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Antidepressant-like effects of paroxetine are produced by lower doses than those which produce nausea

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ABSTRACT

Paroxetine is prescribed to treat depression, but it also produces nausea. The potential of animal models to detect nauseating, antidepressant-like, and rewarding/aversive effects of paroxetine were assessed. In Experiments 1 (spaced conditioning trials) and 3 (massed conditioning trials), a dose of 30 mg/kg, but not lower doses (3 and 10 mg/kg) of paroxetine produced conditioned gaping reactions (reflective of nausea) in the Taste Reactivity (TR) test. In Experiment 2, when administered 23.5, 5 and 1 h prior to a 5 min forced swim test (FST) a dose as low as 3 mg/kg of paroxetine increased swimming and decreased immobility (reflective of antidepression) compared to controls. In Experiment 3, neither 10 nor 30 mg/kg of paroxetine produced a conditioned floor preference/aversion, but both doses decreased activity during conditioning trials. These results suggest that paroxetine produced an antidepressant-like effect at a lower dose (3 mg/kg) than that necessary to produce nausea (30 mg/kg). The TR test may be beneficial for assessing the side effect of nausea in preclinical tests of new compounds.

1. Introduction

Nausea and vomiting are unpleasant and distressing side effects of many pharmacological treatments, including Selective Serotonin Reuptake Inhibitor's (SSRI's) used in treating depression. In fact, nausea is the most commonly reported reason for discontinuation of the use of SSRI's after beginning antidepression therapy before clinical efficacy is seen (Rosenzweig-Lipson et al., 2007). Drugs in this class increase extracellular serotonin (5-Hydroxytryptamine; 5-HT) by inhibiting its reuptake into the presynaptic terminals, and elevated 5-HT is implicated in the production of nausea (Andrews et al., 1988). Paroxetine (Paxil) is one of the most effective antidepressants, but it is also known to induce nausea (Peretti et al., 2000).

Although rats are incapable of vomiting, considerable evidence indicates that they display conditioned disgust reactions (gaping, chin rubbing and paw treading) in the Taste Reactivity (TR) test when they are exposed to a flavored solution previously paired with a drug that produces vomiting in emetic species (see Grill and Norgren, 1978; Parker, 2003). The most reliable measure of conditioned disgust is gaping (a wide opening of the mouth with lower incisors exposed). In fact, this gaping reaction in the rat requires the same orofacial musculature as that required for vomiting in emetic species (Travers and Norgren, 1986). We have argued that the conditioned gaping response can serve as a rat model of nausea (for review see Parker, Rana and Limebeer, 2008) because: 1) only drugs that produce emesis in species capable of vomiting produce conditioned gaping reactions, and 2) anti-emetic treatments consistently interfere with the establishment of conditioned gaping reactions. The gaping reaction is only apparent as a conditioned behavior in rats, as they do not display gaping while experiencing nausea produced by LiCl (Limebeer et al., 2008).

If conditioned gaping reflects nausea in rats, then compounds which elevate 5-HT would be expected to produce these reactions. Indeed, fenfluramine, a drug that selectively elevates extracellular 5-HT by facilitating its release, produces conditioned gaping when paired with a flavoured solution (Parker, 1988). With the elevation of 5-HT and the reported side effect of nausea produced by SSRI treatment, these agents would also be expected to produce conditioned gaping when paired with a novel flavor. Indeed, Limebeer et al. (2009) recently reported that fluoxetine produces conditioned gaping in rats in a dose-dependent manner. The fluoxetine-induced conditioned gaping reactions were prevented by pretreatment with the somatodendritic 5-HT_{1A} autoreceptor agonist, 8-OH-DPAT, which reduces the rate of firing of 5-HT neurons. Here we evaluate the potential of a range of doses of the SSRI, paroxetine, to produce conditioned gaping reactions in the TR test.

The potential of paroxetine to produce conditioned gaping in the TR test was compared with its effectiveness in an animal model of depression, the forced swim test (FST; Porsolt et al., 1977) which measures the behaviors of immobility (no activity, other than that necessary to keep the rat's head above water), swimming (movement

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throughout the test chamber across quandrants) and climbing (upward directed movements of the forepaws along the side of the test chamber). The FST is commonly used due to its quick procedure, reliability across laboratories and selective sensitivity to all major classes of antidepressants (Borsini and Meli, 1988). The SSRI's, fluoxetine and paroxetine, have been reported to decrease immobility and increase swimming time in both rats and mice in the FST (Kulkarni and Dhir, 2007; Rénéric and Lucki, 1998; Sánchez and Meier, 1997; Weiner et al., 2003). Detke and colleagues (1995) administered paroxetine 23.5, 5 and 1 h before the 5-min swim test and found that a dose as low as 5 mg/kg produced increased swimming while a dose of 20 mg/kg produced decreased immobility and increased swimming time (but not increased climbing) compared to that displayed by controls. In the current study we evaluated the potential of the same doses of paroxetine (3, 10 and 30 mg/kg) used to assess nauseating effects to modify behaviours reflective of depression in the FST.

Finally, the potential of paroxetine to produce a conditioned preference or aversion for a distinctive floor cue was assessed to evaluate its rewarding/aversive properties. The literature on reward/aversion produced by drug-induced changes in serotonin levels is mixed, possibly because of differing conditioning procedures. In fact, paroxetine (15 mg/kg) and fluoxetine (5 and 10 mg/kg) have been found to produce a conditioned place preference when paired with the initially unpreferred (called the *biased* place conditioning procedure) chamber (Subhan et al., 2000). However, using an *unbiased* procedure (the chambers are initially equally preferred prior to conditioning and assignment is counterbalanced), fenfluramine produced a conditioned place aversion at the same dose (3 mg/kg) that produced conditioned gaping reactions in the TR test (Davies and Parker, 1993). Thus, Experiment 3 employed an unbiased conditioning procedure to assess the potential of doses of paroxetine tested on TR and FST (10 and 30 mg/kg) to produce a conditioned place preference or aversion.

The potential of a variety of doses of paroxetine to produce nausea (as evaluated by conditioned gaping), antidepressant effects (as evaluated by the FST) and drug reward/aversion (as assessed in the conditioned place aversion/preference test) was investigated. A comparison of the doses of paroxetine in the gaping test, FST and place conditioning may be useful in screening for a therapeutic antidepressant-like effect at doses below those that produce an adverse side effect of nausea.

2. Materials and methods

2.1. Subjects

Male Sprague-Dawley rats obtained from Charles River Canada, St. Constant QC. were pair-housed in polycarbonate cages (44×25×21 cm), except for those in Experiments 1 and 3 which were singly-housed. Subjects were provided with food pellets (Highland Rat Chow) and water *ad libitum* throughout the experiment. The animal quarters were kept on a reversed 12-h light/dark cycle (lights on from 19:00 to 07:00 h) and maintained at 22±2 °C and 45±20% relative humidity. All animals were drug naïve and acclimatized to the animal quarters for one week, as well as handled for a minimum of two days, prior to experimental procedures. Behavioural testing was conducted during the dark cycle from 7:00 to 18:00 h. The guidelines set out by the Canadian Council on Animal Care Committee and the Animals for Research Act were strictly followed in the treatment of the subjects. The experiments were approved by the University of Guelph Animal Care Committee.

2.2. Drugs

All injections were administered intraperitoneally (i.p.). The doses of paroxetine administered were 0 (vehicle), 3, 10 and 30 mg/kg. Paroxetine (provided by Theravance and Kemprotec, UK) was prepared in sterile water at a concentration of 1. 5 mg/ml, 5 mg/ml, and 6 mg/ml. All agents were administered in a volume of 2 ml/kg, except the highest dose of paroxetine which was administered at a volume of 5 ml/kg; the higher volume was required to dissolve the drug in sterile water. The half-life of paroxetine in rats is approximately 8 h (Owens et al., 2000).

2.3. Apparatus and procedures

2.3.1. Experiment 1: conditioned gaping reactions: 72 h between conditioning/testing trials

2.3.1.1. Intraoral cannulation surgery. All of the experimental animals were implanted with intra-oral cannulae according to the procedures previously described (Limebeer and Parker, 2000). Briefly, 30 min prior to surgery, all rats were subcutaneously (s.c.) injected with an antibiotic (Depocillin: 100,000 IU). At the time of surgery, the rats were anaesthetized with isoflorane gas and administered Carprofen (5 mg/kg, s.c.; Merial), a non-steroidal anti-inflammatory drug (NSAID) with analgesic properties. Once the rats were anaesthetized, a thin walled (15-gauge) stainless steel needle was inserted at the back of the neck and then directed subcutaneously around the ear and brought out behind the most caudal molar in the mouth. A 10 cm length of Intra Medic plastic tubing with an inner diameter of 0.86 mm and an outer diameter of 1.27 mm was then drawn through and the needle was subsequently removed. Two-2 cm square elastic discs were placed over the exposed end of the tubing at the back of the neck and drawn tight against the skin to maintain the cannula's position. For three days following surgery the rats were weighed, monitored and the cannulae flushed daily with the anti-septic chlorhexidine.

2.3.1.2. Apparatus. Testing was conducted in a square Plexiglass chamber (22.5×26×20 cm). The rat's cannula was attached to an infusion pump (Harvard Appartus, South Natick, MA) through a hole in the top of the chamber via an infusion tube. A mirror placed at a 45° angle under the testing chamber allowed viewing of the ventral surface of the rat. The observations were recorded using a videocamera attached to a computer.

2.3.1.3. Procedure. Rats were randomly assigned to one of four groups: vehicle ($n=6$), 3 mg/kg ($n=9$), 10 mg/kg ($n=7$), or 30 mg/kg ($n=7$) paroxetine; the group n's reflect the final numbers following the loss of cannulae. Three days post surgery, the rats underwent an adaptation trial where they were placed in the taste reactivity (TR) chamber with their cannula attached to the infusion pump for fluid delivery. Water was infused over a period of 5 min at the rate of 1 ml/min after which they were returned to their home cage.

Twenty-four hours following the adaptation trial, the conditioning trials began. The rats received a total of three conditioning trials followed by a test trial. Each trial was 72 h apart. During each trial, the rats were individually placed in the TR chamber and then intraorally infused with a highly salient 17% sucrose solution for 5 min at a rate of 1 ml/min. During the infusion, gaping reactions (large amplitude opening of the mandible with retraction of the corners of the mouth) were recorded by a videocamera connected to a computer. Immediately following the sucrose infusion, the rats were given a drug injection (0, 3, 10 or 30 mg/kg paroxetine; i.p.) and returned to their home cage. All trials were identical except that no injection was given at the end of trial 4 (test trial). A rater blind to the experimental conditions employed an event recording program "The Observer" (Noldus, Inc, NL) to measure the number of gaping reactions displayed during the intraoral infusions.

2.3.2. Experiment 2: Forced Swim Test (FST)

2.3.2.1. Apparatus. A Plexiglas vertical tube (50 cm height × 23 cm diameter) filled with 25 °C (±0.5°) water to a height of 30 cm was used as the FST chamber. Another Plexiglas chamber (40 × 40 × 40 cm^3) placed beside a heater was used to dry the rats following each test. A videocamera located in front of the four FST chambers was attached to a computer and used to record each trial.

2.3.2.2. Procedure. On Day 1, rats were placed in one of four FST chambers for a 15 min pretest and their behavior was videotaped. Immediately following the pretest, they were removed from the chamber, towel dried by the experimenter and placed in the heated drying chamber for 30 min and then returned to their home cage. Twenty-four hours later, on Day 2, the rats were again placed in the FST chamber for 5 min. All rats were injected 23.5, 5 and 1 h before the Day 2 FST with the appropriate drug ($n = 8$/group: vehicle, 3, 10 or 30 mg/kg paroxetine).

A rater blind to the experimental treatment conditions employed "The Observer" to record duration (in second) of three escape responses: swimming (movement throughout the test chamber across quadrants), climbing (upward directed movements of the forepaws along the side of the testing chamber), and immobility (no activity other than that necessary to keep the rat's head above water). The rater scored the initial 5 min of the first session (Trial 1) and the entire duration of the second session (Trial 2).

2.3.3. Experiment 3: conditioned gaping reactions: massed conditioning trials

To compare the potential of doses of paroxetine to modify behaviors reflective of depression with those reflective of nausea, Experiment 3 evaluated the potential of paroxetine to produce conditioned gaping when administered at the same intervals as in the FST in Experiment 2.

Following intraoral cannulation and recovery, the rats were treated as in Experiment 1, except that, 24 h after a 2-min adaptation trial, they were given a 2-min exposure to 17% sucrose solution immediately prior to an injection of the appropriate solution separated by intervals (as in Experiment 2) of 18.5 h (Trial 1 and 2) and 4 h (Trial 2 and 3). Seventy-two hours later they were given a 5-min TR test as in Experiment 1. The groups were Vehicle ($n = 7$), 3 mg/kg paroxetine ($n = 8$), 10 mg/kg paroxetine ($n = 7$) and 30 mg/kg paroxetine ($n = 7$).

2.3.4. Experiment 4: conditioned floor preference/aversion

2.3.4.1. Apparatus. The floor-conditioning apparatus consisted of a black Plexiglass rectangular box (60 × 25 × 25 cm^3) with a wire-mesh lid. The tactile features of the floors in each box were manipulated to provide conditioned stimuli (CSs) for conditioning. The grid floors were made from 2.3 mm stainless steel rods mounted 13 mm apart in an acrylic frame. The hole floors were made from perforated stainless steel (16-gauge) with 13 mm round holes on 19 mm staggered centres. These floors were modeled after the apparatus used by Cunningham et al. (2006). During conditioning trials the tactile cues on both sides of the box were identical. During choice tests, one side of the chamber had a grid floor and the other side had a hole floor (counterbalanced), with a defined neutral zone (10 cm × 25 cm) at the intersection of the two floors that did not enter into the time spent on either side. After each trial the chambers and the floors were wiped with a damp sponge.

The number of seconds spent on each of the floors as well as the distance (cm) traveled during all trials and tests were automatically recorded using a camera mounted to the ceiling which sent the signal to a computer. The signal was recorded and subsequently analyzed by the Noldus EthoVision videotaping system (Noldus Information Technology, Sterling, VA). Pilot studies indicated that rats show no spontaneous significant preference for either floor.

2.3.4.2. Procedure. In order to evaluate the natural preference for the two floors, all rats were administered a 20 min pretest in the apparatus and the amount of time spent on each floor was measured. The rats received three cycles of conditioning trials. During each conditioning cycle, rats were injected with paroxetine (10 mg/kg [$n = 12$] or 30 mg/kg [$n = 12$]) or vehicle 10 min prior to being placed into the chamber with a distinctive floor (grid or holes) for 45 min. The paroxetine and vehicle trials were separated by 24 h. Each of the conditioning cycles was separated by 48–72 h. The order of the paroxetine trial within a cycle and the floor paired with paroxetine were counterbalanced. The mean distance (cm) traveled was recorded during each conditioning trial.

Forty-eight hours after the last conditioning cycle, rats were tested for a floor preference in a drug-free state. During this test, the two distinctive floors were placed inside the chambers and time spent on each floor was measured over 20 min. Additionally, distance moved (cm) while on each floor was assessed to derive a measure of rate of locomotion (distance/time on floor).

3. Results

3.1. Experiment 1: conditioned gaping reactions: spaced (72 h) conditioning trials

Fig. 1 presents the mean (±SEM) number of gapes measured during each 5-min intraoral infusion of 17% sucrose solution paired with various doses of paroxetine across trials. Only at a dose of 30 mg/kg did paroxetine produce conditioned gaping reactions. Paroxetine produced a dose-dependent increase in the reaction of conditioned gaping across trials. A 4 × 4 (group × trial) mixed factor ANOVA revealed a main effect of group, $F(3, 25) = 12.29$, $p < .001$, and trial, $F(3, 75) = 3.34$, $p = .02$. Bonferroni post-hoc test showed that the 30 mg/kg paroxetine group significantly differed from all other groups (p's < .01). The ANOVA also indicated a significant group × trial interaction, $F(9, 75) = 2.13$, $p = .04$. In analyses of simple main effects of dose, a significant difference was found for trial 3, $F(3, 25) = 10.87$, $p < .001$, and trial 4, $F(3, 25) = 4.76$, $p = .01$. Bonferroni post-hoc tests showed that the highest dose of paroxetine (30 mg/kg) was

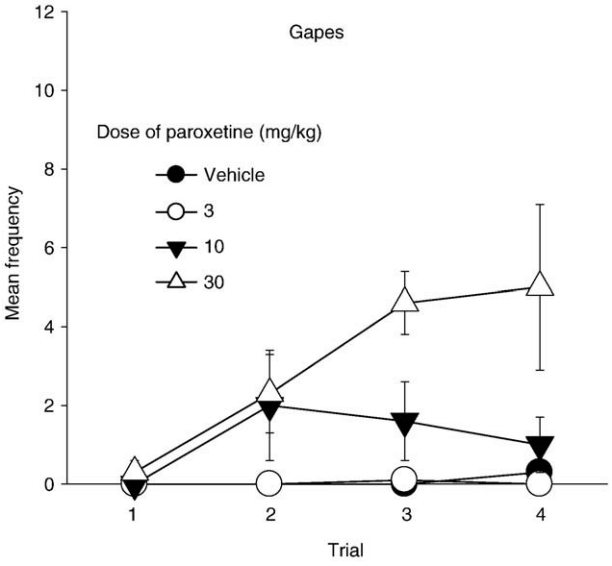

Fig. 1. Mean (±SEM) number of gapes displayed by rats conditioned with 0, 3, 10 and 30 mg/kg of paroxetine on each trial (separated by 72 h) of Experiment 1.

significantly different than any other dose for both of the last two trials (all p's<.05).

3.2. Experiment 2: Forced Swim Test

Rats treated with paroxetine (3–30 mg/kg) prior to trial 2 of the FST displayed enhanced swimming and reduced immobility (reflective of antidepressant-like efficacy) relative to those treated with vehicle.

3.2.1. Swimming

The mean number of seconds that the rats displayed swimming behavior is depicted in the upper section of Fig. 2. The 4×2 mixed factors ANOVA revealed significant effects of group, $F(3, 28) = 14.16$, $p<.001$, trial, $F(1, 28) = 90.79$, $p<.001$, and a group×trial interaction, $F(3, 28) = 22.78$, $p<.001$. Although the groups did not differ on trial 1, they did significantly differ on trial 2, $F(3, 28) = 32.22$, $p<.001$. Bonferroni pairwise comparison tests revealed that on trial 2, the vehicle group displayed significantly less swimming than all paroxetine groups (p's<.025). Additionally, the 3 mg/kg paroxetine group displayed less swimming than the 10 mg/kg ($p<.001$) and the 30 mg/kg ($p<.001$) paroxetine groups which did not differ from each other.

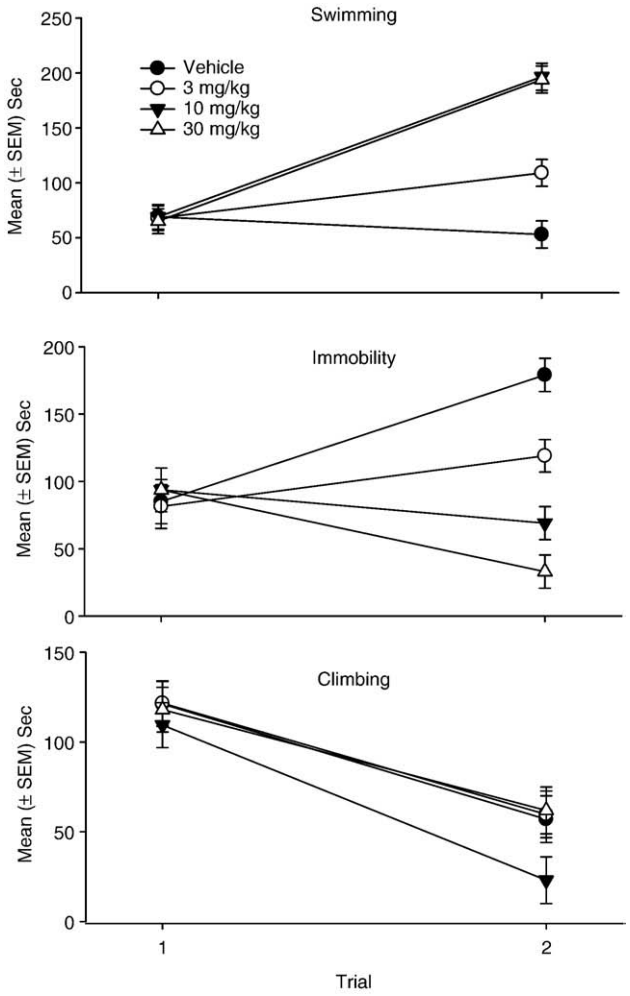

Fig. 2. Mean (±SEM) number of seconds that rats spent swimming, immobile and climbing during the first 5 min of trial 1 and during the 5 min trial 2 of the FST Rats were injected with either 0, 3, 10 or 30 mg/kg paroxetine 23.5, 5, and 1 h before trial 2.

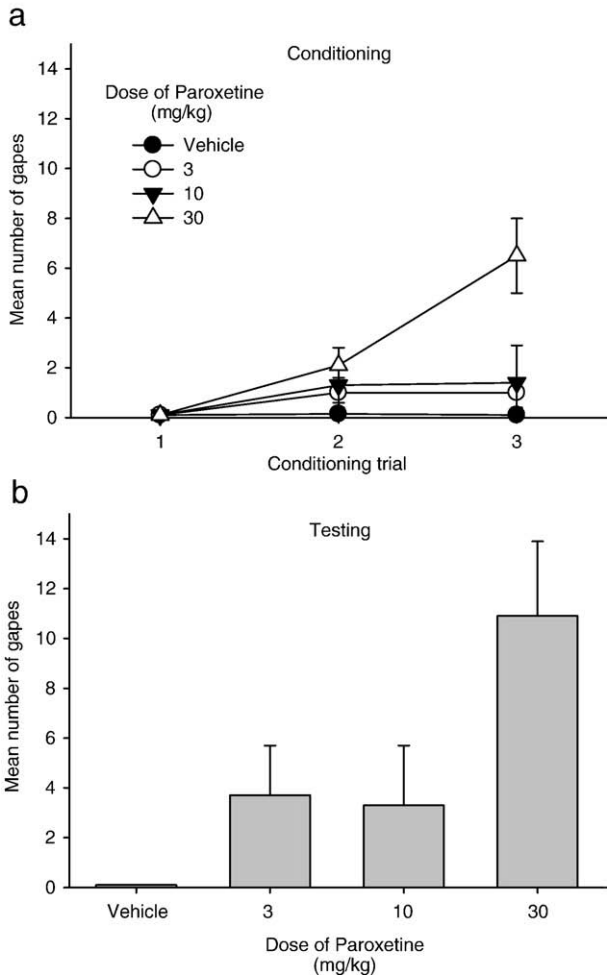

Fig. 3. Mean (±SEM) number of gapes displayed by rats conditioned with 0, 3, 10 and 30 mg/kg of paroxetine in Experiment 3. a) Conditioning trials with 18.5 h between trials 1 and 2 and 4 h between trials 2 and 3. b) Test trial (72 h after trial 3).

3.2.2. Immobility

The mean number of seconds that the rats remained immobile is depicted in the middle section of Fig. 2. The 4×2 mixed factors ANOVA revealed significant effects of group, $F(3, 28) = 5.35$, $p = .005$, and a group×trial interaction, $F(3, 28) = 23.97$, $p<.001$. The groups did not differ on trial 1, but significantly differed on trial 2, $F(3, 28) = 26.37$, $p<.001$. On trial 2, Bonferonni pairwise comparison tests revealed that the vehicle group remained immobile for significantly longer than all paroxetine groups (all p's<.025). Additionally, the 3 mg/kg paroxetine group was immobile longer than either the 10 mg/kg ($p<.01$) or 30 mg/kg ($p<.001$) paroxetine groups and less than the vehicle group ($p<.025$). Finally, the 10 mg/kg paroxetine group was more immobile than the 30 mg/kg paroxetine group ($p<.05$).

3.2.3. Climbing

The mean number of seconds that the rats spent climbing during each trial is depicted in the bottom section of Fig. 2. The 4×2 mixed factors ANOVA only revealed a significant main effect of trial, $F(1, 28) = 109.19$, $p<.001$. Rats displayed significantly less climbing on trial 2 than on trial 1; but this effect did not significantly differ amongst the groups.

3.3. Experiment 3: conditioned gaping reactions: massed conditioning trials

A dose of 30 mg/kg paroxetine, but not 3 or 10 mg/kg paroxetine, produced conditioned gaping reactions in rats when the conditioning trials were spaced 18.5 h (trials 1 and 2) and 4 h (trials 3 and 4) apart.

This pattern of paroxetine administration was similar to that of Experiment 2. Fig. 3a presents the mean (±SEM) number of gapes elicited by intraoral infusions of 17% sucrose solution on each of the 2-min conditioning trials The 4×3 mixed factors ANOVA revealed significant effects of dose, $F(3, 25) = 3.4$; $p<.05$, trials, $F(2, 50) = 6.2$; $p<.01$ and a dose by trials interaction, $F(6, 50) = 3.3$; $p<.01$. On conditioning trial 3 only the rats in group 30 mg/kg paroxetine displayed significantly more conditioned gaping reactions than any other group (p's<.05).

Fig. 3b presents the mean (±SEM) number of gapes elicited by 17% sucrose solution during the 5-min test 72 h after the final conditioning trial. The one way ANOVA revealed a significant effect, $F(3, 25) = 3.3$; $p<.05$; subsequent Bonferroni t tests revealed that group 30 mg/kg displayed more conditioned gaping reactions than any other group and no other groups differed significantly from the vehicle group.

3.4. Experiment 4: conditioned floor preference/aversion

On the conditioned floor preference test the rats did not differ in the time spent on the vehicle-paired and drug-paired floors in either the 10 mg/kg or 30 mg/kg paroxetine group (see Fig. 4). The mean number of seconds that each rat spent on the drug-paired and vehicle-paired floor was entered into a 2×2 mixed factors ANOVA, with the between groups factor of dose (10 and 30 mg/kg paroxetine) and the within groups factor of floor (paroxetine-paired floor or saline-paired floor), which revealed no significant effects (floor, $F(1, 21) = 0.88$, $p = .36$; group, $F(1, 21) = 1.90$, $p = .18$; group×floor interaction , $F(1, 21) = 0.40$, $p = .53$) The rate of activity (distance traveled/s on floor) on the paroxetine-paired floor and the saline-paired floor did not differ. The 2×2 (dose×floor) mixed factors ANOVA revealed no significant effects (group, $F(1, 21) = 1.90$, $p = .18$; drug, $F(1, 21) = 0.88$, $p = .36$; group×-drug interaction, $F(1, 21) = 0.40$, $p = .53$).

On the other hand, paroxetine decreased activity across conditioning trials in comparison to vehicle as seen in Fig. 5. The mean distance (cm) traveled during conditioning trials on the vehicle- and paroxetine-paired floors for the 10 mg/kg and 30 mg/kg doses was entered into a 2×2×3 (dose×conditioning trial×conditioning cycle) mixed factors ANOVA with the between group factor of dose (10 and 30 mg/kg paroxetine) and the within group factors of conditioning trial drug (paroxetine/saline) and conditioning cycle (cycles 1–3). The analysis revealed only a significant main effect of conditioning trial drug, $F(1, 21) = 83.67$, $p<.001$. Rats showed significantly less activity on all paroxetine conditioning trials than on the saline conditioning trials, but this effect did not differ across doses and did not change across trials.

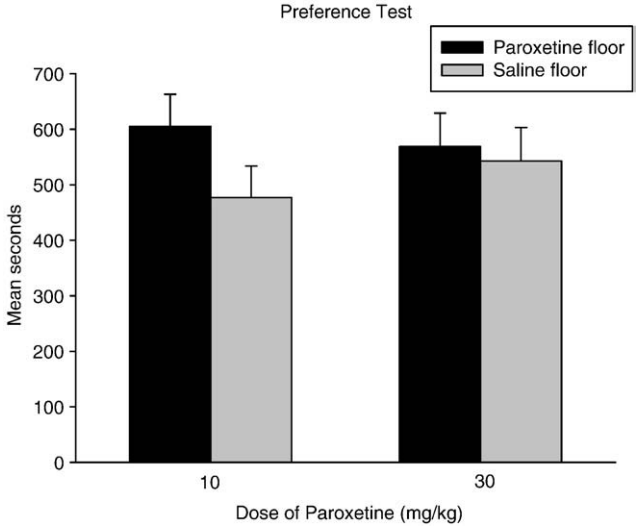

Fig. 4. Mean (±SEM) seconds spent on the vehicle-paired floor and the paroxetine-paired floor during a preference test that followed 3 conditioning trials in Experiment 4.

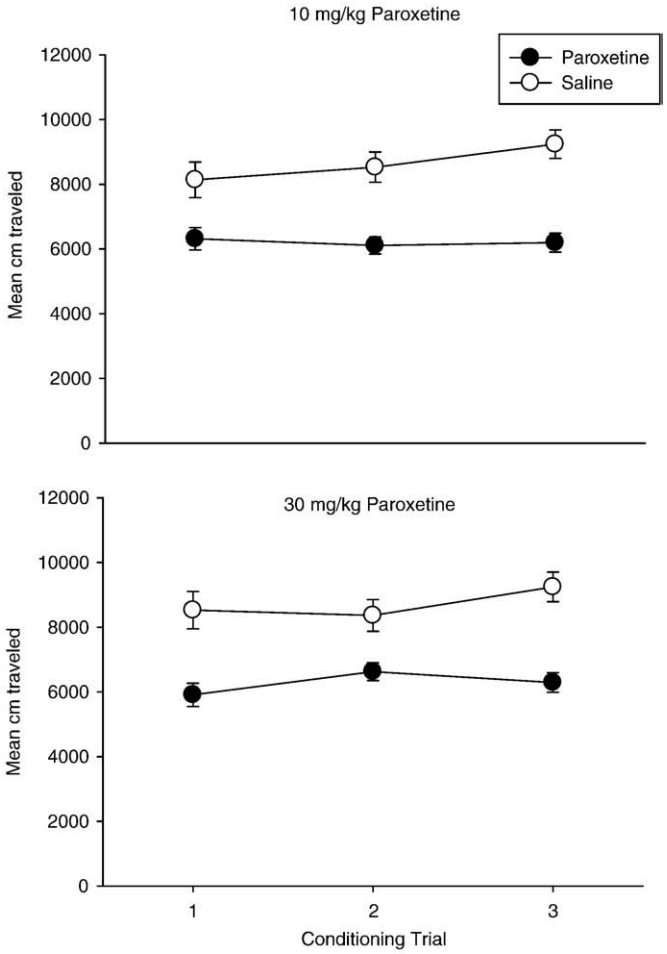

Fig. 5. Mean (±SEM) distance traveled (cm) during each of the vehicle and paroxetine conditioning trials in Experiment 4.

4. Discussion

Paroxetine produced an antidepressant-like effect (assessed in the FST) at a lower dose than that required to produce nausea (as assessed by conditioned gaping in Experiments 1 and 3), suggesting that the FST and the conditioned gaping test may be used in tandem to evaluate the potential of antidepressant treatments to be clinically effective at doses lower than those that produce the side effect of nausea. A dose as low as 3 mg/kg of paroxetine enhanced swimming and decreased immobility in the FST relative to controls; however doses of 10 and 30 mg/kg were more effective. These effects are predictive of the antidepressant efficacy of paroxetine. However, only the higher dose of 30 mg/kg established conditioned gaping reactions whether administered in spaced trials (72 h apart) or massed trials (18.5 and 4 h apart as paroxetine is administered in the FST). If conditioned gaping reactions are only established by nauseating treatments as suggested by Parker (2003), then a dose of 30 mg/kg of paroxetine would be required to produce nausea. Doses of paroxetine that were most effective in the FST (10 and 30 mg/kg), were neither rewarding nor aversive in the conditioned floor preference test.

Paroxetine produces its antidepressant-like effect by preventing the reuptake of 5-HT, thereby elevating extracellular levels of this neurotransmitter. However, elevated 5-HT also produces nausea (Andrews and Horn, 2006). Interestingly, the difference among intervals between conditioning trials in Experiment 1 and Experiment

3 did not change the pattern of findings; after two conditioning trials, rats displayed conditioned gaping reactions during intraoral infusion of sucrose paired with 30 mg/kg of paroxetine. The finding that paroxetine produced conditioned nausea, as reflected by conditioned gaping reactions, is consistent with reports that other agents which elevate extracellular 5-HT levels, fenfluramine (Parker, 1988) and fluoxetine (Limebeer et al., 2009), also produce conditioned gaping reactions in rats.

Given the ability of 30 mg/kg of paroxetine to produce conditioned gaping reactions reflective of nausea, it was surprising that it did not produce a conditioned floor aversion, especially in light of Davies and Parker's (1993) finding that fenfluramine produced a conditioned place aversion. However, it is possible that the onset of nausea produced by the highest dose of paroxetine was not contiguous with exposure to the conditioning floor. Fenfluramine elevates serotonin by facilitating its release, but paroxetine elevates serotonin by blocking its reuptake. Therefore, it is conceivable that the extracellular serotonin accumulates with a longer latency when rats are administered paroxetine than when they are administered fenfluramine. If the extracellular 5-HT accumulation was not sufficient to produce nausea within the 45 min conditioning trial, then the floor cues would not co-occur with the nausea and the association would not be established. On the other hand, it is well known that flavor cues can become associated with aversive drug effects over delays as long as 12 h (Garcia et al., 1974). Therefore, the establishment of conditioned gaping reactions when sucrose was paired with 30 mg/kg of paroxetine may occur even if the nausea produced by the drug is delayed. Clearly, paroxetine had a physiological effect upon the animals during the conditioning trials, given its ability to reduce activity level during the conditioning trials (as has been previously reported by Detke et al., 1995), but the relationship between reduced activity and nausea is not known. It is also possible that the 20 min pretest exposure to the apparatus produced some latent inhibition effects which could account for the failure to find a weak conditioning effect.

Although paroxetine did not display rewarding or aversive effects in the floor preference test, it did show the expected antidepressant-like action in the FST. Each dose of paroxetine tested increased swimming duration and decreased immobility compared to vehicle on trial 2 of the FST. Despite methodological differences in the FST procedures across laboratories, this pattern of results is consistent with the pattern produced by SSRIs that has been reported in previous studies (Detke et al., 1995; Reed et al., 2007; Weiner et al., 2003). The failure to find a paroxetine-induced increase in climbing behaviour is also consistent with Detke et al. (1995) who suggest that SSRIs do not affect this escape response in rats.

Together the results of these animal experiments are consistent with the profile seen with humans. Although paroxetine is an effective treatment for depression in humans, the most commonly reported side effect is nausea. The results reported here suggest that the dose that induced nausea (30 mg/kg) also produced an antidepressant-like effect. However, lower doses of paroxetine (3 and 10 mg/kg) that did not produce nausea also produced an antidepressant-like effect. The combination of using the TR test, to assess a drug's nausea-inducing properties (by conditioned gaping reactions), with the FST, a measure of antidepressive effects, may help to develop new compounds with a greater efficacy/side effect ratio (e.g., therapeutic index) for treating depression.

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