Psychopharmacology (2011) 215:505–512
DOI 10.1007/s00213-010-2157-4

ORIGINAL INVESTIGATION

Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews

Erin M. Rock · Jennifer M. Goodwin · Cheryl L. Limebeer · Aviva Breuer · Roger G. Pertwee · Raphael Mechoulam · Linda A. Parker

Received: 21 June 2010 / Accepted: 19 December 2010 / Published online: 18 January 2011

Abstract
Rationale The interaction between two non-psychotropic cannabinoids, cannabidiol (CBD) and cannabigerol (CBG), which have been reported to act as a 5-hydroxytryptamine 1A (5-HT_{1A}) agonist and antagonist, respectively, was evaluated.
Objective To evaluate the potential of CBG to reverse the anti-nausea, anti-emetic effects of CBD.
Materials and methods In experiment 1, rats were pre-treated with CBG (0.0, 1, 5, and 10 mg/kg, ip), 15 min prior to being treated with CBD (experiment 1a: VEH or 5 mg/kg, ip) or 8-OH-DPAT (experiment 1b: VEH or 0.01 mg/kg, ip). Thirty minutes later, all rats received a pairing of 0.1% saccharin solution and LiCl (20 ml/kg of 0.15 M, ip). Seventy-two hours later, the rats received a drug-free taste reactivity test with saccharin to evaluate the effects of the treatments on the establishment of conditioned gaping reactions (a model of nausea). As well, conditioned saccharin avoidance was measured. In experiment 2, *Suncus murinus* were injected with CBG (5 mg/kg, ip) or VEH 15 min prior to CBD (5 mg/kg) or VEH and 30 min later were injected with LiCl (60 ml/kg of 0.15 M, i.p.), and the number of vomiting episodes were measured.
Results CBD (5 mg/kg) suppressed conditioned gaping in rats and vomiting in shrews, which were reversed by pre-treatment with all doses of CBG. CBG also prevented the anti-nausea effects of 8-OH-DPAT.
Conclusions Interactions between moderate doses of CBG and CBD may oppose one another at the 5-HT_{1A} receptor in the regulation of nausea and vomiting.

Keywords Nausea · Vomiting · Cannabinoids · Cannabigerol · Cannabidiol · Serotonin · 5-HT_{1A} · Phytocannabinoid

E. M. Rock · J. M. Goodwin · C. L. Limebeer · L. A. Parker
Department of Psychology, University of Guelph, Guelph, ON N1G 2W1, Canada

A. Breuer · R. Mechoulam
Institute of Drug Research, Hebrew University Medical Faculty, Jerusalem, Israel

R. G. Pertwee
School of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, UK

L. A. Parker (✉)
Department of Psychology, University of Guelph, Guelph, ON N1G 2W1, Canada
e-mail: parkerl@uoguelph.ca

Introduction

Considerable evidence suggests that cannabinoids are effective in the treatment of nausea and vomiting (see Abrahamov et al. 1995; Parker and Limebeer 2008; Parker et al. 2005; Tramer et al. 2001). The primary psychoactive cannabinoid found in marihuana, Δ^9-tetrahydrocannabinol (Δ^9-THC; Gaoni and Mechoulam 1964a), has been shown to suppress nausea and vomiting in humans (e.g., Orr et al. 1980; Sallan et al. 1975; see Tramer et al. 2001) and vomiting in other animals (e.g. for review see Parker et al. 2005; 2008). As well, Δ^9-THC interferes with the establishment and expression of conditioned gaping reactions (a measure of nausea-like behaviour) in the Taste Reactivity (TR) test (Grill and Norgren 1978) in rats (Limebeer and Parker 1999; Parker and Mechoulam 2003;

Parker et al. 2004). The effects of Δ^9-THC and other synthetic psychoactive cannabinoids (e.g., HU-210, WIN 55, 212-2, CP 55,940) on both nausea (Parker et al. 2003) and vomiting (Darmani 2001; van Sickle et al. 2001; Parker et al. 2004; Kwiatkowska et al. 2004) are mediated by their action on the Cannabinoid 1 (CB_1) receptor because these effects are reversed by pre-treatment with the CB_1 antagonist/inverse agonist, rimonabant.

Another prominent cannabinoid found in marihuana is cannabidiol (CBD) which is non-psychotropic (Mechoulam 1970; see also Mechoulam et al. 2007). CBD has a wide range of therapeutic effects (see Mechoulam et al. 2007; Pertwee 2004, for reviews) including the suppression of nausea and vomiting (see Parker and Limebeer 2008). Low doses (but not high doses of 20 mg/kg or greater; Darmani et al. 2007; Parker et al. 2004; Kwiatkowska et al. 2004) of CBD interfere with conditioned gaping reactions in rats (Parker et al. 2002; Parker et al. 2003; Rock et al. 2008) as well as vomiting (Kwiatkowska et al. 2004; Parker et al. 2004) and conditioned retching (Parker et al. 2006) in shrews. This suppression of nausea and vomiting is not mediated by action at the CB_1 or CB_2 receptors (see Mechoulam et al. 2002; Parker et al. 2004). Russo et al. (2005) showed that micromolar concentration of CBD displaces [^{3}H]8-OH-DPAT (a 5-HT_{1A} receptor agonist) from cloned human 5-HT_{1A} receptors in vitro, increases GTP binding to the receptor-coupled G protein, Gi, and reduces cAMP production, all characteristic of a receptor agonist. These findings suggest that CBD may act as a 5-HT_{1A} receptor agonist. Interestingly, the neuroprotective effects of CBD are reversed by WAY100135 (a 5-HT_{1A} antagonist) (Mishima et al. 2005) and not by rimonabant (Hayakawa et al. 2004). Recent experiments by Rock et al. (2010) found that WAY100135 suppresses the ability of CBD to reduce nicotine, cisplatin, and lithium chloride (LiCl)-induced vomiting in shrews (as well as the more selective antagonist WAY100635) and to interfere with the establishment of LiCl-induced conditioned gaping in rats. This is consistent with earlier work that very low doses (0.001–0.01 mg/kg of the 5-HT_{1A} agonist, 8-OH-DPAT, suppressed LiCl-induced gaping in rats (Limebeer and Parker 2003) and vomiting in cats (Lucot and Crampton 1988). Furthermore, Rock et al. (2010) found that when delivered directly to the dorsal raphe nucleus (DRN), CBD prevented LiCl-induced conditioned gaping reactions in rats, and WAY100135 delivered to the DRN reversed the effects of systemic CBD. Thus, it appears that CBD may exert its anti-emetic and anti-nausea effects by agonism of the 5-HT_{1A} somatodendritic autoreceptors located in the raphe.

Another non-psychoactive cannabinoid found in marihuana is cannabigerol (CBG) (Gaoni and Mechoulam 1964b; Mechoulam 1970). CBG has shown potential for the treatment of glaucoma (Colasanti 1990; Colasanti et al. 1984), psoriasis (Wilkinson and Williamson 2007), and pain (De Petrocellis et al. 2008). CBG also shows antitumor activity *in vitro* (Ligresti et al. 2006) and displays antibacterial properties (Eisohly et al. 2006), making it a potential candidate for the treatment of antibiotic-resistant bacteria (Appendino et al. 2008). Recently, Maor et al. (2005) reported that the synthetic dimethylheptyl homolog of cannabigerol (CBG-DMH) displays hypotensive potential. The mechanism of action of CBG is still under investigation. Preliminary evidence suggests that CBG may act as a moderately potent 5-HT_{1A} antagonist (Cascio et al. 2010), as well as having other effects. If CBG indeed acts as a 5-HT_{1A} antagonist, it may block the anti-emetic, anti-nausea effects of CBD.

It is of therapeutic interest to investigate the role of cannabinoids in the regulation of nausea and vomiting as well as the effects of their interactions on such regulation. The following experiment evaluated the potential of CBD and CBG to regulate nausea in rats and vomiting in the *Suncus murinus*. If the hypothesis is correct that CBG acts *in vivo* as a 5-HT_{1A} receptor antagonist, then the anti-nausea, anti-emetic effects of CBD should be blocked by pre-treatment with CBG. As well, the potential of CBG to reverse the anti-nausea effect of the classic 5-HT_{1A} antagonist, 8-OH-DPAT (Limebeer and Parker 2003), was also assessed.

Materials and methods

Animals

Animal procedures were according to the Canadian Council on Animal Care (CCAC) and the National Institutes of Health guidelines. The protocols were approved by the Institutional Animal Care Committee, which is accredited by the CCAC. Male Sprague–Dawley rats, weighing between 262 and 330 g on the day of conditioning, obtained from Charles River Laboratories (St Constant, Quebec) were used in experiment 1. They were single-housed in Plexiglas cages in the colony room at an ambient temperature of 21°C with a 12/12 light/dark schedule (lights off at 8 a.m.) and maintained on ad libitum food and water. Male *S. murinus* (house musk shrews) bred and raised at the University of Guelph colony were used in experiment 2. They were single-housed in cages in a colony room at an ambient temperature of 21°C on a 14/10 light dark schedule (lights off at 9 p.m.) as described in Parker et al. (2009).

Drugs

All drugs were injected intraperitoneally (ip). Both CBG and CBD were prepared in a vehicle (VEH) solution of 45% 2-hydroxypropyl-β-cyclodextrin (Sigma) with sterile

water. CBD (provided by Dr. Raphael Mechoulam, Hebrew University) was prepared as a 5 mg/2 ml solution of the VEH and administered at a volume of 2 ml/kg (5 mg/kg the optimal dose previously demonstrated to interfere with conditioned gaping in rats [Parker et al. 2002] and vomiting in shrews [Parker et al. 2004]). CBG (also provided by Dr. Raphael Mechoulam, Hebrew University) was prepared as 1 mg/2 ml, 5 mg/2 ml, and 10 mg/2 ml in experiment 1a and as a 5 mg/2 ml solution in experiments 1b and 2 and was always administered at a volume of 2 ml/kg. The 8-OH-DPAT was prepared in saline at a concentration of 0.01 mg/ml and administered at a volume of 1 ml/kg. Lithium chloride (LiCl, Sigma) was prepared in a 0.15 M solution with sterile water and administered at a volume of 20 ml/kg (127.2 mg/kg) in experiments 1a and 1b and 60 ml/kg (390 mg/kg) in experiment 2.

Apparatus

A clear Plexiglas chamber (22.5×26×20 cm) with an opaque Plexiglas lid was placed on a table with a clear Plexiglas top for TR procedures with rats and to monitor vomiting in the shrews in different rooms. A mirror beneath the chamber on a 45° angle facilitated viewing of the rat's ventral surface. The room was dark with two 60 W white lights on either side of the chamber. A video camera (Sony DCR-HC48) with firewire feed to a computer was used to record the behaviour from the mirror beneath the chamber.

Procedure

Experiment 1: interaction of CBG and CBD or 8-OH-DPAT on LiCl-induced nausea in rats

Experiment 1a: CBG and CBD All rats were surgically implanted with intra-oral cannulae as described by Limebeer et al. (2010). Three days later, the rats received an adaptation trial to the TR procedure. The rats were placed individually into the chamber with their cannulae attached to an infusion pump (Model KDS100; KD Scientific, Holliston, MA) via an infusion tube inserted through the ceiling of the chamber. They were infused with reverse osmosis water for 2 min at a rate of 1 ml/min, following which they were returned to their home cages.

Twenty-four hours following adaptation, the rats received a conditioning trial in which they were administered a pre-treatment and a treatment injection. The pretreatment drug was CBG (0, 1, 5, or 10 mg/kg) followed 15 min later by a treatment injection of either VEH or CBD (5 mg/kg). This design resulted in the following groups: CBG 0 mg/kg-VEH (n=8), CBG 0 mg/kg CBD (n=9), CBG 1 mg/kg–VEH (n=8), CBG 1 mg/kg–CBD (n=8), CBG 5 mg/kg–VEH (n=9), CBG 5 mg/kg–CBD (n=8), CBG 10 mg/kg–VEH (n=8), and CBG 10 mg/kg–CBD (n=9). Thirty minutes after the treatment injection, the rats were individually placed in the chamber and intra-orally infused with a 0.1% saccharin solution for 2 min at a rate of 1 ml/min, while their orofacial and somatic responses were video-recorded. Immediately following the saccharin infusion, the rats were injected with 20 ml/kg of 0.15 M LiCl and returned to their home cages. Ninety-six hours following the conditioning trial, the rats individually received a single drug-free test trial in which they were returned to the chamber and intra-orally infused with the 0.1% saccharin solution for 2 min (1 ml/min), while their orofacial and somatic responses were video-recorded. The rats were then returned to their home cages.

For 2 days following the test trial, the rats received consumption tests to assess conditioned taste avoidance. At 9 a.m. on the first day, having been water deprived for 17 h, the rats received two graduated drinking tubes, one with the 0.1% saccharin solution and one with water. The tubes were placed on the lids of the home cages, in the usual location of their water bottles, and the amount of solution consumed was recorded at 30, 60, 120, 240, and 360 min to obtain a measure of taste avoidance. On the second day, the rats were given an identical test, except that they received only one drinking tube with the saccharin solution, and consumption was measured at the same time intervals and additionally at 24 h.

The videotapes from the conditioning and test trials were scored by observers blind to the experimental condition using “The Observer” (Noldus, NL) event-recording program. The behavioural measure of interest was gaping, the most reliable measure of conditioned nausea (Breslin et al. 1992). Gaping is defined as large openings of the mouth and jaw, with lower incisors exposed.

Conditioned taste avoidance was assessed in both a two-bottle test and a single-bottle test. For the two-bottle test, the amount consumed of 0.1% saccharin solution, and water was transformed into a saccharin preference ratio which was defined as the amount of saccharin solution consumed divided by the total amount of saccharin and water consumed (saccharin solution/[saccharin solution+water]).

Experiment 1b: CBG and 8-OH-DPAT Experiment 1b was conducted identically to experiment 1a, except that during the conditioning trial, the rats were pre-treated with either VEH or CBG (5 mg/kg) followed 15 min later by a treatment injection of saline or 8-OH-DPAT (0.01 mg/kg) with the following groups: VEH–saline (n=8), CBG–saline (n=8), VEH–8-OH-DPAT (n=7), or CBG–8-OH-DPAT (n=8). Thirty minutes later, rats were intra-orally infused with 0.1% saccharin solution and were immediately injected with LiCl as in experiment 1a.

Experiment 2: interaction of CBG and CBD on LiCl-induced vomiting in shrews

The shrews were moved into the experimental room from the adjacent colony room and given four meal worms in an empty cage 15 min prior to receiving the pre-treatment injection of either VEH or CBG (5 mg/kg). Fifteen minutes later, they were treated with an injection of either VEH or CBD (5 mg/kg), and 30 min later injected with LiCl (390 mg/kg). The shrews were then individually placed into the chamber, and the frequency of vomiting episodes (expulsion of fluids from the stomach) displayed over the next 45 min was measured by an observer blind to experimental conditions. The groups were: CBG–CBD (n=8), CBG–VEH (n=8), VEH–CBD (n=11), VEH–VEH (n=11).

Data analysis

In experiments 1a and 1b, the number of gapes displayed by each rat on the TR test trial was entered into a two-factor ANOVA with the factors of pre-treatment drug (experiment 1a: VEH, 1 mg/kg CBG, 5 mg/kg CBG, 10 mg/kg CBG; experiment 1b: VEH or CBG) and treatment drug (experiment 1a: VEH or CBD; experiment 1b: Saline or 8-OH-DPAT). For conditioned taste avoidance, since the preference ratios and intake measures were cumulative, and therefore not independent, the data for each time point was entered into a 4×2 between-groups ANOVA. For experiment 2, the number of vomiting episodes was entered into a 2×2 between-groups ANOVA with the factors of pre-treatment drug (CBG or VEH) and treatment drug (CBD or VEH). Significance was defined as $p<0.05$.

Results

Experiment 1: interaction of CBG and CBD or 8-OH-DPAT on LiCl-induced nausea in rats

Experiment 1a: CBG and CBD CBD attenuated LiCl-induced conditioned gaping reactions; this attenuated nausea was prevented by pre-treatment with 5 or 10 mg/kg of CBG (and marginally by 1 mg/kg of CBG). The lowest dose of CBG also suppressed LiCl-induced conditioned gaping on its own.

Figure 1 presents the mean number of gaping reactions elicited by intra-oral infusion of 0.1% saccharin solution on the TR test trial for each pre-treatment (0, 1, 5, and 10 mg/kg CBG) and treatment (VEH and CBD) drug. The 4×2 between-groups ANOVA revealed significant effects of pre-treatment, F (3, 59)=4.2; p=0.01, and a significant pre-treatment by treatment interaction, F (3, 59)=3.4; p=0.024. As assessed by separate planned comparison tests for each pre-treatment group, CBD significantly attenuated gaping in the 0 mg/kg CBG pre-treatment group (p < 0.001), but not in any other pre-treatment group. In addition, separate one-way ANOVAs for each treatment drug revealed a significant effect for both the CBD treatment drug, F (3, 30)=3.5; p=0.025, and the VEH treatment drug, F (3, 29)=4.1; p=0.015. Among the CBD treated rats, those pre-treated with 0 mg/kg CBG displayed significantly fewer gapes than those pre-treated with either 5 or 10 mg/kg of CBG (p < 0.025), but they only marginally differed from those pre-treated with 1 mg/kg of CBG (p=0.063). Among the VEH-treated rats, those pre-treated with 1 mg/kg CBG displayed significantly fewer gapes than any other pre-treatment group (p <0.025).

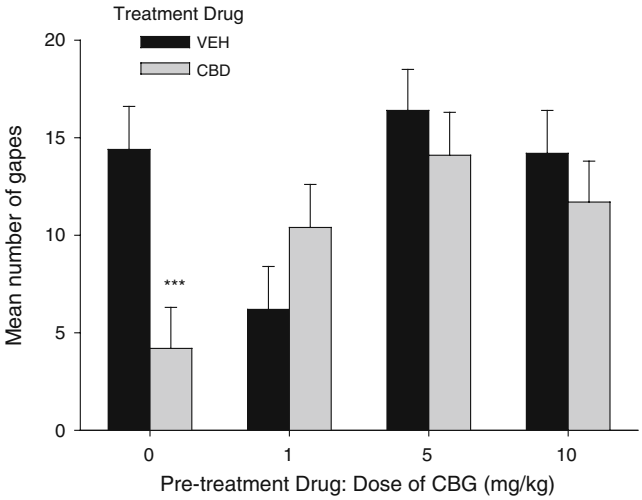

Fig. 1 Mean (±SEM) number of gaping responses elicited by a 2-min intra-oral infusion of 0.1% saccharin solution on the TR test trial for each pre-treatment (0, 1, 5, and 10 mg/kg CBG) and treatment (VEH and CBD) drug. All rats were conditioned with LiCl. ***p <0.001; **p<0.01, significant results

The groups did not differ in mean saccharin preference in the two-bottle test or in mean saccharin consumption in the one-bottle test. Figure 2 presents the mean cumulative saccharin preference ratios during the two-bottle test for the various groups across the 360 min of testing. Separate 4×2 ANOVAs for each time period revealed no significant effects. As well, the mean amount of saccharin solution consumed in the subsequent one-bottle test across 24 h of testing revealed no significant group differences at any time point (data not depicted).

Experiment 1b: CBG and 8-OH-DPAT The classic 5-HT_{1A} agonist, 8-OH-DPAT also suppressed LiCl-induced conditioned gaping reactions in rats as has been previously reported (Limebeer and Parker 2003) and CBG reversed this effect. Figure 3 presents the mean number of gaping reactions elicited by LiCl-paired saccharin solution during the TR test trial in experiment 1b. As is apparent, the 2×2 ANOVA revealed a significant pre-treatment by treatment

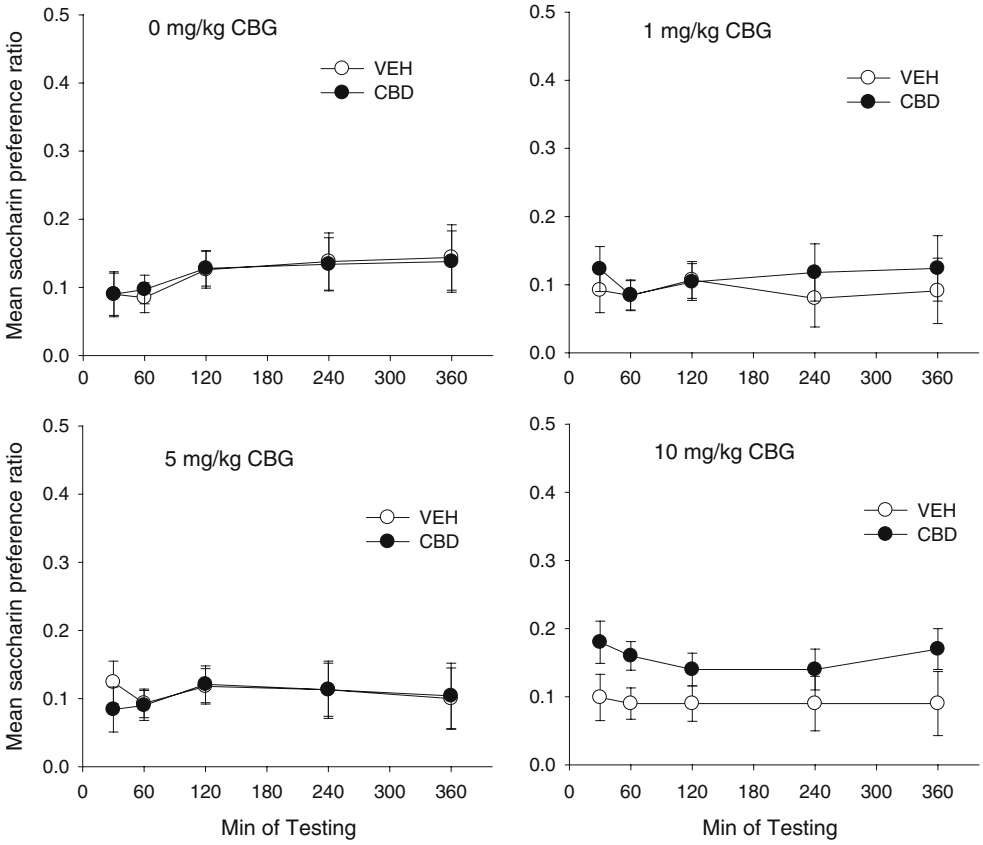

Fig. 2 Mean (±SEM) cumulative saccharin preference ratio (saccharin solution/[saccharin solution+ water]) for the various conditioning groups during the preference test at 30, 60, 120, 240, and 360 min. All rats were conditioned with LiCl

interaction, F (1, 26)=4.2; $p<0.05$. Rats pre-treated with VEH displayed fewer gapes during the TR test when they were treated with 8-OH-DPAT prior to conditioning ($p<0.01$), but this effect was reversed by pre-treatment with CBG. Although not depicted, as in experiment 1a, the groups did not differ in mean saccharin preference in the two-bottle test or in mean saccharin consumption in the one-bottle test.

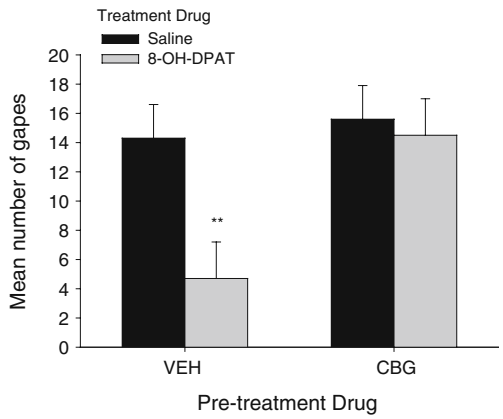

Fig. 3 Mean (±SEM) number of gaping responses elicited by a LiCl-paired saccharin solution during the TR test; in experiment 1b when rats were pre-treated with VEH or CBG and treated with saline or 8-OH-DPAT prior to the conditioning trial **p <0.01

Experiment 2: vomiting in shrews

In experiment 2, CBD suppressed LiCl-induced vomiting in *S. murinus,* an effect which was reversed by pre-treatment with CBG. Figure 4 presents the mean number of vomiting episodes elicited by LiCl for each pre-treatment/ treatment group. The 2×2 between-groups ANOVA revealed a significant interaction, F (1, 34)=5.7; $p<0.025$. Subsequent planned comparisons among all groups revealed that group VEH–CBD displayed significantly less vomiting than any other group ($p<0.01$), which did not differ among themselves.

Discussion

The present results showed that both CBD and 8-OH-DPAT attenuated conditioned gaping produced by LiCl in rats, as has previously been reported (e.g., Parker et al. 2002; Limebeer and Parker 2003). Both effects were prevented by pre-treatment with CBG. CBD may produce this anti-nausea effect by activating the 5-HT_{1A} receptor, as the 5-HT_{1A} receptor antagonist WAY100135 also prevents CBD's suppression of gaping (Rock et al. 2010). Cascio et al. (2010) reported that at high concentrations, CBG antagonizes the 5-HT_{1A} receptor agonist 8-OH-DPAT in [^{35}S]

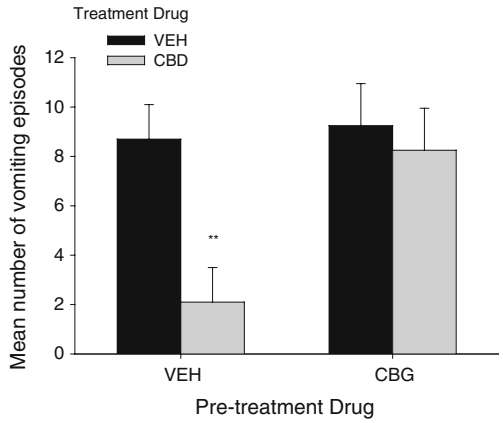

Fig. 4 Mean (±SEM) number of LiCl-induced vomiting episodes when shrews were pre-treated with VEH or 5 mg/kg CBG and treated with VEH or 5 mg/kg CBD

GTPγS binding assays in mouse brain membranes, suggesting that CBG acts as a 5-HT_{1A} receptor antagonist. In support of this interpretation, CBG prevented the suppression of gaping by 8-OH-DPAT. As well, our finding that CBG prevented CBD's suppression of gaping, similar to WAY100135, provides further evidence that CBG may act as a 5-HT_{1A} receptor antagonist and is also consistent with the finding of Cascio et al. (2010) that CBG is a neutral 5-HT_{1A} receptor antagonist and not an inverse agonist.

In experiment 2, CBG also prevented the CBD-induced suppression of LiCl-induced vomiting in shrews. Like nausea in rats, the suppression of vomiting produced by CBD is reversed by the 5-HT_{1A} antagonist, WAY100135 (Rock et al. 2010). The effect of CBD on toxin-induced vomiting in shrews is biphasic with low doses (1–10 mg/kg) suppressing vomiting, but higher doses (20–40 mg/kg) either producing no effect (Darmani 2001) or actually potentiating vomiting (Parker et al. 2004; Kwiatkowska et al. 2004). The effect of CBD on LiCl-induced conditioned nausea in rats may also be biphasic (Rock et al. 2008).

Interestingly, at the lowest dose evaluated here (but not higher doses), CBG appears to have produced an anti-nausea effect among the VEH-pre-treated rats; the mechanism for this effect is unknown. This finding may, however, be related to the concentration specific *in vitro* effects of CBG; that is at low concentrations, CBG stimulates GTPγS binding to mouse brain membranes, and this effect disappears at higher concentrations to be replaced by its action as a 5-HT_{1A} antagonist (Cascio et al. 2010).

Treatment with CBD or 8-OH-DPAT did not modify the strength of conditioned taste avoidance in the saccharin preference test or in the one-bottle test of saccharin consumption in experiment 1. Instead, as has been previously reported (Limebeer and Parker 2003; Parker et al. 2002), the effect of CBD or 8-OH-DPAT was selective to conditioned gaping (the behaviour selectively produced by nausea) and not conditioned taste avoidance (the behaviour that is non-selective to nausea). Since the rats treated with CBD or 8-OH-DPAT did not show attenuated conditioned taste avoidance, these attenuated conditioned gaping reactions cannot simply be explained as interference with learning. Instead, it is more likely that CBD and 8-OH-DPAT suppressed the nausea produced by LiCl, resulting in attenuated conditioned gaping reactions; that is, the nauseating aspect of the unconditioned stimulus (US) property of nausea was attenuated. CBG reversed this effect; however, even with the nausea suppressed, LiCl produced a sufficiently strong change in state (as do rewarding drugs for instance) that even in the absence of nausea, the rats displayed a conditioned avoidance of the taste. These findings replicate previous reports that taste avoidance may not be modified by anti-nausea treatments that dramatically attenuate conditioned gaping reactions (e.g., Parker et al. 2008). Thus, conditioned gaping is a more selective measure of nausea in rats.

Chemotherapy-induced nausea remains a significant clinical problem. Marihuana may be used to treat nausea; however, people who smoke marihuana are exposed to over 60 cannabinoids, some of which counteract one another. Although the Δ^9-THC content in the more potent strains of marihuana has increased over the past 10 years, the concentration of both CBD and CBG has remained constant (Mehmedic et al. 2010). Our findings suggest that it may be more effective to treat nausea with specific cannabinoids that have proven anti-nausea effects, such as CBD, rather than with marihuana, which is psychoactive and contains cannabinoids, such as CBG, that prevent the anti-nausea effects of other cannabinoids.

Acknowledgements The following research was supported by research grants from the Natural Sciences and Engineering Research Council (NSERC) of Canada to LAP, a scholarship from NSERC to EMR, and a grant from NIDA (9789) to RM and RGP. For reprints please contact parkerl@uoguelph.ca.

References

Abrahamov A, Abrahamov A, Mechoulam R (1995) An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci 56:2097–2102

Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Starvi M et al (2008) Antibacterial cannabinoids from *Cannabis sativa*: a structure–activity study. J Nat Prod 71:1427–1430

Breslin PAS, Grill HJ, Spector AC (1992) A quantitative comparison of taste reactivity behaviors to sucrose before and after lithium chloride pairings: a unidimensional account of palatability. Behav Neurosci 106:820–836

Cascio MG, Gauson LA, Ross RA, Pertwee RG (2010) Evidence that the plant cannabionoid cannabigerol is a highly potent α_2-adrenoceptor agonist and moderately potent 5HT_{1A} receptor antagonist. Br J Pharmacol 159:129–141

Colasanti BK (1990) A comparison of the ocular and central effects of delta-9-tetrahydrocannabinol and cannabigerol. J Ocular Pharmacol Ther 6:259–269

Colasanti BK, Craig CR, Allara RD (1984) Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol and cannabigerol. Exper Eye Res 39:251–259

Darmani NA (2001) Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB_1 receptor in the least shrew. Pharmacol Biochem Behav 69:239–249

Darmani NA, Janoyan JJ, Crim J, Ramirez J (2007) Receptor mechanism and antiemetic activity of structurally-diverse cannabinoids against radiation-induced emesis in the least shrew. Eur J Pharmacol 563:187–196

De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P et al (2008) Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and malastatin type-8. J Pharmacol Exp Ther 325:1007–1015

Eisohly HN, Turner CE, Clark AM, Eisohly MA (2006) Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. J Pharm Sci 71:1319–1323

Gaoni Y, Mechoulam R (1964a) Isolation, structure, and partial synthesis of an active component of hashish. J Amer Chem Soc 86:1646–1647

Gaoni Y, Mechoulam R (1964b) The structure and synthesis of cannabigerol, a new hashish constituent. Proc Chem Soc 82

Grill HC, Norgren R (1978) The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res 143:263–279

Hayakawa K, Mishima K, Abe K, Hasebe N, Takamatsu F, Yasuda H et al (2004) Cannabidiol prevents infarction via the non-CB1 cannabinoid receptor mechanism. NeuroReport 15:2381–2385

Kwiatkowska M, Parker LA, Burton P, Mechoulam R (2004) A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the *Suncus murinus* (house musk shrew). Psychopharmacol 174:254–259

Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L et al (2006) Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther 318:1375–1387

Limebeer CL, Parker LA (1999) Delta-9-tetrahydrocannabinol interferes with the establishment and the expression of conditioned rejection reactions produced by cyclophosphamide: a rat model of nausea. NeuroReport 10:3769–3772

Limebeer CL, Parker LA (2003) The 5-HT_{1A} agonist 8-OH-DPAT dose-dependently interferes with the establishment and the expression of lithium-induced conditioned rejection reactions in rats. Psychopharmacol 166:120–126

Limebeer CL, Vemuri VK, Bedard H, Lang ST, Ossenkopp KP, Makriyannis A, Parker LA (2010) Inverse agonism of cannabinoid CB1 receptors potentiates LiCl-induced nausea in the conditioned gaping model in rats. Br J Pharm (in press)

Lucot JB, Crampton GH (1988) 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin, or xylazine. Pharmacol Biochem Behav 33:627–632

Maor Y, Morowitz M, Gallily R, Mechoulam R (2005) Cannabigerol-dimethyl heptyl (CBG-DMH), a synthetic cannabinoid with hypotensive and vasorelaxant properties. Presented at the symposium of the International Cannabinoid Research Society, Clearwater, FL, June

Mechoulam R (1970) Marihuana chemistry. Science 168:1159–1163

Mechoulam R, Parker LA, Gallily R (2002) Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol 42:11S–19S

Mechoulam R, Peters M, Murillo-Rodriquez E, Hanus LO (2007) Cannabidiol—recent advances. Chem Biodiv 4:1678–1692

Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, Ross SA, Khan IA, ElSohly MA (2010) Potency trends of Δ^9-THC and other cannabinoids in confiscated cannabis preparations from 1993–2008. J Forensic Sci 55:1209–1217

Mishima K, Hayakawa K, Abe K, Ikeda T, Egashira N, Iwasaki K et al (2005) Cannabidiol prevents infarction via a serotonergic 5-hydroxytryptamine$_{1A}$ receptor-dependent mechanism. Stroke 36:1071–1076

Orr LE, McKernan JF, Bloome B (1980) Antiemetic effect of tetrahydrocannabinol compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Arch Intern Med 140:1431–1433

Parker LA, Limebeer CL (2008) Cannabinoids and the management of nausea and vomiting. In: Kofalvi A (ed) Cannabinoids and the brain. Springer, New York

Parker LA, Mechoulam R (2003) Cannabinoid agonists and antagonists modulate lithium-induced conditioned gaping in rats. Integr Phsyiol Behav Sci 38:133–145

Parker LA, Mechoulam R, Schlievert C (2002) Cannabidiol, a non-psychoactive component of cannabis, and its dimethylheptyl homolog suppress nausea in an experimental model with rats. NeuroReport 13:567–570

Parker LA, Mechoulam R, Schlievert C, Abbott L, Fudge ML, Burton P (2003) Effects of cannabinoids on lithium-induced conditioned rejection reactions in a rat model of nausea. Psychopharmacol 166:156–162

Parker LA, Kwiatkowska M, Burton P, Mechoulam R (2004) Effect of cannabinoids on lithium-induced vomiting in the *Suncus murinus*. Psychopharmacol 171:156–161

Parker LA, Limebeer CL, Kwiatkowska M (2005) Cannabinoids: effects on vomiting and nausea in animal models. In: Mechoulam R (ed) Cannabinoids as therapeutics. Birkhäuser, Switzerland, pp 183–200

Parker LA, Kwiatkowska M, Mechoulam R (2006) Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in *Suncus murinus*: an animal model of anticipatory nausea and vomiting. Physiol Behav 87:61–71

Parker LA, Limebeer CL, Rana SA (2008) Conditioned nausea in rats: assessment by conditioned disgust reactions, rather than conditioned taste avoidance. Can J Exp Psychol 62:189–209

Parker, LA., Limebeer CL, Rock EM, Litt DL, Kwiatkowska M., and Piomelli D. (2009) The FAAH inhibitor URB-597 interferes with cisplatin- and nicotine- induced vomiting in the *Suncus murinus* (house musk shrew). Physiol Behav 97: 121-124

Pertwee RG (2004) In: DiMarzo V (ed) The pharmacology and therapeutic potential of cannabidiol, in cannabinoids. Kluwer, New York

Rock EM, Limebeer CL, Mechoulam R, Piomelli D, Parker LA (2008) The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. Psychopharmacol 196:389–395

Rock EM, Limebeer CL, Fletcher PJ, Mechoulam R, Parker LA (2010). Cannabidiol (the non-psychoactive component of cannabis) may act as a 5-HT1A auto-receptor agonist to reduce toxin-induced nausea and vomiting. Poster presented at the Society for Neuroscience meeting, San Diego, CA

Russo EB, Burnett A, Hall B, Parker KK (2005) Agonistic properties of cannabidiol at 5-HT_{1A} receptors. Neurochem Res 30:1037–1043

Sallan SE, Zinberg NE, Frei E (1975) Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. New Engl J Med 293:795–797

Tramer MR, Carroll D, Campbell FA, Reynolds DJM, Moore RA, McQuay HJ (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 323:1–8

Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K, Davison JS et al (2001) Cannabinoids inhibit emesis through CB_1 receptors in the brainstem of the ferret. Gastroenterol 121:767–774

Wilkinson JD, Williamson EM (2007) Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have potential therapeutic value in the treatment of psoriasis. J Dermatol Sci 45:87–92