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Nicotine-induced conditioned place preference in adolescent rats

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ABSTRACT

A number of clinical reports have noted that women are more vulnerable to tobacco abuse than men, and adolescent females are especially vulnerable to nicotine addiction. Conditioned place preference (CPP) is a widely used technique for determining the rewarding effects of drugs with abuse potential in animal models. Several studies have reported that nicotine was ineffective in eliciting CPP in rats; while others have observed conditioned place aversion (CPA) rather than preference for nicotine. One recent investigation established CPP in adolescent female rats, however at a reasonably high dose; while a second reported dose dependence of nicotine-induced CPP in male but not female rats. The present study was designed to determine the lowest dose necessary to induce CPP to nicotine in adolescent female rats. Nicotine-induced CPP was obtained at a subcutaneous dose of 0.03 mg/kg (salt content) using a biased conditioning paradigm. Higher doses produced aversion and lower doses provided no rewarding or aversive effects. CPP persisted for at least 3 weeks following conditioning in the absence of further nicotine treatment. In contrast with results from adolescent human females and males, age-matched male rats also evidenced CPP at this very low dose of nicotine. These results indicate that even a low dose of nicotine is reinforcing and addicting in both adolescent male and female rats and brings into question the suggestion that nicotine induces greater addicting capacity in adolescent girls than boys.

1. Introduction

Conditioned place preference (CPP) is a commonly used method for determining the reward and addiction potential of a substance (O'Dell and Khroyan, 2009). Most drugs of abuse elicit robust CPP (e.g. Brown et al., 2007; Cruz et al., 2010), but there have been conflicting results concerning the ability of nicotine to induce CPP. A number of studies have reported either an aversion or no effect following nicotine administration. Several factors such as rat strain, the dosage and route of administration, the type of CPP paradigm, and length of training all potentially affect the ability of nicotine to induce CPP. Studies conducted using the hooded strain of rats show no reinforcing or aversive effects to nicotine indicating diminished sensitivity to this drug (Clarke and Fibiger, 1987; Shoaib et al., 1994). Other studies have shown a wide range of nicotine doses capable of producing either preference or aversion (Harvey et al., 2004; Laviolette et al., 2002; Laviolette and van der Kooy, 2003a,b; Torres et al., 2009). Nicotine-induced conditioned place aversion (CPA) was absent at doses lower than 0.1 and higher than 1 mg/kg across several rat strains (Ashby et al., 2002; Dewey et al., 1999; Fudala and Iwamoto, 1986; Fudala et al., 1985; Horan et al., 1997; Jorenby et al., 1990; Papp et al., 2002; Rogers et al., 2004). Further, there is a recent report (Yararbas et al., 2010) indicating nicotine-induced CPP in both male and female sexually mature Sprague–Dawley rats; however, CPP dose-dependency was seen only in male rats (doses: 0.1, 0.2, 0.4, 0.6 mg/kg, s.c.).Taken together these observations suggest that the induction of CPP by nicotine is a complex process and when successful requires a dose at or above 0.1 mg/kg, s.c.

The present study initially determined the stimulus context and lower range of nicotine doses necessary to elicit CPP in adolescent female rats. Our interest in this particular group stems from the observation that human adolescent females appear to show a particular vulnerability to nicotine (Collins and Izenwasser, 2004; Levin et al., 2003). Adolescent females utilize more tobacco products and have greater difficulty stopping nicotine use as compared with age-matched males (Pauly, 2008; Perkins and Scott, 2008; Pogun and Yararbas, 2009). If females begin smoking during adolescence they have greater difficulty quitting as compared with males (Chen and Millar, 1998). We hypothesized that adolescent girls could be susceptible to nicotine addiction because they find it rewarding at a very low dose. If this is so then adolescent female rats would be expected to show CPP to a much lower dose of nicotine than previously tested, and at a lower dose than adolescent male rats.

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2. Materials and methods

All experiments adhered to the Guidelines for the Care and Use of Laboratory Animals as required by the National Institutes of Health (NIH Publication No. 80-23), and the protocols were approved by the Washington State University Institutional Animal Care and Use Committee.

2.1. Animal housing

Sprague–Dawley female and male rats (breeding stock derived from Taconic, Germantown NY) were housed in groups of 4–5 per cage in a temperature/humidity controlled room and adapted to a 12 h light–dark cycle initiated at 0600 h in an American Association for the Accreditation of Laboratory Animal Care approved vivarium at a temperature of 21 ± 1 °C. Animals had free access to Harlan Teklad F6 rodent diet (Madison, WI) and water. All experiments were started when the animals were at postnatal day 28.

2.2. Drug

Nicotine hydrogen tartrate salt was obtained from Sigma-Aldrich (N 5260, St. Louis MO). The salt was dissolved in sterile PBS to obtain concentrations of 0.01, 0.03, 0.08, and 0.1 mg/ml nicotine solution with pH adjusted to 7.4.

2.3. Conditioned place preference protocol

The CPP apparatus consisted of a wooden box 64 (L) × 20.5 (W) × 40 (H) cm with two main compartments (28 × 20.5 cm) separated by a smaller compartment (8 × 20.5 cm). One of the main compartments was painted black and the other white. The black compartment had wire mesh flooring (1.2 cm squares) and the white had parallel metal rods (dia. = 4.8 mm) spaced 1 cm apart. The central compartment had a black wooden floor. A 15 W lamp was placed over the black compartment to compensate for high initial preference. A video camera was placed directly over the apparatus to record the activity of the rat. The camera was connected to a computer which recorded the activity interpreted by video tracking software that provided quantifiable information on locomotor activity, time spent in each compartment, and number of entries into a compartment. A biased paradigm was used in which the animal was assigned to the non-preferred compartment following nicotine administration. This protocol is thought to be more effective at producing CPP than the unbiased procedure in which the animal is randomly assigned to a chamber after nicotine injection (Acquas et al., 1989; Brielmaier et al., 2008; Calcagnetti and Schechter, 1994).

2.3.1. Preconditioning

During preconditioning, each rat was placed in the middle compartment and allowed free access to the entire box for 15 min. The animal was considered to be in a compartment if its forelimbs were inside the compartment. The time spent in each compartment was measured on 2 consecutive days and the mean of the two sessions was calculated for each compartment.

2.3.2. Conditioning

The conditioning phase began the day after preconditioning and at the same time of day for each animal. The animals received two conditioning sessions per day—one with an injection of nicotine (in sterile PBS, 1 ml/kg, at a dose of 0.01, 0.03, 0.08, or 0.1 mg/kg, s.c.) and the other with an injection of PBS (1 ml/kg, s.c.). Following drug or vehicle administration, the animals were confined to the non-preferred or preferred compartment respectively, for 15 min. The order of the drug injection was randomized each day and the sessions were conducted 4 h apart. Members of a control group received saline injections during both daily sessions. The animals underwent CPP acquisition trials for 5 consecutive days.

2.3.3. Post-conditioning

The day following the conditioning phase (day 6) each rat was tested for conditioning in a drug-free state. The rat was placed in the central compartment and allowed free access to both compartments for 15 min. The time spent in each compartment was measured.

2.3.4. Re-exposure

To test for continued drug preference the rats were maintained in their home cages for 5 additional days without drug injection. On the test day (day12) each rat was re-introduced to the CPP apparatus in a drug-free state and times spent in the nicotine-paired and saline-paired compartments were measured.

2.4. Data analysis

The degree of apparatus bias by female rats was evaluated by the use of a paired *t*-test ($p<0.05$) comparing time spent in the dark and white compartments. A paired *t*-test was also used to compare time spent in each compartment once a 15 W lamp was placed over the dark compartment. The data concerned with establishing an effective dose of nicotine were analyzed using a one-way ANOVA followed by Newman–Keuls post-hoc tests ($p<0.05$). The data sets concerned with time spent in the non-preferred compartment (drug associated compartment) following nicotine or saline injection during 1 to 5 days of conditioning trials were analyzed by one-way ANOVAs. And finally, the data set concerned with time spent in the non-preferred compartment following either nicotine or saline injection during a post-conditioning trial and at 2, 5, 11, and 21 days re-exposure using male rats was analyzed by a 2 × 5 repeated measures ANOVA, followed by Newman–Keuls post-hoc tests.

3. Results

3.1. Apparatus bias

Since preference bias introduced by the CPP apparatus can interfere with interpretation of the results, 6 female rats were first tested to determine time spent in each compartment absent of drug (Cunningham et al., 2003; Roma and Riley, 2005). These preconditioning preference trials were initially performed in the absence of a light source over the black compartment. Our results are in agreement with Roma and Riley (2005) in that the animals showed a strong preference for the black compartment ($t_5 = 20.23$, $p<0.001$; Fig. 1A). We then introduced a 15 W lamp above the black compartment and this neutralized the bias (Fig. 1B).

3.2. Effective nicotine dose determination

In order to establish the susceptibility of adolescent female rats to nicotine we first determined the dose range of nicotine that elicited CPP. We employed four groups of female rats (N = 4 per group) with nicotine doses of 0.01, 0.03, 0.08, and 0.1 mg/kg as shown in Fig. 2, and determined that the 0.03 dose elicited robust CPP ($F_{3,12} = 3.95$, $p<0.05$). Both the 0.08 and 0.1 mg/kg doses produced aversion to the chamber in which the drug was administered (post-hoc tests, $p<0.05$). The 0.01 mg/kg dose failed to elicit any behavioral change in the animals.

3.3. Development of CPP for nicotine

Next, the temporal characteristics concerning the acquisition of nicotine preference were determined. We were particularly interested in finding the minimal number of training days required for adolescent

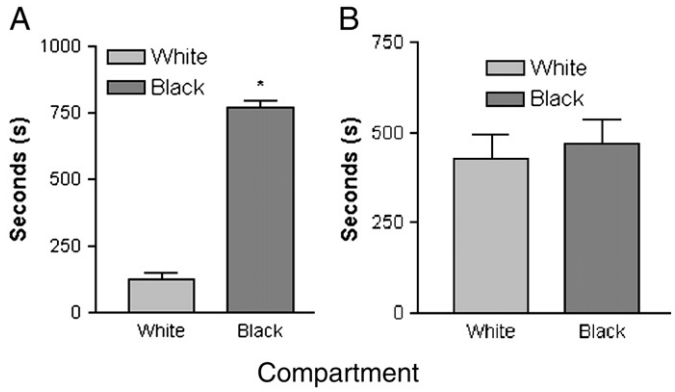

Fig. 1. Initial preference in the CPP chamber. Mean (±SEM) time spent in the white and black compartments of the CPP chamber. These data represent the average of two trials recorded for 15 min ($N=6$). (A) The animals initially preferred the black compartment. (B) No significant preference was noted between black and white compartments following the introduction of a lamp above the black compartment. *$p<0.001$.

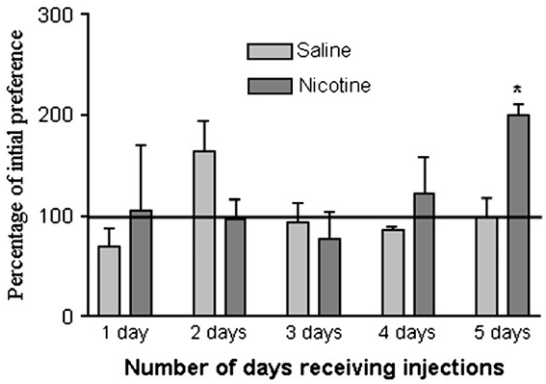

Fig. 3. Development of CPP over 5 days of nicotine injection. Mean (±SEM) time spent in the non-preferred compartment by nicotine treated (0.03 mg/kg) and saline control rats after each day of CPP training. One-way ANOVA indicated a significant groups effect for time spent in the nicotine paired compartment. Post-hoc analysis indicated significant conditioning after 5 days of nicotine administration. *$p<0.05$.

female rats to show conditioning. Thus, following preconditioning separate groups of animals (N=6 per group) were conditioned (two sessions per day) for 1, 2, 3, 4 or 5 days. After each day of conditioning the animals were tested for CPP. The results illustrate that the animals showed significant conditioning only following 5 days of nicotine administration ($F_{4,25}=3.03$, $p<0.05$; post-hoc tests, $p<0.05$; Fig. 3).

3.4. Persistence of nicotine CPP

In order to determine the strength of conditioning, animals were tested for CPP up to 3 weeks following conditioning. Female Sprague–Dawley rats can begin to show signs of sexual maturation such as rhythmic surges in luteinizing hormone levels in the blood as early as 27 days after birth. Ovulation and opening of the vagina can occur as early at 31 days after birth (Rivest, 1991). Since we did not want the physiological changes occurring in a sexually maturing female rat to interfere with the acquisition and maintenance of place preference, we used two groups of adolescent male rats for this experiment (28 days old at the start). One group (N=8) was subjected to the same CPP paradigm described above, and received 0.03 mg/kg nicotine during conditioning. The control group (N=4) received only PBS injections. To test the persistence of nicotine CPP, the animals were re-exposed to the CPP chamber 2, 5, 11, and 21 days after post-conditioning, in the absence of drug. The nicotine conditioned animals showed a persistent preference for the compartment in which the drug was administered even after 21 days of abstinence from nicotine as compared with controls ($F_{1,10}=5.67$, $p<0.05$; Fig. 4). Although re-exposure days did not differ ($F_{4,40}=1.97$, $p>0.10$), the interaction of groups × days was significant ($F_{4,40}=3.28$, $p<0.05$). Post-hoc tests revealed that the nicotine treated animals were different from controls on each re-exposure day.

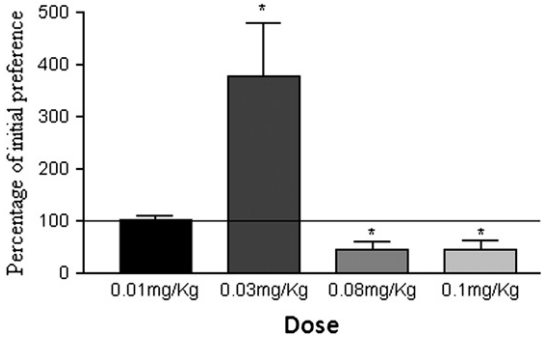

Fig. 2. CPP following different doses of nicotine. Mean (±SEM) time spent in the nicotine paired compartment following the designated doses of nicotine ($N=4$ per group). There were differences among the groups with the 0.03 mg/kg dose inducing CPP; while the 0.08 and 0.1 mg/kg doses produced CPA. The 100% line represents the initial preference for the compartment in the absence of nicotine. *$p<0.05$.

4. Discussion

Several studies have reported that nicotine elicited aversion in the CPP rat model (Fudala and Iwamoto, 1986; Fudala et al., 1985; Horan et al., 1997); however our results indicate that nicotine can produce both aversive and rewarding effects in the adolescent female Sprague–Dawley rat depending on the dose administered. A previous study reported that nicotine administered at 0.4, 0.8 and 1.2 mg/kg failed to produce CPP but did result in CPA at the 0.8 mg/kg dose (Jorenby et al., 1990). At 0.4 and 1.2 mg/kg there was a trend toward aversion. However, in these experiments male Holtzman rats were used and the nicotine solution was not pH balanced. The acidity of the injection could have contributed to the aversion. In contrast with these results, Calcagnetti and Schechter (1994) did obtain nicotine-induced CPP at 0.8 mg/kg following eight conditioning trials. One possible reason for such conflicting results could be that any given dose of nicotine has the potential to be both rewarding and aversive (Goldberg et al., 1981;

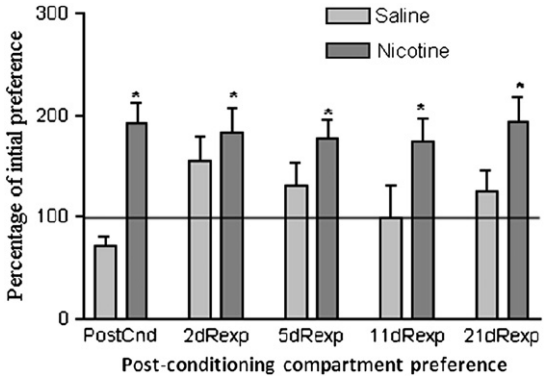

Fig. 4. Persistence of nicotine CPP. Mean (±SEM) time spent in the non-preferred compartment as evidenced by nicotine treated ($N=8$) and saline injected controls ($N=4$) during post-conditioning and re-exposure trials at 2, 5, 11 and 21 days following conditioning. A repeated measures ANOVA indicated a difference comparing the two groups over testing days but no difference comparing re-exposure days. There was a groups × days effect. Post-hoc analyses indicated that the nicotine treated animals spent more time in the non-preferred compartment than the control animals on each day tested. *$p<0.05$.

Harvey et al., 2004; Laviolette and van der Kooy, 2003a,b). If the reward value is greater than the aversion value the dose may produce CPP in the contextual learning model, if not aversion may occur. Even small changes in the procedure such as too low or high a dose, or using a different strain or age of animal, may tip the balance toward aversion. In this regard, as shown in Fig. 1, the manipulation of compartment preference through the use of a light source above the dark compartment was sufficient to overcome the initial bias the animals evidenced for this compartment, thereby unmasking the rewarding aspect of nicotine at the 0.03 mg/kg dose. Thus, eliminating apparatus bias permitted the establishment of low dose nicotine-induced CPP that may have otherwise been undetected.

The results presented in Fig. 2 indicate that nicotine, unlike opiates and other stimulant drugs (Bardo et al., 1995), failed to produce a clear dose-dependent response to conditioning. We noted CPP only at 0.03 mg/kg with the next higher (0.08 mg/kg) and lower (0.01 mg/kg) doses being aversive or ineffective, respectively. This suggests that nicotine could have a step-up dose–response effect in that at one dose no CPP was observed, but at the next higher dose a robust preference was elicited. It is also possible that nicotine has a typical, but steep, dose response curve with a narrow range of doses that trigger preference in adolescent female rats. Conflicting results may also be obtained depending on whether a biased or unbiased procedure is used. Several studies have reported that CPP was elicited only when the biased procedure was used and nicotine was paired with the non-preferred compartment (Clarke and Fibiger, 1987; Calcagnetti and Schechter, 1994). No effect was noted when paired with the preferred compartment, evidenced as no increase from preconditioning levels following nicotine conditioning treatment (Acquas et al., 1989; Calcagnetti and Schechter, 1994; Carboni et al., 1989). The biased paradigm was presently used but we were concerned about the effects of stress on the outcome. High stress levels could certainly contribute to discrepancies concerning the results obtained. It is common practice before CPP trials are initiated that animals be handled and acclimated to the experimental apparatus and testing area for several days in order to minimize stress level. In our experiments we used animals that were weaned only 1 week prior to the start of the experiment. The stress levels in these animals may have been high due to separation from the mother and novelty of the home cages. Since nicotine is an anxiolytic there is the possibility that these animals preferred the anxiolytic effect of nicotine rather than the rewarding aspects (Glassman, 1993; Kassel and Unrod, 2000; Levin et al., 2007; Scheufele et al., 2000). Although this hypothesis is countered by the observation that preference for the nicotine-paired compartment was evidenced for up to 21 days following drug administration, we cannot rule it out.

The last experiment utilized male adolescent rats in order to avoid the possible influence of estrous cycle related bias. Rats were conditioned with nicotine or saline and tested for preference 2, 5, 11 and 21 days later. Between testing the animals remained in their home cages in a drug free state without undergoing extinction of conditioning. This experiment revealed that nicotine CPP persisted out to at least 21 days. Thus, the same nicotine dose of 0.03 mg/kg that produced robust CPP in adolescent female rats also resulted in CPP in same age males.

The present results are difficult to compare with recent findings by Torres et al. (2009) who also tested adolescent (postnadal 28–43 days) and young adult (postnadal 60–75 days) female rats for nicotine-induced CPP. These investigators used doses of 0, 0.2, 0.4, 0.6, 0.8, 1.2, and 1.8 mg/kg, s.c. and found that nicotine produced CPP in adolescent rats at 0.6 mg/kg, and at the higher dose of 1.2 mg/kg in adult rats. CPA was only seen in the adult rats at a dose of 1.8 mg/kg. Since we extended our doses only to 0.1 mg/kg there was no overlap in regimens between these two investigations. It is possible that adolescent female rats display a bimodal dose response curve with nicotine-induced CPP at 0.03 and at 0.6 mg/kg. This hypothesis remains to be tested.

The present results demonstrate that nicotine induces robust CPP in both adolescent female and male rats at a low dose. This outcome agrees with reports from human studies implicating nicotine in the development of addiction in adolescent girls (Pogun and Yararbas, 2009; Silverstein et al., 1980; Zeman et al., 2002), but also suggests a similar sensitivity in males. In comparing these results with humans it appears that nicotine may produce smaller reward effects in animals. This could be due to the absence of important contributions from environmental and social stimuli, and additional chemical components present in cigarettes that are important to drug-seeking and drug-taking behaviors. Smoking is accompanied by the formation of associations among sensory, olfactory, and visual cues and these associations appear to condition the smoker to crave nicotine. The absence, or minimization, of such associated environmental influences could reduce the reinforcing effect of nicotine in animals. Further studies concerning the effects of nicotine administration and cigarette smoking in animals and humans will be required to understand these differences as well as the apparent bimodal nature of the dose response curve in adolescent female rats.

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