previously been hypothesised that the neural systems recruited in conditioned taste aversions are the same as those that mediate emesis (Grant, 1987). However, this theory remains controversial. The tachykinin NK_1 receptor antagonist tested in the present study, GR205171, is one of the most potent and highly selective antagonists at the NK_1 receptor to have been identified. A dose of 0.03 mg kg^{-1} s.c. produced almost complete inhibition of emesis induced by

whole-body X-irradiation in the ferret (Gardner et al., 1996). Furthermore, it has been shown to be effective in controlling emesis evoked by a wide variety of different emetogenic stimuli (Gardner et al., 1996). The antiemetic action of tachykinin NK_1 receptor antagonists is thought to be centrally mediated (Gardner et al., 1994; Hargreaves et al., 1994) based upon the inability of peripherally acting NK_1 receptor antagonists to prevent emesis. However, there is as yet no information on whether the ability of GR205171 to block apomorphine-induced conditioned taste aversions is a centrally mediated effect.

Despite the fact that apomorphine-induced emesis is mediated through the area postrema, which lies on the peripheral side of the blood–brain barrier (Borison and Wang, 1953), this does not appear to be the case for apomorphine-induced conditioned taste aversions, as lesioning the area postrema does not prevent apomorphine-induced conditioned taste aversions (van der Kooy et al., 1983). Further support for apomorphine-induced conditioned taste aversions being centrally mediated is that centrally acting, but not peripherally acting, dopamine receptor antagonists block apomorphine-induced conditioned taste aversions (Pratt and Stolerman, 1984). Taken together, this may suggest that GR205171 is blocking apomorphine-induced conditioned taste aversions at receptors located within the central nervous system.

GR205171 (0.3 and 0.5 mg kg^{-1} s.c.) blocked conditioned taste aversions induced by amphetamine over a similar dose range to that in which it blocked conditioned taste aversions induced by apomorphine. In contrast to conditioned taste aversions produced by apomorphine, the area postrema may play a role in mediating conditioned taste aversions evoked by low doses of amphetamine, such as the dose of 0.5 mg kg^{-1} used in the present study (Rabin et al., 1987). Previous studies have indicated that complete elimination of conditioned taste aversions produced by amphetamine requires blockade of both a central dopaminergic mechanism and a peripheral component mediated by the area postrema (Rabin and Hunt, 1989). Thus, the ability of GR205171 to completely block the acquisition of a conditioned taste aversion induced by amphetamine in this study may be due to the tachykinin NK_1 receptor antagonist partially acting at the area postrema, although it is unknown whether NK_1 receptors are present at this anatomical location. Other structures that are implicated are the nucleus of the solitary tract and the dorsal motor nucleus of the vagus. Indeed, high levels of binding of radiolabelled SP have been found in these brainstem structures of the rat and ferret (Maubach et al., 1995). Moreover, NK_1 receptor-mediated responses have been recorded in these structures (Maubach and Jones, 1997). Both these brain structures are associated with the emetic reflex (Leslie, 1985), and furthermore, focal injections of amphetamine into these areas induce a conditioned taste aversion (Carr and White, 1986). The precise central site of action remains to be elucidated, but NK_1 receptors are known to be present in many central sites, including the amygdala (Saffroy et al., 1983), a structure which has been implicated in conditioned taste aversion learning (Ashe and Nachman, 1980).

A comparative study using the 5-HT_3 receptor antagonist, ondansetron, (0.001–0.1 mg kg^{-1} s.c.) revealed a dose-dependent blockade of apomorphine (0.25 mg kg^{-1})-induced conditioned taste aversions. This result contrasts with the lack of ability of ondansetron to block apomorphine-induced emesis (Andrews and Bhandari, 1993), which indicates that apomorphine-induced conditioned taste aversions and apomorphine-induced emesis are separate phenomena. Conversely, ondansetron (0.01–0.1 mg kg^{-1}) showed only an attenuation of conditioned taste aversions evoked by amphetamine. It seems unlikely that the failure of ondansetron to block amphetamine-induced conditioned taste aversions is due to the dose of amphetamine employed as both apomorphine and amphetamine produce a conditioned taste aversion of a similar magnitude. Previous studies have revealed that ondansetron is ineffective in preventing conditioned taste aversions evoked by cisplatin (Mele et al., 1992), although it prevents cisplatin-induced emesis (Andrews et al., 1990). Furthermore, ondansetron (0.1 mg kg^{-1}) only partially blocks the acquisition of nicotine-induced conditioned taste aversions (Mitchell and Pratt, 1990).

The conditioned taste aversions induced by low doses of amphetamine (< 1.5 mg kg^{-1}) are thought to be mediated by the area postrema along with a central dopaminergic component (Rabin and Hunt, 1989). The present results suggest that 5-HT_3 receptor antagonists block one of these components. However, further studies are required to resolve the precise anatomical location, as 5-HT_3 receptors are found both in peripheral sites such as the area postrema and in many central sites (Kilpatrick et al., 1987, 1988).

One of the explanations for the ability of tachykinin NK_1 receptor antagonists and 5-HT_3 receptor antagonists to block conditioned taste aversions is that they are exhibiting proximal pretreatment effects, where prior exposure to drugs induces a malaise which prevents the subsequent association between taste experience and drug treatment (Domjan, 1980). However, this is unlikely, as the pretreatment drugs used in this study, namely GR205171 and ondansetron, did not exhibit any aversive effects on fluid consumption at any of the doses tested. In the present study, the effects of both the tachykinin NK_1 receptor antagonist, GR205171 and the 5-HT_3 receptor antagonist, ondansetron, upon conditioned taste aversions induced by both apomorphine and amphetamine, were dose-related. Furthermore, GR205171 (0.3–1.0 mg kg^{-1}) and ondansetron (0.001–0.1 mg kg^{-1}) do not induce conditioned taste aversions when administered alone.

In summary, the present results suggest that both NK_1 and 5-HT_3 receptors are involved in the neural circuitry recruited during the acquisition of conditioned taste aversions induced by drugs that evoke conditioned taste aver-

sions through dopaminergic mechanisms. Both ondansetron and GR205171 could completely block the conditioned taste aversions produced by apomorphine. Ondansetron appeared slightly more effective in this respect as a dose of 0.1 mg kg^{-1} (0.27 mmol kg^{-1}) blocked apomorphine-induced conditioned taste aversions, whereas a dose of 0.3 mg kg^{-1} (0.6 mmol kg^{-1}) of GR205171 was required to block these taste aversions. In contrast, ondansetron did not appear to be as effective as GR205171 in blocking amphetamine-induced conditioned taste aversions since ondansetron could only attenuate amphetamine-induced conditioned taste aversions. Further studies could examine the importance of the area postrema in the responses to these drugs by examining the ability of GR205171 to affect conditioned taste aversions induced by lithium chloride which is known to be dependent on the area postrema for producing conditioned taste aversions (Ritter et al., 1980). This, in turn, may lead to a dissociation of neural circuits recruited by different drugs which induce conditioned taste aversions. Interestingly, the tachykinin NK_1 receptor antagonist, GR205171, seems to be very effective in preventing emesis induced by a wide variety of emetogens (Gardner et al., 1996) and potently blocks apomorphine and amphetamine-induced conditioned taste aversions. This is in contrast to ondansetron which has a more limited antiemetic profile (Andrews and Bhandari, 1993) and is also less effective in blocking drug-induced conditioned taste aversions (Mitchell and Pratt, 1990; Mele et al., 1992). This raises the possibility that tachykinin NK_1 receptor antagonists may be more effective than 5-HT_3 receptor antagonists in preventing aversive responses which could have an implication for these compounds in the control of nausea and other drug-induced aversive states.

It is of interest to note that 5-HT_3 receptor antagonists have been shown to block the rewarding effects of some drugs in the conditioned place preference paradigm. However, they appear to be more effective in blocking conditioned place preference induced by morphine than that induced by amphetamine (Carboni et al., 1989; Higgins et al., 1992). Taken together with results from the present conditioned taste aversion study, this suggests that ondansetron may not be particularly effective in blocking either conditioned aversive or conditioned rewarding responses associated with amphetamine. Given the ability of GR205171 to completely block conditioned taste aversions produced by apomorphine and amphetamine, it would seem appropriate to evaluate the potential role of NK_1 receptors in models of conditioned drug reward in future investigations.

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