Cannabinoid Agonists and Antagonists Modulate Lithium-induced Conditioned Gaping in Rats

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Considerable evidence indicates that conditioned gaping in rats reflects nausea in this species that does not vomit. A series of experiments evaluated the potential of psychoactive cannabinoid agonists, Δ–9-THC and HU–210, and non-psychoactive cannabinoids, Cannabidiol (CBD) and its dimethylheptyl homolog (CBD-dmh), to interfere with the establishment and the expression of conditioned gaping in rats. All agents attenuated both the establishment and the expression of conditioned gaping. Furthermore, the CB1 antagonist, SR–141716, reversed the suppressive effect of HU–210 on conditioned gaping. Finally, SR–141716 potentiated lithium-induced conditioned gaping, suggesting that the endogenous cannabinoid system plays a role in the control of nausea.

Key Words—classical conditioning, nausea, emesis, taste avoidance learning, taste aversion learning, cannabinoids, taste reactivity

WHEN SWEET SUCROSE SOLUTION is paired with a drug that produces illness, rats not only avoid consuming that solution in the future, but they also display conditioned disgust reactions upon exposure to that solution (Garcia, Hankins & Rusiniak, 1974). According to Garcia (1989), the only change in physiological state that produces "conditioned disgust" is one that induces nausea; that is, one that acts on the emetic system of the midbrain and brainstem. Although rats are incapable of vomiting, they display conditioned disgust reactions (i.e., gaping) when exposed to a flavor previously paired with drug-induced nausea.

Rats are a non-emetic species, but their gastric vagal afferents respond in a similar manner to physical and chemical (intragastric copper sulfate and cisplatin) stimulation that precedes vomiting in the ferret (Blackshaw & Grundy, 1993; Davis et al., 1986). Furthermore, serotonin ($5\text{-}HT_3$) antagonists that block vomiting in ferrets disrupt this neural afferent reaction in both ferrets and rats. In the rat, the mechanism that detects gastrointestinal distress is present, but the vomiting response is absent (Davis et al., 1986). Although rats are incapable of vomiting, they display conditioned gaping upon re-exposure to a flavor previously paired with treatments that produce vomiting in emetic species (Grill & Norgren, 1978). In fact, Travers and Norgren (1986) suggested that the muscular movements involved in gaping mimic those seen in species capable of vomiting.

The insectivore, *Suncus murinus* (house musk shrew), vomits when injected with emetic agents such as lithium chloride (Parker & Kemp, 1999; Parker et al., in press). Prior to

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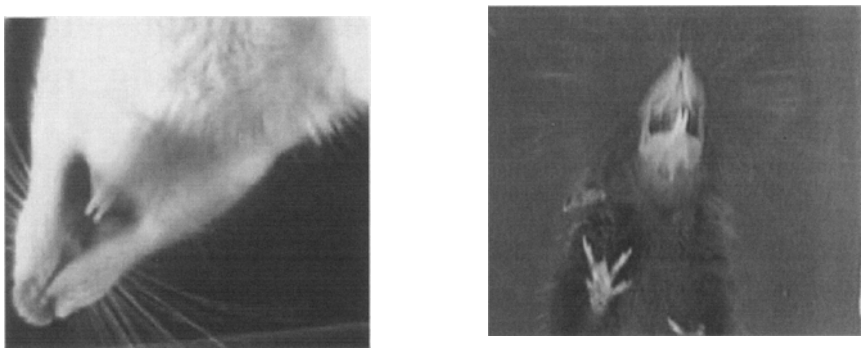

FIG. 1. The orofacial characteristics of the rat gape are very similar to those of the shrew retch. Unlike the rat, the shrew vomits in response to emetic stimulation.

displaying the vomiting response, shrews display retching. The orofacial topography of the shrew retch is very similar to that of the rat gape, as is seen in Figure 1. We have argued (Parker, 2003) that the gaping response in the rat represents an incipient vomiting response in this animal that does not display the full vomiting response. Non-emetic treatments, such as amphetamine, do not produce conditioned gaping when paired with a flavored solution, even at doses that are titrated to produce taste avoidance equivalent to that produced by the emetic agent, lithium chloride (Parker, 1982; Pelchat et al., 1983; Parker, 1995; Zalaquett & Parker, 1989).

The typical measure of flavor-illness associations is the amount of solution consumed from a bottle containing the flavored solution–conditioned taste avoidance. This measure requires the rat to approach the bottle in order to sample the flavored solution; therefore, it involves an appetitive and consummatory phase in responding (Konorski, 1967). An alternative measure of a flavor-illness association is called the taste reactivity (TR) test (Grill & Norgren, 1978). This test measures the orofacial and somatic reactions elicited by a flavor infused directly into a rat's mouth. The experimenter controls exposure to the Conditioned Stimulus (CS) flavored solution and the rat reacts with only the consummatory phase of responding. When infused with a flavored solution previously paired with nausea, rats display conditioned gaping—a direct measure of taste aversion. Rats display conditioned gaping to flavored solutions that have been paired with low to high doses of lithium chloride (Berridge, Grill & Norgren, 1981; Grill & Norgren, 1978; Parker, 1982), cyclophosphamide (Parker, 1998; Limebeer & Parker, 1999), high doses of nicotine (Parker, 1991) and apomorphine (Parker & Brosseau, 1990), naloxone-precipitated morphine withdrawal (McDonald, Parker & Siegel, 1997), and full body rotation (Cordick, Parker & Ossenkopp, 1999). Each of these treatments produces vomiting in species that are capable of vomiting.

Anti-emetic drugs interfere with conditioned gaping in rats (Limebeer & Parker, 1999; Limebeer & Parker, 2000; Parker et al., 2002). The 5-HT_3 antagonist, ondansetron, one of

the most effective treatments for reducing nausea and vomiting in humans, reduces lithium-induced conditioned gaping in rats—by interfering with its establishment during conditioning with its expression during testing (Limebeer & Parker, 2000). We were surprised to discover that ondansetron did not modify lithium-induced taste avoidance; in fact, when gaping was measured during a consumption test, ondansetron suppressed conditioned gaping, but did not modulate the amount consumed (Limebeer & Parker, 2000; see also Rudd et al., 1998). In a similar manner, THC interferes with conditioned gaping elicited by cyclophosphamide-paired saccharin solution, but does not interfere with conditioned avoidance of that flavor. Conditioned gaping, but not conditioned taste avoidance, appears to reflect nausea in rats.

Cannabinoid drugs have been reported to have anti-emetic and anti-nausea properties. Early clinical trials demonstrated that cannabinoids reduce nausea in humans (Sallan et al., 1975). Indeed, Δ–9-tetrahydrocannabinol (THC) and nabilone are approved anti-nausea drugs in human patients. There is considerable evidence that cannabinoid agonists attenuate vomiting in emetic species. Cannabinoid agonists reduce vomiting in cats (McCarthy & Borison, 1984), dogs (Lowe, 1946), pigeons (Feigenbaum et al., 1989; Ferrari et al., 1999), ferrets (Simoneau II et al., 2001; VanSickle et al., 2001), and least shrews, Cryptotis parva (Darmani 2001a-c, 2002). The selective CB_1 receptor antagonist SR–141716 blocks the anti-emetic activity of cannabinoid agonists in the least shrew (Darmani 2001c) and produces vomiting on its own in least shrews (Darmani 2001a). Darmani (2002) has shown that the endocannabinoid, 2-arachidonoyl glycerol (2-AG), is a potent emetogenic agent, whereas anandamide may have weak anti-emetic effects (Darmani, 2002; Van Sickle et al., 2001). These results suggest that endogenous cannabinoids may play a role in emesis.

We (Parker, et al, 2002; Parker et al, 2003) have reported the potential of low doses of Δ–9-THC, Cannabidiol (CBD), Cannabidiol-dimethylheptyl (CBD-dmh) and the potent, cannabinoid agonist, (-) 11-hydroxy-delta–8-tetrahydrocannabinol-dimethylheptyl (HU–210), to interfere with the establishment of lithium-induced conditioned rejection reactions (gapes + chin rubs + paw pushes), presumably by interfering with lithium-induced nausea. However, pretreatment with these cannabinoid agonists did not affect the strength of lithium-induced taste avoidance. Since gaping is the predominant and most reliable of the conditioned rejection reactions, here we report the effect of the cannabinoids on the establishment and or the expression of conditioned gaping in the rat. We also report the ability of the CB_1 receptor antagonist, SR–141716, to reverse the effects of HU–210 and to modulate lithium-induced conditioned gaping on its own.

Method

Subjects

The subjects were 188 male Sprague-Dawley rats (Charles River Laboratories, St. Constant, Quebec), which weighed 250 – 350 gm on the conditioning day. They were individually housed in stainless steel hanging cages in a colony room kept at 21°C on a 12:12 hr light:dark schedule with the lights on at 0700 h. Throughout the experiment, the rats were maintained on ad-libitum Rat Chow and water. The procedures were approved by the Wilfrid Laurier University Animal Care Committee according to the guidelines of the Canadian Council on Animal Care.

Surgery

The rats were surgically implanted with intra-oral cannulae as described by Limebeer and Parker (2000). The surgical anesthesia preparation included intraperitoneal (ip) administration of 0.4 mg/kg atropine solution 15-min prior to ketamine (75 mg/kg, ip) combined with xylazine (10 mg/kg, ip) which was dissolved in sterile water and administered at a volume of 1 ml/kg. A thin walled 15-gauge stainless steel needle was inserted at the back of the neck and directed subcutaneously (sc) around the ear and brought out behind the first molar inside of the mouth. Intramedic polyetheline tubing with an inner diameter of 0.86 mm and an outer diameter of 1.27 mm was then run through the needle after which the needle was removed. A B-D Intramedic leur stub adapter (20 gauge) was attached to the exposed tubing at the back of the neck. The tubing was held secure in the oral cavity by an o-ring, which was sealed behind the tubing. On each of three subsequent days during recovery from surgery, the cannulae were flushed with a chlorhexidine rinse (Nolvasan; 0.1% chlorhexidine) to prevent infection.

Drugs

All drugs were injected intraperitoneally (ip). Cannabidiol (CBD), Cannabidiol dimethylheptyl (CBD-dmh), THC, HU–210, and SR–141716 were all prepared in a solution of 1 ml ethanol/1 ml Emulpher (Sigma)/ 18 ml saline. CBD and CBD-dmh were prepared as a 5 mg/ml solution of the vehicle and were administered in a volume of 1 ml/kg (5 mg/kg). Δ–9-THC (obtained from NIDA) was prepared as a 1 mg/ml solution of the vehicle and was administered in a volume of 0.5 ml/kg (0.5 mg/kg). This dose of THC is lower than those that have been found to be aversive in rats (Parker & Gillies, 1995; Mallet & Beninger, 1998). HU–210 was prepared as a 0.01 mg/ml solution of the vehicle and was administered at volumes of 1 ml/kg (.01 mg/kg), 0.5 ml/kg (.005 mg/kg), and 0.1 ml/kg (.001 mg/kg). SR–141716A (provided by the National Institute on Drug Abuse) was prepared as a 1 mg/ml solution of the vehicle and was administered at a volume of 2.5 ml/kg (2.5 mg/kg). Lithium chloride was prepared in a .15 M (wt/vol) solution with sterile water and was administered at a volume of 20 ml/kg.

Procedure

Experiments 1 & 2: Effects of CBD, CBD-dmh, THC, and HU–210 on lithium-induced conditioned gaping. One week following the surgery, the rats were adapted to the conditioning procedure. On the adaptation trial, each rat was transported into the room that contained a Plexiglas test chamber (25 cm x 25 cm x 12 cm). The room was illuminated by four 25-W light bulbs located 30 cm from either side of the chamber. Each rat was placed individually into the test chamber, and a 30-cm infusion hose was then connected to the cannula through the ceiling of the chamber. A syringe was connected to the hose and placed into the holder for the infusion pump (Model 22; Harvard Apparatus, South Natick, MA). After 60 s, the pump delivered water through the tube into the rat's mouth at the rate of 1 ml/min for 2 min. The rat was then returned to its home cage.

The conditioning trial occurred on the following day. Thirty minutes prior to the conditioning trial, the rats were injected with the appropriate pretreatment drug or with the vehicle in which the drug was mixed. The pretreatment drugs were 5 mg/kg CBD, 5 mg/kg

CBD-dmh, 0.5 mg/kg THC or vehicle in Experiment 1, and HU–210 (0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg) or vehicle in Experiment 2. The conditioning procedure was similar to that of the adaptation trial, except that the rats were infused with 0.1% saccharin solution rather than water. Immediately following the infusion of saccharin solution, the rats were injected with lithium chloride or saline (n=6–8 rats per group). During the intraoral infusion, the orofacial and somatic responses displayed by the rats were videotaped from a mirror mounted at a 45° angle beneath the test chamber. Immediately following the taste reactivity (TR) conditioning trial, the rat was returned to its home cage.

The TR test trials were administered 4 and 6 days after the conditioning trial; on the day prior to the first test trial, the rats received an adaptation trial as described above. On the test trial(s), the rats were injected with a test drug or vehicle, 30 min prior to receiving an infusion of saccharin solution for 2 min at the rate of 1 ml/min, and their orofacial reactions were videotaped. In Experiment 1, the test drug was 0.5 mg/kg THC, 5 mg/kg CBD, or 5 mg/kg CBD-dmh on one day and vehicle on the other test day; and in Experiment 2, the test drug was HU–210 (at the same pretreatment dose) on one day and vehicle on the other test day. In both experiments the order of the test trials was counterbalanced among the rats in each group. In Experiment 2, among the vehicle pretreated groups approximately one-third of the group (n=4–6) was administered each dose of HU–210 (0.001, 0.005 or 0.01 mg/kg) on the drug test trial. The dose of the test drug did not effect the conditioned gaping on either the drug test or the saline test among the vehicle pretreated groups; therefore, for clarity the groups were pooled in the overall analysis.

The videotapes were later scored in slow motion (1/5 speed) by two raters for the frequency of gaping reactions (large triangular opening of the mouth revealing the bottom teeth, see Figure 1). The interater reliability of the two sets of scores was significant ($r(28) = .95$).

Experiment 3: Reversal of HU–210 effects by SR–141716 and effects of SR–141716 on lithium-induced conditioned gaping. In Experiment 3, 64 rats were randomly assigned to independent groups on the basis of pretreatment 1 (SR–141716 [2.5 mg/kg] or vehicle), pretreatment 2 (HU–210 [0.01 mg/kg] or vehicle), and the conditioning drug (lithium or vehicle) with 8 rats in each group. Thirty minutes prior to receiving a 2-min intraoral infusion of 0.1% saccharin solution in the TR chamber, the rats were administered pretreatment 1 followed 5 min later by pretreatment 2. Immediately following the infusion, the rats were injected with lithium or saline. Four days after the conditioning trial, all rats were administered a single TR test trial in a drug-free state and their orofacial reactions were videotaped.

Data Analysis

For all experiments, data were evaluated by analysis of variance (ANOVA) with the alpha level set at 0.05. In Experiments 1 and 2, pre-exposure group and conditioning group were treated as between-group factors, whereas test drug or trials were treated as within-group factors. In Experiment 3, pre-exposure drug 1 (SR–141716 or vehicle), pre-exposure drug 2 (HU–210 or vehicle), and conditioning drug (lithium or saline) were treated as between-group factors.

Results

Experiment 1: THC, CBD, and CBD-dmh

As is evident in Figure 2, the pattern of results for THC, CBD, and CBD-dmh was very similar. All cannabinoids interfered with the establishment of lithium-induced conditioned gaping and with the expression of previously established conditioned gaping in Experiment 1. For each pretreatment drug, 2 by 2 by 2 mixed factors ANOVA revealed a significant three-way interaction, smallest $F(1, 25) = 3.8$; $p < .025$. For all analyses, the triple interaction is accounted for by group vehicle-lithium displaying more conditioned gaping than any other group (p's $< .05$).

Experiment 2: HU–210

Figure 3 presents the mean frequency of conditioned gapes displayed by the various groups in Experiment 2 during the test trials. The upper figure presents the results of the vehicle test trial and the lower figure presents the results of the HU–210 test trial. A 4 by 2 by 2 mixed factors ANOVA with the between-group factors of pretreatment drug (0.0, 0.001, 0.005 and 0.01 mg/kg of HU–210) and conditioning drug (Lithium or Saline) and the within-group factor of test drug (Vehicle or HU–210) revealed a significant three-way interaction, $F(1, 56) = 4.56$; $p < .025$.

Separate 4 by 2 between groups ANOVAs were conducted for each test trial. On the vehicle test, there was a significant pretreatment by conditioning drug interaction, $F(3, 65) = 2.87$; $p < .05$. A subsequent simple main effects analysis revealed a significant effect of conditioning drug only for the vehicle pretreated group, $F(1, 27) = 8.56$; $p < .01$; on the vehicle test group vehicle–lithium displayed more gaping than did any other group HU–210-lithium. For none of the HU–210 pretreatment groups was there a significant effect of conditioning drug on the vehicle test. On the HU–210 test trials, the 2 by 4 between groups ANOVA revealed only a significant effect of conditioning drug, $F(1, 65) = 9.15$; $p < .01$; regardless of pretreatment condition, rats displayed more gaping during infusion of the lithium-paired saccharin than saline-paired saccharin. HU–210 did not completely block the expression of lithium-induced conditioned gaping. However, it did suppress conditioned gaping as revealed by the planned comparison of the mean frequency of conditioned gaping displayed by group vehicle-lithium during the vehicle test and the HU–210 test, $t(15) = 3.74$; $p < .01$.

Experiment 3: SR–141716 and HU–210

SR–141716 reversed the effects of HU–210 on conditioned gaping. Furthermore, SR–141716 potentiated the conditioned gaping elicited by lithium-paired saccharin solution. Figure 4 presents the mean frequency of gapes displayed during the TR test trial with the various groups. The 2 by 2 by 2 between groups ANOVA revealed a significant 3-way interaction, $F(1, 56) = 4.56$; $p < .025$.

Subsequent pairwise comparison tests for the conditioning drug effect revealed that all groups conditioned with lithium displayed more gapes than groups conditioned with saline (p's $< .05$), except the group given vehicle as pretreatment 1 and HU–210 as pretreatment 2; that is, HU–210 prevented the establishment of lithium-induced conditioned gaping. Additionally, among the lithium-conditioned rats, those rats pretreated with SR–141716 —

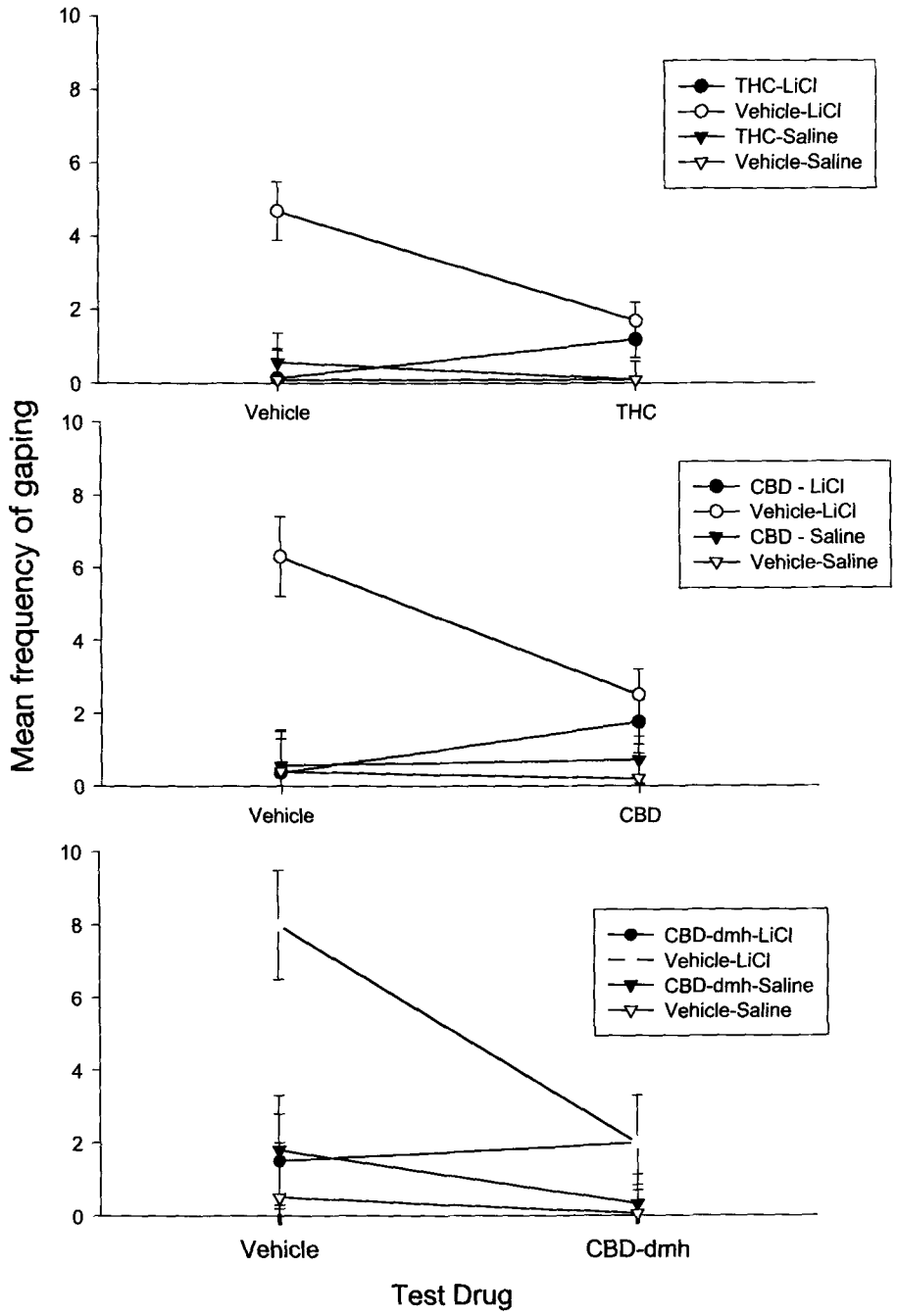

FIG. 2. Mean (±sem) frequency of gapes elicited by a 2-min infusion of 0.1% saccharin solution for the groups pretreated with THC (top section), CBD (middle section), and CBD-dmh (bottom section) in Experiment 1. The abscissa presents the test drug, a within-subjects variable, counterbalanced for order of test. Circles refer to the lithium-conditioned groups and triangles refer to the saline-conditioned groups. Filled symbols represent the cannabinoid-pretreated groups and the open symbols represent the vehicle-pretreated groups.

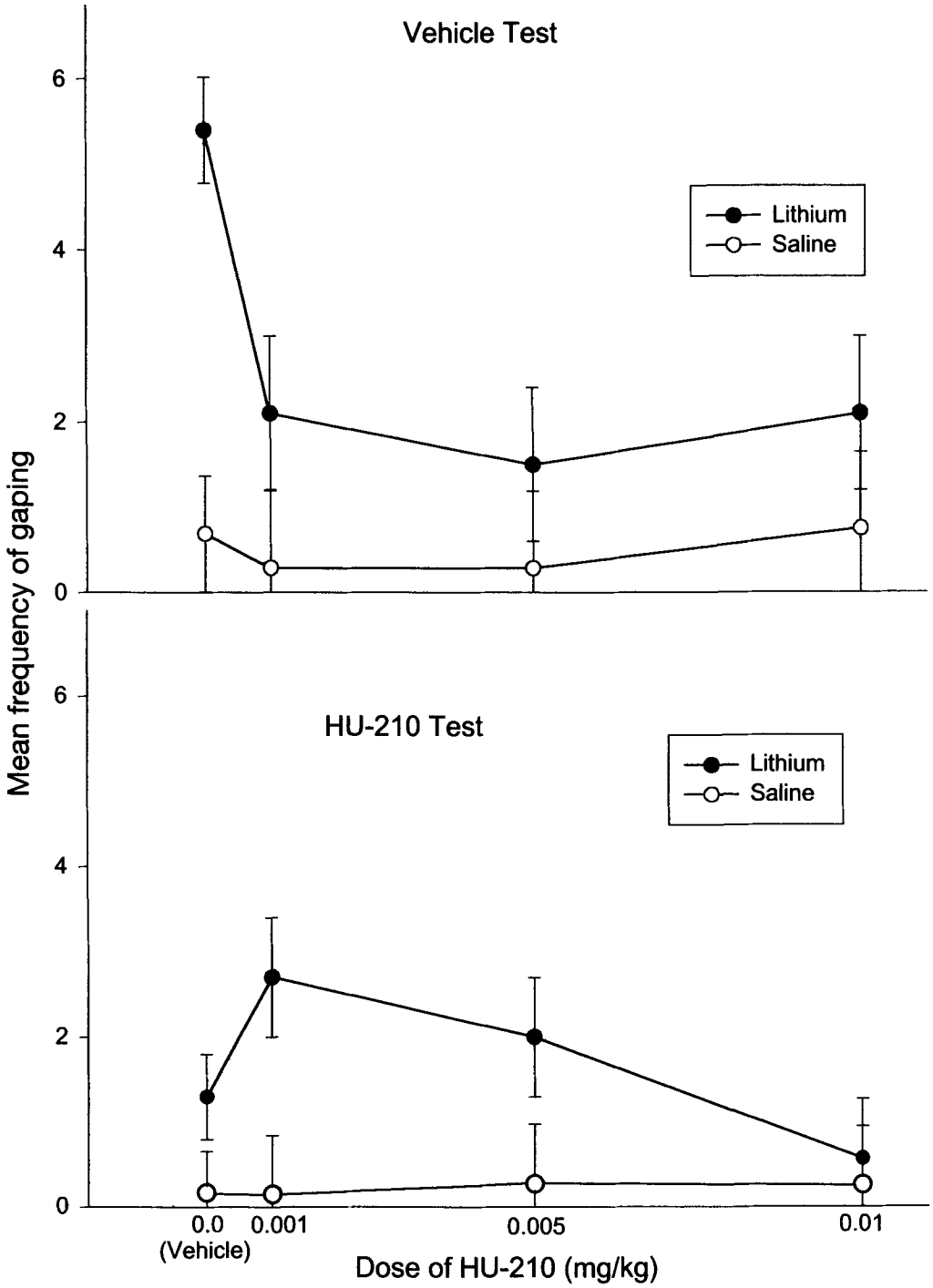

FIG. 3. Mean (±sem) frequency of gapes displayed by the lithium (filled circles) and saline (open circles) conditioned groups in Experiment 2. The top section presents the results of the vehicle test trial and the bottom section presents the results of the HU–210 test trial. The abscissa presents the dose of HU–210 that was administered prior to conditioning and prior to testing during the drug test trial.

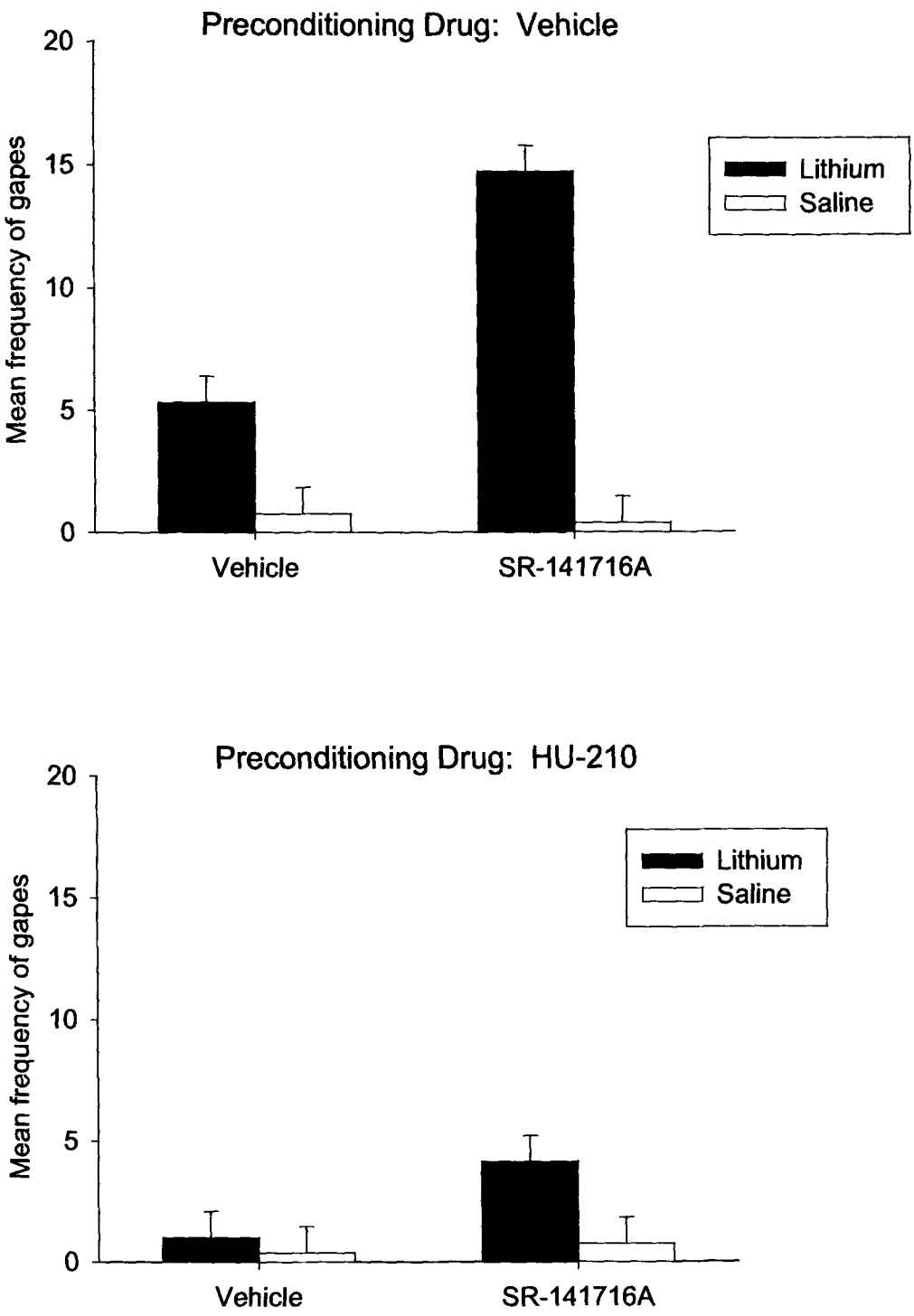

FIG. 4. Mean (±sem) frequency of gapes displayed by the lithium (filled bars) and saline (open bars) conditioned groups during the drug-free test trial of Experiment 3. Conditioning pretreatment 1 (vehicle or SR-141716) is depicted on the abscissa and pretreatment 2 (vehicle [top section] and HU-210 [bottom section]) is depicted in separate sections of the figure.

HU–210 displayed more conditioned gaping than those rats pretreated with vehicle—HU–210 [$P < .01$], suggesting that the CB_1 antagonist reversed the effects of HU–210. Finally, among the lithium-conditioned groups, those rats pretreated with SR–141716—Vehicle displayed more conditioned gaping than those rats pretreated with Vehicle-Vehicle ($p < .01$), suggesting that the CB_1 antagonist potentiated the effect of lithium on gaping.

General Discussion

Conditioned gaping displayed in the taste reactivity test is selectively produced by treatments that produce emesis in species capable of vomiting (Parker, 1982; Pelchat et al., 1983; Parker, 1998) and is prevented by pretreatment with anti-emetic agents (Parker & McLeod, 1991; Limebeer & Parker, 2000). Anti-emetic drugs do not, however, suppress unconditioned gaping elicited by bitter quinine solution (Parker & McLeod, 1991; Limebeer & Parker, 2000). Anti-emetic drugs also do not prevent the establishment of lithium-induced taste avoidance (Limebeer & Parker, 2000; Parker et al., 2002). Although non-emetic treatments often produce taste avoidance, they do not produce conditioned gaping (Parker, 1995). We have, therefore, argued that conditioned gaping in the taste reactivity test specifically reflect nausea in the rat, a species that does not vomit.

The preceding experiments demonstrated that the cannabinoid agonists, CBD, CBD-dmh, THC and HU–210, prevent the establishment of conditioned gaping, presumably by interfering with lithium-induced nausea. Furthermore, these agents interfered with the expression of conditioned gaping, presumably by interfering with conditioned nausea. The effects of HU–210 are mediated by the CB_1 receptor because pretreatment with the selective CB_1 antagonist, SR–141716, reversed the suppressive effect of HU–210 on the establishment of lithium-induced conditioned gaping.

CBD, CBD-dmh, and THC, however, do not modulate the strength of lithium-induced taste avoidance (Parker et al., 2001; Parker et al., 2003). This result is similar to the pattern of results evident when ondansetron (Limebeer & Parker, 2000) was administered as an anti-nausea pretreatment drug. The failure of the cannabinoid agonists to interfere with the establishment of lithium-induced taste avoidance suggests that the interference with the establishment of conditioned gaping is not the result of interference with the association between saccharin and lithium. We have argued that this dissociation indicates that conditioned gaping, but not conditioned taste avoidance, reflects nausea in rats (Limebeer & Parker, 2000).

Marijuana contains significant quantities of the psychoactive cannabinoid, THC, and the non-psychoactive cannabinoid, CBD. Although CBD is non-psychoactive (Mechoulan et al. 2002), it and its dimethyl-heptyl homolog, CBD-dmh, suppress both the establishment and the expression of conditioned gaping, a rat model of nausea. This finding provides promise that a non-psychoactive compound found in marijuana may play a role in the suppression of nausea.

A most interesting finding was that pretreatment with SR–141716 potentiated the effect of lithium on the establishment of conditioned gaping. This suggests that endogenous cannabinoids (endocannabinoids), such as anandamide (Devane et al., 1992), 2-arachidonoyl glycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995), or 2-arachidonyl glyceryl ether (Hanus et al., 2001), play a role in the control of nausea. Anandamide is normally present in low concentrations in the brain, but is synthesized on demand from the precursor, N-arachidonoyl-phosphatidylethanolamine (NAPE) (Schmid

et al., 1995). A number of researchers have shown that the concentration of endocannabinoids increases upon injury (Schmid et al., 1995; Shen et al., 1996; Shen & Thayer, 1998; Hampson et al., 1998; Jin et al., 2000). This work suggests that the endocannabinoid system is involved in neuroprotection. Our finding that SR–141716 potentiates lithium-induced conditioned gaping in rats suggests that this system may also play a role in protection against nausea in response to challenge by toxins.

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