Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 89 (2008) 94–100
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Nicotine place preference in a biased conditioned place preference design

Jennifer M. Brielmaier, Craig G. McDonald *, Robert F. Smith

Department of Psychology, George Mason University, MS 3F5, Fairfax, VA, 22030 USA

Received 18 April 2007; received in revised form 14 November 2007; accepted 15 November 2007
Available online 22 November 2007

Abstract

Conditioned place preference (CPP) is often more effectively produced with nicotine using a biased procedure. Interpretation of results can be problematic, however, given that doses that produce CPP in rats have acute anxiolytic and residual anxiogenic effects. We tested three groups of male rats in a biased, 2-chambered apparatus. Over eight conditioning days, one group (paired group) received four alternating injections of nicotine paired with the non-preferred (white) chamber and of saline in the preferred (black) chamber. A second group (counterbalanced group) received two nicotine injections each paired with the black and white chambers, with saline pairings on alternate days. A third group (saline control) received saline injections paired with both chambers. Following conditioning, the paired group spent significantly more time in the initially non-preferred chamber relative to saline-treated controls, suggesting CPP. The counterbalanced group did not show a significant preference shift, providing evidence that the observed preference shift in the paired group was not due to a drug-induced unconditioned reduction in aversion. Although this finding is consistent with the notion that nicotine produced CPP through its rewarding effects, we cannot discount the possibility of a conditioned reduction in aversion to the non-preferred chamber. For the paired group, a negative correlation was found between time spent in the white chamber before conditioning and preference shift following conditioning, suggesting that animals showing greater initial aversion to a non-preferred context are more likely to form CPP.

Keywords: Nicotine; Conditioned place preference; Reward; Anxiety

1. Introduction

Studies using rats and mice have demonstrated that psychostimulant drugs such as cocaine and amphetamine and opiate drugs such as morphine and heroin reliably produce a conditioned place preference (CPP) for a context that has been repeatedly paired with the drug (reviewed in Tzschentke, 1998). However, studies with nicotine have yielded mixed results. Several studies have found dose-dependent CPP to nicotine-paired environments (e.g. Fudala, Teoh, and Iwamoto, 1985; Risinger and Oakes, 1995; Le Foll and Goldberg, 2005) whereas others have found no effect or conditioned place aversion (CPA) (e.g. Jorenby et al., 1990; Horan et al., 1997). It has been proposed that methodological differences across studies, such as the strain of the animal, dose(s) used during conditioning, and number and duration of conditioning sessions have led to conflicting results (Tzschentke, 1998). Le Foll and Goldberg (2005) provide an excellent review of the published studies on nicotine-induced CPP in rats.

Perhaps the most important factor, however, is that of a "biased" vs. "unbiased" testing apparatus and/or procedure. A biased apparatus refers to one in which animals show a significant preference for one chamber over the other prior to conditioning. A biased procedure, on the other hand, typically refers to the pairing of the CS (drug or otherwise) with individual animals' initially preferred or non-preferred chamber (Cunningham et al., 2003). Studies using heroin (Schenk et al., 1985), cocaine (Nomikos and Spyraki, 1998), ethanol (Cunningham et al., 2003) and morphine (Vindenes et al., 2006) have found that the side of the apparatus with which the drug is paired can affect CPP outcome. In their review of the literature, Le Foll and Goldberg (2005) found that two-thirds of the studies that found nicotine-induced CPP used a biased procedure. Their study as well as two others (Acquas et al., 1989; Calcagnetti and Schecter, 1994) directly examined how using a biased or unbiased procedure affects nicotine-induced CPP, and all three

* Corresponding author. Tel.: +1 703 993 1358.
E-mail addresses: jbrielma@gmu.edu (J.M. Brielmaier), cmcdona3@gmu.edu (C.G. McDonald), bsmith@gmu.edu (R.F. Smith).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.11.005

found that nicotine must be paired with the animal's initially non-preferred chamber to produce significant CPP. Similar results have been found in preliminary studies conducted in this laboratory (unpublished data).

As discussed by Bardo and Bevins (2000) and Roma and Riley (2005), interpretation of CPP results can be problematic regardless of which procedure is used when the apparatus is biased. When the CS is paired with the initially preferred chamber, a ceiling effect may emerge and prevent detection of CPP. When the CS is paired with the initially non-preferred chamber, interpretation of results is confounded by the possibility of a preference shift due to reduction of aversion (Tzschentke, 1998). This has been termed the "motivational interaction hypothesis" (see Le Foll and Goldberg, 2005), which holds that nicotine's unconditioned rewarding effects may interact with animals' initial motivational state (characterized by avoidance of the non-preferred side) to cause them to shift their preference following conditioning.

There is considerable evidence that both acute and chronic nicotine administration can produce either anxiolytic effects or residual anxiogenic effects. Mice spend increased time in the light side of a light–dark box following acute nicotine injections (Costall et al., 1989). Rats have shown unconditioned reductions in anxiety-like behavior following acute systemic nicotine administration as measured using the social interaction test (File et al., 1998) and a fear conditioning model (Szyndler et al., 2001). Repeated-acute nicotine administration causes adolescent male rats to spend more time in the open arms of an elevated plus maze (Elliott et al., 2004). Human smokers partly attribute the maintenance of smoking behavior to its anxiety-reducing properties (Spielberger, 1986; Frith, 1971; Kassel and Unrod, 2000), and some laboratory studies have demonstrated that acute exposure to nicotine via cigarette smoking reduces subjective reports of anxiety (Perkins et al., 1992; Pomerleau and Pomerleau, 1987). Conversely, it has been shown that rats can exhibit elevated anxiety-like behavior in the twenty-four hours following chronic, systemic nicotine exposure (Irvine et al., 2001), suggesting that CPP could be affected by residual anxiogenic effects of the drug.

In a comparison of nicotine-induced place conditioning in adolescent and adult male rats, Torella et al. (2004) found that adolescent animals receiving nicotine in the initially non-preferred side of a 3-chambered, biased apparatus showed a significant increase in time spent in the non-preferred side relative to their saline-treated counterparts, but did not show an outright preference for this side on the posttest day. It was concluded that shifts in preference were seen in nicotine-treated animals via an anxiolytic effect of the drug. It was argued that the chamber animals spent more time in on the pretest day might simply be the less aversive one, and that nicotine-treated animals had learned to associate a reduction in aversion with the chamber nicotine was administered in. Similar results have been obtained using other drugs (e.g. Papp and Moryl, 1994).

Studies using the biased CPP technique have traditionally compared the responses of a nicotine-treated group or groups that receive the drug consistently in one side of the apparatus (usually the non-preferred side) with those of a control group that received alternating saline injections in each side of the apparatus. If repeated exposure to nicotine is by itself capable of producing a reduction in aversion to a context by exerting general anxiolytic effects or otherwise alleviating stress, one might expect to see shifts in side preference following conditioning that are not due to explicit pairing of the drug with the initially non-preferred side. Moreover, potential residual anxiogenic effects of repeated nicotine may also affect preference shift, and could conceivably produce place aversion. The present study investigated the nature of nicotine-induced CPP by comparing the responses of three treatment groups of adolescent and adult male rats tested in a biased, 2-chambered black and white apparatus. One group of animals, which we labeled the paired group, received nicotine consistently paired with the initially non-preferred (white) chamber and saline paired with the initially preferred (black) chamber. A second nicotine-treated group, termed the counter-balanced group, received pairings of nicotine in both the white and the black chambers, with alternate pairings of saline. A third group, the saline control, was administered saline injections paired with both the black and white chambers. The response to nicotine among the age and treatment groups was assessed by measuring the time spent in the white chamber before and after conditioning. Through the use of this novel three-group design, we were able to compare preference shifts in animals conditioned to associate the effects of nicotine with their non-preferred chamber to those seen in animals exposed to nicotine under comparable conditions, but without the opportunity to form a specific drug-context association.

An important design aspect of our apparatus was that it mimicked a light–dark box in that one chamber was black and the other white. Thus, we hypothesized that the animals would express an initial preference for the black chamber as has been shown in previous studies using a black and white apparatus (e.g. Papp et al., 2002; Tapper et al., 2004; Janhunen et al., 2005). We further hypothesized that if nicotine produces a preference shift through an unconditioned reduction in aversion to a non-preferred context, then both nicotine treatment groups would exhibit increased time spent in the white chamber. We also considered the possibility that nicotine might produce a residual anxiogenic effect that could be expected to exacerbate place aversion to the initially non-preferred context. An outcome where only the paired group spent more time in the initially non-preferred chamber after conditioning would be consistent with the notion that nicotine produces a preference shift via a conditioned response rather than via a nonspecific alteration in anxiety-like behavior. That is, such an outcome would suggest that animals have indeed formed an association between a drug-paired context and nicotine's neurobehavioral effects, most plausibly its rewarding effects as is traditionally assumed in CPP studies (Bardo & Bevins, 2000).

2. Methods

2.1. Subjects

Subjects were adolescent ($n=25$) and adult ($n=33$) male Sprague–Dawley rats obtained from Harlan (Indianapolis, IN,

USA). Adolescents began testing at postnatal day (P) 33–34 and adults at P73–74. All animals arrived at the laboratory at least one week prior to the beginning of testing and were subjected to individual handling by an animal care technician to reduce handling stress during experimentation. Animals were housed in groups of four on a 12 h light/12 h dark schedule (lights on at 0700) and given *ad libitum* access to food and water throughout the experiments. Procedures were conducted between 1000 and 1600 h. All experiments were completed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (National Research Council, 1996) and the guidelines of the University Institutional Animal Care and Use Committee.

2.2. Place conditioning apparatus

CPP testing was carried out in a 2-chambered conditioned place preference insert (Med Associates, VT) located in a very dimly lit (4–6 lx) testing room. The apparatus consisted of 2 Plexiglas chambers measuring 21×42×30 cm. One chamber consisted of black walls with a stainless steel rod floor and black tray paper lining, whereas the other chamber consisted of white walls with a stainless steel mesh floor and white tray paper lining. A black removable guillotine door separated the two chambers. A camera mounted above the apparatus recorded each trial, and data were acquired using Videotrack software (Viewpoint, Montreal, QC, Canada).

2.3. Drugs

(--)-Nicotine hydrogen tartrate was purchased from Sigma Chemical Company (St, Louis, MO). Saline and nicotine were administered subcutaneously (SC) between the shoulder blades at an injection volume of 1 mL/kg body weight. The dose level of nicotine (0.5 mg/kg) was chosen based on experiments that have indicated that this dose has produced place preference in both adolescent (Belluzzi et al., 2004) and adult (Janhunen et al., 2005) rats. To minimize the discomfort of the younger animals, $26^{1/2}$ gauge needles were used for all injections. Nicotine was dissolved in 0.9% NaCl and the dose level is expressed as the free base.

2.4. Place conditioning procedure

The experiment included a pretest phase, a conditioning phase, and a posttest phase. The pretest and posttest phases consisted of a single session, while the conditioning phase consisted of eight consecutive sessions. The experiment was conducted over 10 consecutive days with one session per day. Before the beginning of each day of testing, animals were weighed, placed in individual hanging wire cages and transported to the testing room, where they were allowed a habituation period of 20 min. Between trials on all experimental days, both chambers of the apparatus were cleaned with 70% EtOH and tray paper changed to remove odor cues.

2.4.1. Pretest

A 15-minute, drug-free pretest was used to determine initial chamber preference. Following habituation to the testing room, all animals were placed in the CPP apparatus with the guillotine door removed to allow free access between both chambers. Placement was counterbalanced within each treatment group such that half the animals started in one chamber and half started in the other. Time spent in each chamber was hand-scored by two observers blind to experimental conditions. An animal was determined to be "in" a chamber when all four of its paws were situated in that chamber.

2.4.2. Conditioning

One day following the pretest, animals were randomly assigned to one of three treatment groups. Animals in the paired group ($n=10$ adolescents and 11 adults) received four nicotine injections (0.5 mg/kg, SC) paired with the initially non-preferred (white) chamber of the conditioned place preference (CPP) apparatus and four saline injections paired with the initially preferred (black) chamber. Animals in the counterbalanced group ($n=7$ adolescents and 11 adults) received two nicotine injections paired with the white chamber of the CPP apparatus and two injections paired with the black chamber. A saline-treated group ($n=8$ adolescents and 11 adults) received eight injections of saline (SC) alternately paired with each chamber of the apparatus. The order in which alternating nicotine and saline injections were given was counterbalanced within the paired and counterbalanced treatment groups. The order of exposure to the black or white chamber was counterbalanced within the saline-treated group. All trials lasted for 15 min on conditioning days.

2.4.3. Posttest

One day after the last conditioning trial, a 15-minute, drug-free posttest was conducted to determine chamber preference following conditioning. Conditions on the posttest day were identical to those on the pretest day, meaning that animals were again placed in the CPP apparatus with the guillotine door removed to allow free access to both chambers. Placement was again counterbalanced within groups such that half the rats in each group started in one chamber and half started in the other. Time spent in each chamber was again hand-scored by two observers blind to experimental conditions, and animals were determined to be "in" a chamber when all four paws were situated there.

2.4.4. Data analysis

The outcome of the experiment was analyzed using analyses of variance (ANOVAs). Following significant main effects and interaction effects, simple effects analyses and Bonferroni-corrected post hoc mean comparisons were performed. To assess the correlation between the magnitude of initial bias and preference shift following conditioning of the paired nicotine-treated animals, Pearson's test was used. All data analyses were conducted using SPSS 14.0 statistical software.

3. Results

3.1. Apparatus bias

A paired samples *t*-test comparing time spent in the white and black chambers revealed that animals showed a significant

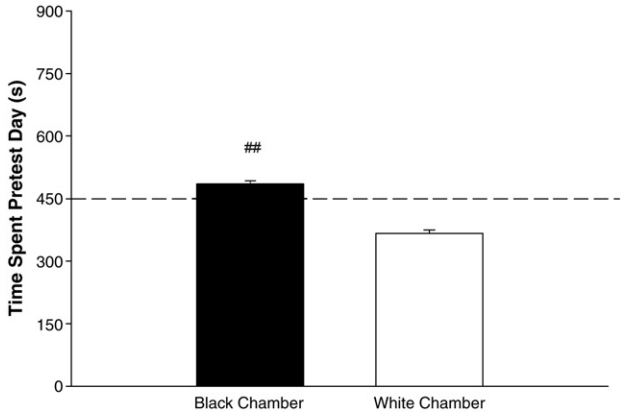

Fig. 1. Apparatus bias. Time spent in the black and white chambers of the CPP apparatus during the 15-minute (900 s) drug-free pretest. ##$p<.001$ vs. White Chamber.

preference for the black chamber on the pretest day ($t(57)=8.92$, $p<.001$). As shown in Fig. 1, animals spent an average of 485.25±7.43 s in the black chamber vs. 367.19±7.21 s in the white chamber across the 15-minute (900 s) test. Thus, the white chamber of the apparatus was designated as the initially non-preferred one for all animals, as has been done in previous studies investigating nicotine CPP (Fudala et al., 1985; Papp et al., 2002; Tapper et al., 2004). Animals spent an average of 48 s in between the black and white chambers (i.e., with two paws situated in each chamber). Time spent in between chambers was not counted when determining apparatus bias; nor was it counted when determining preference shift following conditioning.

3.2. Expression of nicotine-induced CPP

Data were analyzed in two ways. First, time (in seconds) spent in the white chamber before and after conditioning were compared using a 2 (Age)×3 (Treatment Group) ANOVA with test (Pretest and Posttest) as a repeated-measures factor. A significant Test×Treatment Group interaction was found (F (2, 52)=6.06, $p<.005$), as was as a significant main effect of Treatment Group (F (2, 52)=6.56, $p<.005$. No significant main effects of Test or Age were found, nor were there significant Test×Age or Test×Treatment Group×Age interaction effects. A 2 (Age)×3 (Treatment Group) ANOVA indicated no significant differences among age or treatment groups in time spent in the white chamber on the Pretest. A comparison of time spent in the white chamber on the Posttest yielded a significant main effect of Treatment Group (F (2, 52)=8.25, $p=.001$) but no other significant main effects or interaction effects As shown in Fig. 2A, post hoc comparisons indicated that animals in the paired group spent significantly more time in the white chamber on Posttest when compared to animals in both the counterbalanced group ($p<.01$) and the saline-treated group ($p=.001$). No significant difference was found between animals in the counterbalanced group and the saline-treated group.

Second, a difference score was computed for each animal by subtracting time in seconds spent in the white chamber on the Pretest from the time spent in the white chamber on the Posttest. Difference scores were analyzed using a 2 (Age)×3 (Treatment Group) ANOVA. A comparison of difference scores revealed a significant main effect of Treatment Group (F (2, 52)=6.06, $p<.005$) with no significant main effect of Age; nor was there a significant Age×Treatment Group interaction. As shown in Fig. 2B, post hoc comparisons indicated that animals in the paired group showed significantly higher difference scores (i.e., increased time spent in the white chamber on the Posttest relative to the Pretest) when compared to animals in the saline-treated ($p<.05$) and counterbalanced groups ($p<.005$). No significant difference was found when comparing the difference scores of animals in the counterbalanced group with those of animals in the saline-treated group. Because there were no main or interaction effects involving Age, we collapsed across this factor when

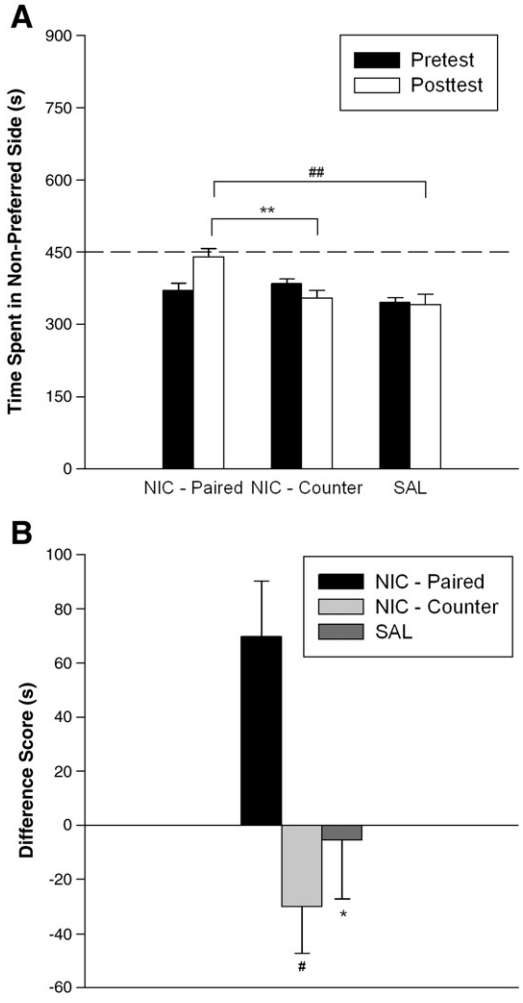

Fig. 2. Expression of nicotine CPP. A. Time spent in the initially non-preferred (white) chamber of the apparatus on the pretest and posttest days. **$p<.01$; ##$p<.001$ vs. NIC-Paired. B. Difference scores (time spent in the white side on posttest minus time spent in the white side on pretest). *$p<.05$; #$p<.005$ vs. NIC-Paired. "NIC-Paired" refers to animals that received four pairings of nicotine (0.5 mg/kg, SC) in the white chamber. "NIC-Counter" refers to animals that received two pairings of nicotine in the white chamber and two pairings of nicotine in the black chamber (counterbalanced pairings). "SAL" refers to animals that received saline paired with both chambers.

performing all post hoc analyses. Thus, age differences were not further considered in the present study.

3.3. Relationship between magnitude of initial bias and difference scores

To determine whether the magnitude of initial preference for the black chamber of the apparatus was related to the shift in chamber preference following conditioning in rats displaying significant nicotine-induced CPP (i.e. the paired treatment group), a correlational analysis was conducted using Pearson's r as the test statistic. As shown in Fig. 3, a significant negative correlation was found (r (20)=−.54, p<.025), indicating that animals with higher initial preference for the black chamber tended to spend increased time in the white chamber following conditioning.

4. Discussion

The present study explored the mechanism by which nicotine produces CPP when using a biased apparatus and procedure. The majority of animals tested spent significantly more time in the black chamber when given a choice on the pretest day, making the white chamber of the apparatus the non-preferred chamber. Though age was initially of interest, place conditioning data from adolescents and adults were examined together due to a lack of main or interaction effects involving this factor. Animals receiving nicotine paired consistently with the white chamber spent significantly more time in that chamber on the posttest day relative to counterbalanced nicotine-treated and saline-treated animals, providing evidence of nicotine CPP. Animals that received equal pairings of nicotine in both sides of the apparatus did not display significant shifts in preference relative to saline-treated animals. The present study also assessed the relationship between the magnitude of initial chamber preference on the pretest day and the shift in preference observed between the pretest and posttest days in the paired nicotine-treated animals. A significant negative correlation was found between these two measures, indicating that difference scores were higher for animals that showed a greater initial avoidance of the white chamber.

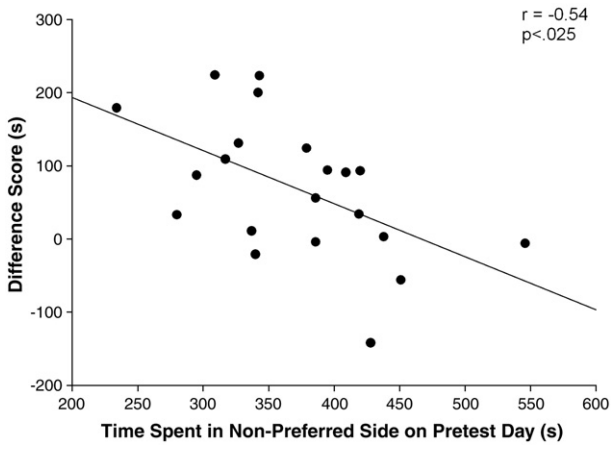

Fig. 3. Relationship between initial bias and preference shift. Correlation between time spent in the white chamber on the pretest day and difference scores for animals in the paired nicotine-treated group.

The finding that animals in the paired group spent significantly more time in the non-preferred chamber following conditioning when compared with animals in both the saline-treated and nicotine-treated counterbalanced groups provides evidence that nicotine did not produce an unconditioned reduction in aversion to the non-preferred context, a finding consistent with the hypothesis that nicotine is capable of producing CPP through its rewarding effects. If the CPP observed in the present study were solely due to an unconditioned reduction in the avoidance of the white chamber, the paired and counterbalanced groups would likely have shown similar mean difference scores. Though the mean difference score for animals in the counterbalanced group was actually slightly lower than that for animals in the saline-treated group (−30±17.29 s vs. −5.37±21.68 s, respectively), this difference did not approach significance. Such a result suggests that counterbalanced nicotine administration in the context of the CPP apparatus did not influence preference shift by producing residual anxiogenic effects on the posttest day. We note that although the paired group spent significantly more time in the initially non-preferred chamber following conditioning, it did not display an absolute preference for this chamber. Thus, we cannot rule out the possibility that the observed preference shift was the result of a conditioned reduction in aversion to the initially non-preferred chamber.

Some studies have reported a similar outcome to ours when using a biased design (e.g. Papp et al., 2002; Janhunen et al., 2005), while others have found an outright preference for the non-preferred chamber after conditioning (e.g. Le Foll and Goldberg, 2005). Importantly, Le Foll and Goldberg found only a weak initial bias using a design where the floor composition was the sole feature that distinguished the two chambers. In the present study, as well as those by Papp et al. and Janhunen et al., the initial bias was quite strong, likely due to the fact that the preferred chamber was black. As discussed earlier, the black chamber was hypothesized to be the preferred one given that our CPP apparatus (and those used by Papp et al. and Janhunen et al.) was similar in many respects to a light–dark box. We argue that animals from the paired group did not demonstrate an absolute preference for the initially non-preferred chamber because its putative anxiogenic properties likely opposed nicotine's rewarding effects.

Nicotine is similar to other drugs that support place conditioning (e.g. psychostimulants and opioids) in terms of its actions on the brain's reward circuitry, namely the mesocorticolimbic dopamine system (Pich et al., 1997; Picciotto, 1998). Acquisition and expression of nicotine-induced CPP have been inhibited by systemic administration of antagonists at dopamine D3 receptors (Le Foll et al., 2005; Pak et al., 2006), which have a demonstrated role in the rewarding effects of drugs (Le Foll et al., 2000). Similar effects have been shown following antagonism of D1 receptors (Acquas et al., 1989), including those in the nucleus accumbens shell (Spina et al., 2006), which are involved in Pavlovian incentive learning (Di Chiara, 2002). Therefore, it is reasonable to conclude that the doses at which nicotine produces

CPP (between 0.25 and 0.6 mg/kg s.c. in these studies) are doing so via a reward mechanism.

The correlational result suggests that animals that show greater initial preference for the black chamber are more likely to form a nicotine-induced CPP. This result lends support to the notion that a biased apparatus and procedure provide a means of investigating how individual differences in tendency to explore a novel environment, which may be indicative of anxiety-like behavior (Crawley, 1985), relates to the propensity to develop nicotine CPP. A black and white apparatus such as the one used here might be especially suited for such an investigation, as it can be expected to function similarly to a light–dark box. Shimosato and Watanabe (2003) found that increased anxiety-like behavior, as assessed by measuring the latency to cross from the black to the white chamber of a CPP apparatus, was related to greater expression of cocaine CPP. It is possible that animals that show increased baseline anxiety (expressed through increased preference for the black chamber) are more sensitive to the rewarding properties of nicotine. Such a finding would be in line with evidence that anxiety-like symptoms are associated with an increased risk of initiating smoking during adolescence (Patton et al., 1998), when smoking often begins (Dappen, Schwartz, and O'Donnell, 1996).

Taken together, the present results point to the usefulness of a biased apparatus and design when investigating nicotine CPP in rats. Most important was the lack of preference shift seen in animals exposed to nicotine equally in each chamber of the apparatus (the counterbalanced group). This finding provides strong evidence that the observed preference shift in the paired group was not due to an unconditioned alteration of anxiety-like behavior during or following conditioning with nicotine. A potential caveat of this study is that it was not possible to establish whether the observed preference shift was indicative of a conditioned reduction in aversion to the initially non-preferred chamber or a conditioned approach response. We note that it remains to be determined whether these two possibilities reflect different neurobehavioral processes. Indeed, it is possible that an outright preference was not observed in the present study because of the relatively strong apparatus bias. We hope that this information eases interpretation of results from nicotine CPP studies and sheds light on additional pertinent questions pertaining to the relationship between nicotine addiction and anxiety-like behavior.

Acknowledgements

We thank Juliza Chan for animal care, Megan Lawhead and Michelle Dunbar for assistance with data collection and the three anonymous reviewers for their constructive comments. Research supported by the Virginia Tobacco Settlement Foundation.

References

Acquas E, Carboni E, Leone P, Di Chiara G. SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? Psychopharmacology 1989;99:151–5.

Bardo MT, Bevins RA. Conditioned place preference: what does it add to our understanding of drug reward? Psychopharmacology 2000;153:31–43.

Belluzzi JD, Lee AG, Oliff HS, Leslie FM. Age-dependent effects of nicotine on locomotor activity and conditioned place preference in rats. Psychopharmacology 2004;174:389–95.

Calcagnetti DJ, Schecter MD. Nicotine place preference using the biased method of conditioning. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:925–33.

Costall B, Kelly ME, Naylor RJ, Onaivi ES. The actions of nicotine and cocaine in a mouse model of anxiety. Pharmacol Biochem Behav 1989;33:197–203.

Crawley JN. Exploratory behavior models of anxiety in mice. Neurosci Biobehav Rev 1985;9:37–44.

Cunningham CL, Ferree NK, Howard MA. Apparatus bias and place conditioning with ethanol in mice. Psychopharmacology 2003;170:409–22.

Dappen A, Schwartz RH, O'Donnell R. A survey of adolescent smoking patterns. J Am Board Fam Pract 1996;9:7–13.

Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res 2002;137:75–114.

Elliott BM, Faraday MM, Phillips JM, Grunberg NE. Effects of nicotine on elevated plus maze and locomotor activity in male and female adolescent and adult rats. Pharmacol Biochem Behav 2004;77:21–8.

File SE, Kenny PJ, Ougazzal AM. Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. Behav Neurosci 1998;112:1423–9.

Frith C. Smoking behaviour and its relation to the smoker's immediate experience. Br J Soc Clin Psychol 1971;10:73–8.

Fudala PJ, Teoh KW, Iwamoto T. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 1985;22:237–41.

Horan B, Smith M, Garnder EL, Lepore M, Ashby Jr CR. (−)-Nicotine produces conditioned place preference in Lewis, but not Fischer 344 rats. Synapse 1997;26:93–4.

Irvine EE, Cheeta S, File SE. Tolerance to nicotine's effects in the elevated plus-maze and increased anxiety during withdrawal. Pharmacol Biochem Behav 2001;68(2):319–25.

Janhunen S, Linnervuo A, Svensk M, Ahtee L. Effects of nicotine and epibatidine on locomotor activity and conditioned place preference in rats. Pharmacol Biochem Behav 2005;82:758–65.

Jorenby DE, Steinpreis RE, Sherman JE, Baker TB. Aversion instead of preference learning indicated by nicotine place conditioning in rats. Psychopharmacology 1990;101:533–8.

Kassel JD, Unrod M. Smoking, anxiety, and attention: support for the role of nicotine in attentionally mediated anxiolysis. J Abnorm Psychology 2000;109:161–6.

Le Foll B, Schwartz JC, Sokoloff P. Dopamine D3 receptor agents as potential new medications for drug addiction. Eur Psychiatr 2000;15:140–6.

Le Foll B, Goldberg SR. Nicotine induces conditioned place preferences over a large range of doses in rats. Psychopharmacology 2005;178:481–92.

Le Foll B, Sokoloff P, Stark H, Goldberg SR. Dopamine D3 receptor ligands block nicotine-induced conditioned place preferences through a mechanism that does not involve discriminative-stimulus or antidepressant-like effects. Neuropsychopharmacology 2005;30:720–30.

Nomikos GG, Spyraki C. Cocaine-induced place conditioning: importance of route of administration and other procedural variables. Psychopharmacology 1998;94:119–25.

Pak AC, Ashby Jr CR, Heidbreder CA, Pilla M, Gilbert J, Xi ZX, Gardner EL. The selective dopamine D3 receptor antagonist SB-277011A reduces nicotine-enhanced brain reward and nicotine-paired environmental cue functions. Int J Neuropsychopharmacol 2006;9:585–602.

Papp M, Gruca P, Willner P. Selective blockade of drug-induced place preference conditioning by ACPC, a functional NDMA-receptor antagonist. Neuropsychopharmacology 2002;27:727–43.

Papp M, Moryl E. Rewarding properties of non-competitive and competitive NMDA antagonists as measured by place preference conditioning in rats. Pol J Pharmacol 1994;46:79–81.

Patton GC, Carlin JB, Coffey C, Wolfe R, Hibbert M, Bowes G. Depression, anxiety, and smoking initiation: a prospective study over 3 years. Am J Public Health 1998;88:1518–22.

Perkins KA, Grobe JE, Fonte C, Breus M. "Paradoxical" effects of smoking on subjective stress versus cardiovascular arousal in males and females. Pharmacol Biochem Behav 1992;42:301–11.

Picciotto MR. Common aspects of the action of nicotine and other drugs of abuse. Drug Alcohol Depend 1998;51:165–72.

Pich EM, Pagliusi SR, Tessari M, Talabot-Ayer D, Hooft van Huijsduijnen R, Chiamulera C. Common neural substrates for the addictive properties of nicotine and cocaine. Science 1997;275:83–6.

Pomerleau CS, Pomerleau OF. The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. Psychophysiology 1987;24:278–85.

Risinger FO, Oakes RA. Nicotine-induced conditioned place preference and conditioned place aversion in mice. Pharmacol Biochem Behav 1995;51: 457–61.

Roma PG, Riley AL. Apparatus bias and the use of light and texture in place conditioning. Pharmacol Biochem Behav 2005;82:163–9.

Schenk S, Ellison F, Hunt T, Amit Z. An examination of heroin conditioning in preferred and nonpreferred environments and in differentially housed mature and immature rats. Pharmacol Biochem Behav 1985;22: 215–20.

Shimosato K, Watanabe S. Concurrent evaluation of locomotor response to novelty and propensity toward cocaine conditioned place preference in mice. J Neurosci Methods 2003;128:103–10.

Spielberger CD. Psychological determinants of smoking behavior. In: Tollison RD, editor. Smoking and society. Lexington, MA: Lexington Books; 1986. p. 89–134.

Spina L, Fenu S, Longoni R, Rivas E, Di Chiara G. Nicotine-conditioned single-trial place preference: selective role of nucleus accumbens shell dopamine D1 receptors in acquisition. Psychopharmacology 2006;184:447–55.

Szyndler J, Sienkiewicz-Jarosz H, Maciejak P, Siemiatowski M, Rokicki D, Czlonkowska AI, Plaznik A. The anxiolytic-like effect of nicotine undergoes rapid tolerance in a model of contextual fear conditioning in rats. Pharmacol Biochem Behav 2001;69:511–8.

Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Larbarca C, Whiteaker P, Marks MJ, Collins AC, Lester HA. Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. Science 2004;306:1029–32.

Torella TA, Badanich KA, Philpot RM, Kirstein CL, Wecker L. Developmental differences in nicotine place conditioning. Ann NY Acad Sci 2004;1021: 399–403.

Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 1998;56:613–72.

Vindenes V, Handal M, Ripel A, Boix F, Morland J. Conditioned place preference induced by morphine and morphine-6-glucuronide in mice. Pharmacol Biochem Behav 2006;85:292–7.