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Exposure to a lithium-paired context elicits gaping in rats: A model of anticipatory nausea

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Abstract

Chemotherapy patients report anticipatory nausea and vomiting upon re-exposure to the cues previously associated with the treatment. Although rats do not vomit, they display a distinctive gaping reaction when exposed to a toxin-paired flavored solution. Here we report that rats also display gaping reactions during exposure to a context previously paired with the illness-inducing effects of lithium chloride (Experiment 1). This gaping reaction is suppressed by pretreatment with the antiemetic agent, Δ^9-tetrahydrocannabinol, but not ondansetron (Experiment 2). The finding that gaping is elicited by an illness-paired context confirms the proposal that an illness-paired context can evoke a conditioned state of nausea and supports the case of context-aversion as a rat model for anticipatory nausea.

Keywords: Anticipatory nausea; Gaping; Taste; Aversion; Context; Rat; Lithium chloride; Saccharin; Emetic; Δ^9-THC; Ondansetron

1. Introduction

Patients undergoing life-saving chemotherapy treatment often report that the most distressing aspect of their treatment is chemotherapy-induced nausea and vomiting [1,2]. The occurrence of nausea and vomiting can complicate the interim post-treatment care of the cancer patient and management of these symptoms can be a deciding factor for patients continuing with their recommended course of treatment [3,4]. Although antiemetic drugs have greatly improved the management of nausea and vomiting for chemotherapy patients, vomiting still occurs in approximately 40% of patients and nausea is reported by 75% [5]. The efficacy of any antiemetic treatment regimen is dependent upon several factors, the most significant of which is the time at which the medication is administered relative to toxin administration [3].

In addition to the nausea and vomiting directly induced by the treatment, some patients also show these responses in anticipatory form, prior to subsequent treatment sessions [6]. The development of anticipatory nausea and vomiting may occur following as little as one treatment cycle and has been shown to correlate with the management of acute nausea and vomiting as well as the frequency and intensity of nausea and vomiting following subsequent treatment cycles [5–8]. Furthermore, anticipatory nausea and vomiting is especially refractory to antiemetic treatment and develops in approximately 30% of patients by the fourth treatment cycle [5,7].

It has been argued that anticipatory nausea and vomiting is a consequence of classical conditioning. Specifically, it is proposed that the contextual stimuli of the clinic environment, such as the smell, sounds and even the sight of hospital staff, are the conditioned stimuli (CS) that become associated with the unconditioned stimulus (US) of chemotherapy treatment that evokes the unconditioned response (UR) of nausea and vomiting. Following one or more contingent pairings (chemotherapy treatments in the clinic environment), the patient may develop the conditioned response (CR) of nausea and/or vomiting upon re-entering the clinic. Support for a classical conditioning explanation is provided by studies that show that the development of anticipatory nausea and vomiting is correlated with the emetogenicity of the chemotherapy drug as well as the severity and number of episodes

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of nausea and vomiting following treatment [9,10]. These results demonstrate that the development of anticipatory nausea and vomiting (CR) is dependent upon the reliability of information provided by the CS (clinic environment) to predict the onset of the US (chemotherapy drug) combined with the intensity of the US, conventional requirements for the occurrence of classical conditioning.

A classical conditioning explanation for anticipatory nausea and vomiting prompts the attempt to develop an animal model designed for the study of nausea and vomiting. The purpose of using an animal model to study mechanisms of nausea and vomiting is to provide a means by which efficacious treatments can be identified and assessed, before being clinically evaluated in patients. Vomiting is a directly observable response to emetogenic stimuli that can be easily quantified and animal species capable of emesis have been used to evaluate the efficacy of antiemetic drugs [11–15]. However, nausea is a subjective response that relies almost entirely upon self-report in humans for diagnosis and treatment and antiemetic treatments that effectively manage vomiting are less effective in the management of nausea [8].

The development of a rat model of anticipatory nausea requires: (1) that the UR is a behavior representative of sickness induced by the US, (2) that rats are able to acquire an aversion to a contextual conditioned stimulus (CS) in the presence of which they experienced the physiological effects of a toxin, and (3) a sickness CR is elicited by the conditioned contextual cues. Experimental evidence for such a model has recently been presented [16,17]. When rats are made ill by an injection of lithium chloride (LiCl), they unconditionally suppress consumption of a novel, distinctively flavored solution [18]; that is, they demonstrate illness-induced enhanced neophobia. Rats will also show the CR of suppressed consumption when the solution is presented in a context previously paired with LiCl [16,17] and the degree of this suppression can be manipulated by procedures known to affect the strength of the CR [17]. Taken together, these reports suggest that suppressed consumption is a measure that conforms to the parameters of classical conditioning and may provide a reasonable measure of anticipatory nausea in rats.

Rodriguez et al. [16] have argued that suppressed consumption of a distinctively flavored solution by rats can be used as a model for anticipatory nausea utilizing a traditional classical conditioning paradigm that mimics the effects noted in human studies. However, suppressed consumption is a measure that is not necessarily selective to nausea. The consumption test includes both an appetitive and a consummatory phase of responding in which motivation, emotional, and motoric factors, as well as nausea, may influence consumption of a flavored solution. According to Parker [19], injection of LiCl has two major effects—not only does it produce a state of nausea, but it also produces a novel change in physiological state that signals danger to the rat. Both of these effects can support conditioning. A taste associated with nausea will acquire conditioned aversiveness that will be evident in the rat's consummatory behavior when it encounters that taste again. This is made apparent by the taste reactivity test [20] in which the conditioned substance is introduced into the rat's oral cavity by means of a cannula and the orofacial reactions of the animal are noted. In these circumstances, the rat exhibits characteristic rejection responses, the most notable of which is an open-mouthed gaping, a response that is perhaps as close to vomiting as this species can get and which requires the same orofacial musculature as the vomiting response in emetic species [21]. But this effect is not held to be responsible for the suppression of intake observed in a standard consumption test for flavor aversion learning. Suppressed consumption is attributed to taste *avoidance* (as opposed to taste *aversion*)—to conditioning (akin to fear conditioning) supported by an association between the taste and the dangerous change of physiological state.

A possible implication of this analysis is that the learning produced by context conditioning procedures might be based on avoidance rather than aversion—that the context comes to signal potential danger but does not actually evoke a state of conditioned nausea. The results obtained on the consumption test [17] might reflect the fact that rats will be reluctant to consume an otherwise palatable substance when it is presented in a fear-evoking context. Proof that the conditioning procedure does indeed endow the context with the power to evoke nausea requires a test that specifically evaluates consummatory responding; and to this end, we present the results of a further study using the taste reactivity test.

The taste reactivity test [20] systematically evaluates the aversiveness of a flavored solution in the absence of an appetitive response component (approaching a bottle). The rat is intraorally infused with a tastant and the distinctive orofacial responses expressed during infusion are quantified. Rats display the characteristic response of gaping when intraorally infused with a flavor previously paired with LiCl. The gaping response of the taste reactivity test appears to be a selective marker of nausea in rats. Only drugs that produce emesis in species capable of vomiting produce conditioned gaping [19,22]. Furthermore, administration of the antiemetic drugs, ondansetron [23] and Δ^9-tetrahydrocannabinol (Δ^9-THC) [24], prior to re-exposure to the toxin-paired saccharin, selectively interferes with the expression of conditioned gaping but not conditioned suppression of consumption. Therefore, conditioned gaping appears to be a more selective marker of nausea than is conditioned taste avoidance in rats.

If suppressed consumption of a novel solution while in a LiCl-paired context reflects conditioned nausea [17], then rats should gape during an intraoral infusion of a novel saccharin solution while in a LiCl-paired context. Experiment 1 tested this hypothesis. Experiment 2 evaluated the potential of anti-nausea agents to alleviate conditioned gaping in a LiCl-paired context. Both experiments test the validity of conditioned gaping as a model of anticipatory nausea in rats.

2. Experiment 1: conditioned gaping as a model of anticipatory nausea

2.1. Method

2.1.1. Subjects

The subjects were 17 male Sprague–Dawley rats (Charles River Lab, St Constant, Quebec) weighing from 283 to 341 g at the beginning of the experiment. The animals were individually

housed in wire hanging cages in the colony room at an ambient temperature of 21 °C with a 12/12-light/dark schedule (lights on at 7 AM) and maintained on an ad lib schedule of food (Highland Rat Chow [8640]) and water. All procedures adhered to the guidelines of the Canadian Council of Animal Care and were approved by the Animal Care Committee of Wilfrid Laurier University.

2.1.2. Apparatus

The conditioning chamber was made of black opaque Plexiglas sides (22.5×26×20 cm) with a black lid and was placed on a table with a clear Plexiglas top. A mirror beneath the chamber on a 45° angle facilitated viewing of the ventral surface of the rat. A 10-ml test tube was permanently attached to a hole at one side of the chamber in which a cotton dental roll saturated with vanilla flavor extract (Clubhouse; 35% alcohol) was placed to create the olfactory cue in the chamber. The cotton roll was inaccessible to the rat and a newly saturated cotton roll was used for each rat placed in the context. The room was dark with two 50-W red lights on either side of the chamber.

2.1.3. Cannulation surgery

All rats were implanted with intraoral cannulae as previously described [23]. To ensure patency of the cannulae at the time of testing, the cannulation surgery occurred 72 h after the 2 weeks of conditioning trials. They were anaesthetized with isoflorane gas and administered Anafen (7 mg/kg, s.c.; Merial), a non-steroidal anti-inflammatory drug with analgesic properties. A thin-walled 15-gauge stainless steel needle was inserted at the back of the neck, directed subcutaneously around the ear and brought out behind the first molar inside the mouth. A length of Intra Medic plastic 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. Two circular elastic discs were placed over the tubing and drawn to the exposed skin at the back of the neck for the purpose of stabilizing the cannula. The tubing was held secure in the oral cavity by an o-ring, which was sealed behind the tubing prior to cannulation surgery. For the purposes of testing, the indwelling cannula was connected to the infusion pump for delivery of the saccharin solution by attaching the cannula to a length of tubing attached to the infusion pump. Following surgery, the rats were weighed and their cannulae flushed daily for 3days with chlorhexidine to prevent infection. The novel taste of this rinse was experienced by rats in both Groups Paired and Unpaired.

2.1.4. Procedure

The conditioning trials began 1 week following arrival of the rats in the facility. On each of 4 conditioning trials (separated by 72 h), rats in Group Paired ($n=9$) were intraperitoneally (i.p.) injected with LiCl solution (0.15 M; 20 ml/kg) and rats in Group Unpaired ($n=8$) were injected with 20 ml/kg of saline solution immediately prior to being placed in the distinctive context for 30 min. To ensure equal familiarization with illness, the rats in Group Unpaired were injected i.p. with LiCl (0.15 M; 20 ml/kg) and rats in Group Paired were injected with 20 ml/kg saline, 24 h after each conditioning trial while in their home cage.

Seventy-two hours following the 4th conditioning trial, the rats were surgically implanted with intraoral cannulae. The test trial occurred 72 h after the surgery. Each rat was placed in the conditioning chamber and its cannula was attached to the infusion pump for delivery of the 0.1% saccharin solution. The rat was placed in the CS chamber for 30 min during which time it received a total of six intraoral infusions of saccharin solution, one every 5 min for 1 min (1 ml/min), while its reactions were video-recorded. During the inter-infusion-interval (time between saccharin infusions), the frequency of gaping reactions (large-amplitude opening of the mandible with retraction of the corners of the mouth) was scored manually by an observer in the room.

2.1.5. Observational measures

The frequency of gaping reactions (rapid, large-amplitude opening of the mandible) expressed while rats were infused with 0.1% saccharin (6–1-min infusions during the 30 min in the conditioning context) was scored by an experienced rater blind to group assignments using the Observer (Noldus Information Technology, Sterling, VA) event recording program. The total number of gapes displayed during all saccharin infusions for each rat was divided by the 6-min duration to produce a rate measure of gaping (gapes/min). In addition, an overall activity duration score during infusions was obtained by summing the frequency of 2-s instances of forward locomotion (movement of the rat's forepaws along the floor of the chamber) and rearing (both front forepaws lifted of the floor and not touching the wall of the chamber) during the saccharin infusions and converting these scores to an activity/min score. During the inter-infusion-intervals (a total of 24 min), the frequency of gaping was assessed and transformed into a gaping/min score.

2.2. Results

Rats in Group Paired displayed significantly more gaping responses than rats in Group Unpaired. Fig. 1 presents the mean (±S.E.M.) number of gapes/min expressed by Group Paired and Group Unpaired during the saccharin infusions and during the inter-infusion-interval. Rats in Group Paired had a significantly

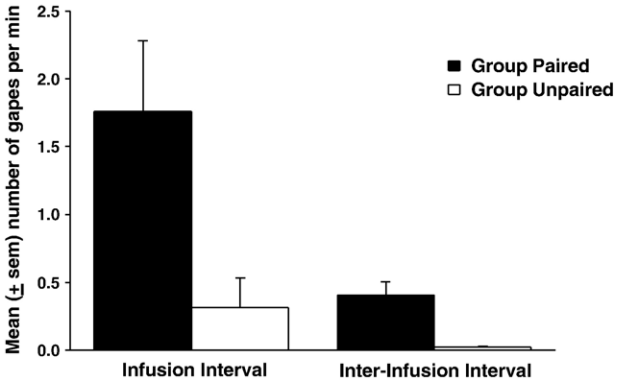

Fig. 1. Mean (±S.E.M.) number of gapes/min displayed by rats in Group Paired (closed bars) and Group Unpaired (open bars) during saccharin infusions and during the inter-infusion-intervals.

higher mean rate of gaping than rats in Group Unpaired during the infusion of novel saccharin [$t(15)=2.5$; $p<0.05$] and during the inter-infusion-interval [$t(15)=3.6$; $p<0.01$]. Group Paired and Unpaired did not significantly differ in their mean rate of activity during the infusion of novel saccharin solution.

2.3. Discussion

As previously suggested [17], following a number of pairings with the illness-inducing drug, LiCl, a context may acquire the ability to elicit conditioned nausea. Rodriguez et al. [16] measured conditioned nausea by suppression of intake of a sucrose solution during re-exposure to the LiCl-associated context. The present experiment measured conditioned nausea by scoring the gaping reactions elicited by intraoral infusion of a novel saccharin solution and expressed during inter-infusion-intervals in the LiCl-associated context. The present results confirm that suppressed consumption of a novel flavored solution in an illness-paired context reflects conditioned nausea in rats.

3. Experiment 2: effect of OND and Δ^9-THC on the expression of anticipatory nausea

The results of Experiment 1 suggest that the gaping reaction shown by rats upon re-exposure to a LiCl-paired context can serve as a model of anticipatory nausea. This gaping measure allows for more precise evaluation of treatments for the symptoms of anticipatory nausea.

Further support for the view that contextual stimuli can acquire the ability to elicit conditioned nausea comes from the results of studies carried out on the house musk shrew (*Suncus murinus*), which retches and vomits when injected with a toxin, such as LiCl [25]. When shrews were injected with LiCl prior to placement in a distinctive chamber, they vomited and retched in the presence of the contextual CS cues. Following repeated pairings of the CS chamber with vomiting, the shrews displayed a conditioned retching reaction when exposed to the chamber alone [26,27].

S. murinus has been used to evaluate the anti-emetic potential of drug compounds [13,28]. The 5-HT_3 antagonists, such as ondansetron [OND], suppress cisplatin-induced [11] and LiCl-induced [25] vomiting in this species. However, the same dose of OND that suppresses acute vomiting in *Suncus* does not suppress conditioned retching when administered prior to exposure to a chamber previously paired with LiCl. This dose of OND also has no effect on general activity level of the shrews. The finding that OND does not affect conditioned retching in the shrew is consistent with a demonstration in rats [29] that OND does not affect the expression of anticipatory nausea (assessed by suppressed sucrose consumption) elicited by a context previously paired with lithium. In fact, human chemotherapy patients report that 5-HT_3 antagonists do not combat anticipatory nausea and vomiting when it develops [6,7,10,30]. On the other hand, the testimony of numerous chemotherapy patients indicates that marijuana reduces both acute and anticipatory nausea and vomiting associated with chemotherapy. Indeed, the psychoactive compound found in marijuana, Δ^9-THC, suppresses vomiting and retching elicited by LiCl and cisplatin in *Suncus* [11,25]. In contrast to OND, Δ^9-THC also suppresses conditioned retching in *Suncus* [26,27].

Experiment 2 evaluated the potential of OND and Δ^9-THC to attenuate the expression of conditioned gaping in rats elicited by a LiCl-paired context. The doses of OND (0.1 mg/kg) and Δ^9-THC (0.5 mg/kg) employed were the same as those previously shown to interfere with the establishment of conditioned gaping elicited by a LiCl-paired flavor [22,23]. These low doses have no effect on general activity and are below the threshold for producing an effect on retrieval of reference memory [31].

3.1. Method

3.1.1. Subjects

The subjects were 42 male Sprague–Dawley rats (Charles River Lab, St Constant, Quebec) weighing from 306 to 411 g at the beginning of the experiment. The rats were maintained as in Experiment 1.

3.1.2. Procedure

The conditioning procedure was similar to that of Experiment 1. Rats were randomly assigned to Group Paired ($n=23$) or Group Unpaired ($n=19$) groups. Each rat received 4 conditioning trials (separated by 72 h) consisting of an i.p. injection of LiCl (0.15 M; 20 ml/kg) or saline (20 ml/kg) immediately prior to placement in the distinctive context, which was followed 24 h later by the alternate non-contingent injection in the home cage. Seventy-two hours following conditioning, the rats were surgically implanted with intraoral cannulae and monitored for 72 h before testing.

Rats in Group Paired and Group Unpaired received a test trial, 30 min following an i.p. pretreatment injection of VEH (Vehicle), 0.1 mg/kg OND or 0.5 mg/kg Δ^9-THC. Both OND and Δ^9-THC were mixed in a vehicle of 1 ml ethanol/1 ml Cremaphor (Sigma)/18 ml of physiological saline which served as the VEH and all agents were administered at a volume of 1 ml/kg. The groups were: Group Paired—VEH pretreated ($n=7$), Group Paired—OND pretreated ($n=8$), Group Paired—Δ^9-THC pretreated ($n=8$), Group Unpaired—VEH pretreated ($n=6$), Group Unpaired—OND pretreated ($n=6$), and Group Unpaired—Δ^9-THC pretreated ($n=7$). The 30-min test was identical to that described in Experiment 1. That is, rats received an intraoral infusion of 0.1% saccharin solution every 5 min for 1 min (at a rate of 1 ml/min), resulting in a total of 6 infusions. During the intraoral infusions, the rats somatic and orofacial responses were video-recorded and later scored for gaping, rearing and active locomotion. The number of gapes expressed during the inter-infusion-intervals (a total of 24 min) was also observed and recorded during the test (see Section 2.1.5).

3.2. Results

Rats in Group Paired displayed a significantly higher rate of gaping than rats in Group Unpaired, both during the novel saccharin infusions and during the interval between infusions. Pretreatment with Δ^9-THC, but not OND, attenuated the gaping responses. Fig. 2 presents the mean number of gapes/min

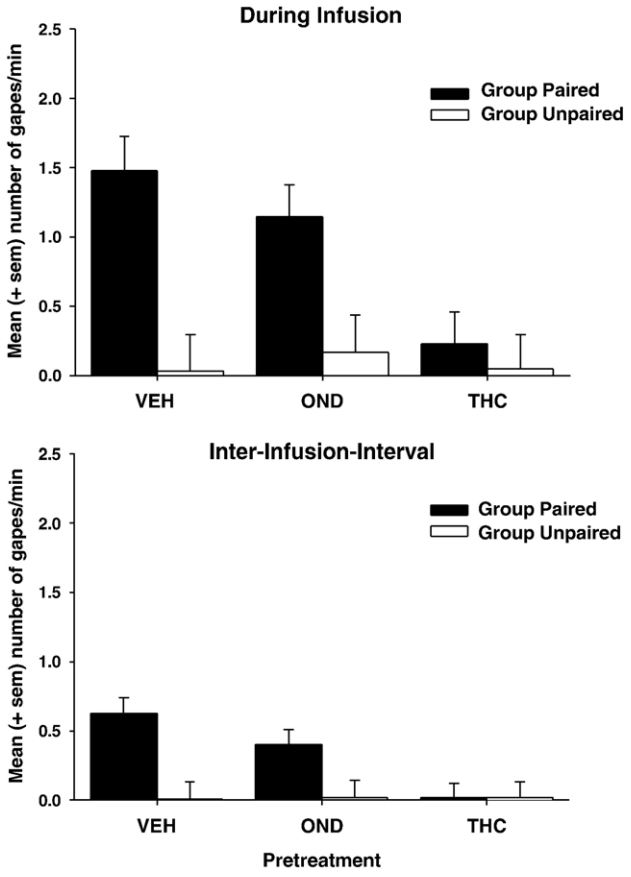

Fig. 2. Mean (±S.E.M.) number of gapes/min expressed by Group Paired (closed bars) and Group Unpaired (open bars) during the test following pretreatment with VEH, OND (0.1 mg/kg), or Δ^9-THC (0.5 mg/kg).

displayed by Group Paired (closed bars) and Group Unpaired (open bars) pretreated with VEH, OND, or Δ^9-THC during the saccharin infusions (upper half) and during the inter-infusion-intervals (lower half). Separate 2 (group) by 3 (pre-treatment) between groups analyses of variance (ANOVAs) were conducted for the rate of gaping responses during the saccharin infusions and during the inter-infusion-intervals. Analysis of the rates of gaping during the saccharin infusion revealed significant main effects of group [$F(1,36)=18.2$; $p<0.001$] and pre-treatment [$F(2,36)=3.6$; $p<0.05$] as well as a significant group by pre-treatment interaction [$F(2,36)=3.3$; $p<0.05$]. Rats in Group Paired gaped at a significantly higher rate than those in Group Unpaired following pretreatment with VEH [$t(11)=2.6$; $p<0.05$] and OND [$t(11)=3.3$; $p<0.01$], but not Δ^9-THC. Additionally, separate single factor ANOVAs for Groups Paired and Unpaired revealed a significant effect of pre-treatment for Group Paired [$F(2,20)=4.8$; $p<0.025$] but not for Group Unpaired. For Group Paired, rats pretreated with Δ^9-THC displayed significantly fewer gapes/min than rats pretreated with VEH ($p<0.01$) or OND ($p<0.05$), but rats pretreated with VEH or OND did not differ. The 2 by 3 ANOVA of the rate of activity during the novel saccharin infusion revealed no significant effects. Neither OND nor Δ^9-THC modified overall activity level.

Analysis of the rate of gaping during the inter-infusion-interval (lower half of Fig. 2) followed the same pattern as the rate of gaping during the saccharin infusions, revealing significant main effects of group [$F(1,36)=12.6$; $p<0.01$] and pre-treatment [$F(2,36)=3.4$; $p<0.05$] as well as a significant group by pre-treatment interaction [$F(2,36)=3.9$; $p<0.05$]. Rats in Group Paired gaped at a significantly higher rate during the inter-infusion-interval than rats in Group Unpaired following pretreatment with VEH [$t(11)=2.4$; $p<0.05$] and OND [$t(12)=2.6$; $p<0.05$], but not Δ^9-THC.

3.3. Discussion

Pretreatment with Δ^9-THC, but not OND, interfered with the expression of conditioned gaping in a rat model of anticipatory nausea. These results are similar to those reported using the *S. murinus* model of conditioned retching and are consistent with the findings in the human clinical literature that 5-HT_3 antagonists are ineffective in alleviating anticipatory nausea or vomiting if they develop [6,7,10,30]. One might argue that the suppression of conditioned gaping by Δ^9-THC may have been the result of interference with retrieval of the memory of the context–illness association, rather than interference directly with conditioned nausea. However, there is considerable evidence that at the low dose of 0.5 mg/kg (i.p.), Δ^9-THC does not affect retrieval of reference memory and does not affect attentional processes [31]. Furthermore, this dose of Δ^9-THC also did not affect activity during the infusion of novel saccharin. Although Δ^9-THC can disrupt fine motor control in rats [32], the minimum dose necessary to produce this disruption was 4 times higher (2.0 mg/kg) than the dose that disrupted gaping here. At a dose of 0.5–1.0 mg/kg, Δ^9-THC did not affect motor execution.

4. General discussion

The principal finding of this study is that, when they are re-exposed to a LiCl-paired context, rats show a gaping reaction both during infusion of a saccharin solution and during the inter-infusion-intervals. This reaction is what would be expected if the contextual cues have acquired the power to elicit a state of conditioned nausea. For the most part, previous work on context–aversion conditioning has made use of a less direct measure (suppression of consumption of a novel-flavored solution). The present results provide support for the assumption that this suppression is a consequence of nausea conditioned to the contextual cues.

A rat model of anticipatory nausea provides a valuable preclinical tool for evaluating the effectiveness of anti-nausea treatments. Experiment 2 confirmed previous findings with *S. murinus* [26,27] and anecdotal reports of humans that the psychoactive compound found in marijuana, Δ^9-THC, attenuated gaping induced by a LiCl-paired context in rats. On the other hand, OND did not reduce gaping in this rat model as it also did not reduce conditioned suppression of consumption in rats [29] or retching in *Suncus* [27] that was elicited by a LiCl-paired context. This pattern is also consistent with that reported by human chemotherapy patients [6,7,10,30]. It remains to be seen if Δ^9-THC attenuates the suppressed intake of a novel flavored solution in a LiCl-paired context.

Marijuana contains over 60 cannabinoids, with Δ^9-THC serving as the primary psychoactive compound. A major non-intoxicating compound is cannabidiol (CBD). In the *S. murinus*, low doses of CBD suppress cisplatin- [11] and LiCl-induced [25] vomiting and retching, as well as conditioned retching elicited by a LiCl-paired context [27]. CBD also suppresses conditioned gaping elicited by a LiCl-paired flavor in rats [33,34]. Future experiments will examine the potential of CBD to interfere with gaping in the present contextual model of anticipatory nausea in rats.

The capacity for conditioned gaping to be a selective measure of nausea highlights the utility of this measure as a model for anticipatory nausea. This selectivity allows for more precise evaluation of experimental manipulations designed to interfere with the development of anticipatory nausea as well as clinical treatment for the symptoms of anticipatory nausea.

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