Available online at www.sciencedirect.com

SCIENCE DIRECT

Pharmacology, Biochemistry and Behavior 80 (2005) 87–92

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Differential behavioral responses to nicotine in Lewis and Fischer-344 rats

Scott D. Philibin[a], Robert E. Vann[b], Stephen A. Varvel[b], Herbert E. Covington III[b], John A. Rosecrans[b], John R. James[c], Susan E. Robinson[b,*]

[a]Department of Psychology, Virginia Commonwealth University, Richmond, VA, United States
[b]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, United States
[c]Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, United States

Received 23 April 2004; received in revised form 4 October 2004; accepted 19 October 2004
Available online 18 November 2004

Abstract

Individual and strain variability in the effects of nicotine suggests the involvement of a genetic component in nicotinic cholinergic receptor (nAChR) function, which may help explain nicotine's variable behavioral and pharmacological effects in different individuals. The present study evaluated differential responses to the discriminative stimulus (DS) and rewarding properties of nicotine in Lewis (LEW) and Fischer-344 (F-344) rats. Drug discrimination (DD) data suggest that the LEW rat is more sensitive to nicotine as LEW rats acquired the nicotine discrimination at a dose of 0.4 mg/kg, whereas F-344 rats acquired the dose of 0.9 mg/kg (all nicotine doses expressed as free base). Similarly, LEW rats exhibited nicotine-conditioned place preference (CPP) at 0.6 mg/kg, whereas the F-344 rats did not. Subsequent testing with a higher dose (0.9 mg/kg) failed to maintain the nicotine-CPP in the LEW rats. Conversely, nicotine-place preference in the F-344 rats was not changed at the higher dose. Taken together, these results suggest potential differences of sensitivities in LEW and F-344 rats to the rewarding and discriminative stimulus (DS) properties of nicotine. These findings support previous research by demonstrating that the F-344 rat is less sensitive to nicotine compared to the LEW rat.

Keywords: Nicotine; Drug discrimination; Conditioned place preference; Lewis; Fischer-344; Nicotinic receptor desensitization; Rat

1. Introduction

Nicotine, the purported pharmacologically active chemical in tobacco products, has been observed to induce variable effects in both experimental animals and humans. For example, nicotine (via tobacco) appears to have differential effects between and within individuals based on their smoking experience, level of dependence, and time since most recent exposure (Russell, 1989). Furthermore, light smokers who regularly use tobacco without developing dependence (i.e., "chippers") differ in their initial responses to nicotine and in their family's history of smoking and cessation when compared to dependent smokers (Shiffman, 1989). Similar to humans, the variable effects of nicotine have been observed in laboratory animals such that locomotor activity effects are often contingent on baseline behavioral levels (Hendry and Rosecrans, 1982). For example, nicotine elevates activity in individual rats that initially exhibit low activity, whereas activity decreases in individual rats that initially show high activity (Rosecrans, 1971).

Individual and strain differences in responsiveness to nicotine suggest an important genetic component in the functioning of nicotinic cholinergic receptors (nAChRs). Increasingly, studies relating rat strain, brain chemistry, and drug abuse sensitivity to drugs of abuse are being used to understand why humans may initiate substance abuse behaviors (Goeders and Guerin, 1996a,b; Simar et al., 1996; Brodkin et al., 1998). Differential responses to nicotine within or between strains may be linked with vulnerability to the rewarding properties of nicotine as well

* Corresponding author. Tel.: +1 804 828 8396; fax: +1 804 828 2117.
E-mail address: serobins@vcu.edu (S.E. Robinson).

0091-3057/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.10.009

as the ability to abstain from using tobacco products. The importance of genetics and individual responsiveness to the effects of nicotine has been emphasized by Collins (see Collins, 1990, for review) and colleagues (Bhat et al., 1991; Collins and Marks, 1991; de Fiebre et al., 1991; Marks et al., 1991; Pauly et al., 1991; Sangster et al., 1991).

Conditioned place preference (CPP) detects both reward and aversion and allows for simultaneous locomotor activity assessment (see review by Bardo and Bevins, 2000). Nicotine has been shown to induce CPP after peripheral (Fudala et al., 1985; Fudala and Iwamoto, 1986) and central (Iwamoto, 1990) administration. Nicotine has also been reported to produce conditioned place aversion (CPA) as well as CPP (Jorenby et al., 1990; Horan et al., 1997). In addition, Horan et al. (1997) demonstrated a genetic role in the sensitivity to nicotine's effects by demonstrating that Lewis (LEW) rats exhibited place preference to nicotine, whereas Fischer-344 (F-344) rats did not. During chronic nicotine administration, in a similar paradigm, the nAChR antagonist mecamylamine produced CPA (presumably reflecting nicotine withdrawal) in LEW but not in F-344 rats (Suzuki et al., 1999). Thus, LEW and F-344 rats seem to differ in responsiveness to the rewarding and aversive properties of nicotine.

The overall goal of this research was to further evaluate the CPP properties of nicotine and to evaluate whether its DS properties differ within and/or between F-344 and LEW rats. Previous research comparing the behavioral effects of nicotine in Sprague–Dawley and F-344 rats (Schechter and Rosecrans, 1971) showed that the F-344 rat exhibited differential effects that did not correlate with differences in brain nicotine levels, thus suggesting pharmacokinetics is not central to behavioral differences between those two strains. Once differential behavioral effects of nicotine in the LEW and F-344 rat have been identified, these subjects can be exploited for determination of possible genetic differences responsible for these differences in nicotine responses.

2. Methods

2.1. Subjects

This study was conducted in accordance with the National Institute of Health Guidelines for the Care and Use of Animals in Research and under protocols approved by the Animal Care and Use Committee of Virginia Commonwealth University. Male LEW and F-344 rats (200–250 g) were used for all behavioral studies (Charles River Labs, Wilmington, MA for DD and Harlan Labs, St. Louis, MO for CPP studies). Rats were housed in plastic cages (one per cage for DD and two per cage for CPP) at a constant temperature and humidity with a 12-h light/dark cycle. Water was available ad libitum in home cages, while food (Harlan Teklad) was restricted to maintain 85% free-feeding weights for the DD rats. Food and water were available ad libitum during the CPP experiments. All rats were acclimated to the colony 1 week prior to behavioral experiments.

2.2. Drugs

(−) Nicotine tartrate was purchased from Sigma, Saint Louis, MO. All nicotine concentrations are expressed as free base and dissolved in 0.9% saline, with the pH adjusted to 7.4. Subcutaneous (sc) injections were given 5 min prior to testing at a volume of 1 mg/ml.

2.3. Experiment 1: drug discrimination (DD)

2.3.1. Apparatus

DD training and testing sessions were conducted in eight standard sound-attenuated two-lever operant chambers (Lafayette Instrument, Model #80015 or BRS/LVE Model #020) with food pellet delivery (Noyes Formula P 45 mg pellet, Research Diets, New Brunswick, NJ).

2.3.2. Training procedure

16 LEW and 13 F-344 rats were trained in 15-min sessions to discriminate nicotine from vehicle under a variable interval (VI) 15-s schedule of food reward. Nicotine versus vehicle two-lever drug discrimination procedures have been previously established in this laboratory (Rosecrans et al., 1989; James et al., 1994; Zhang et al., 2000). Initially, rats were trained to lever-press on a fixed ratio (FR)-1 schedule until responding was stable (50–60 total responses), at which time the reinforcement schedule progressed from an FR-1 to a VI-3. As lever-press behavior was being established, the reinforcement schedule was increased until a stable level of performance was reached under the final VI-15 schedule of reinforcement (~40–60 reinforcements per session).

Then, two-lever DD procedures were begun during which daily training sessions were conducted with nicotine or saline. Briefly, rats were trained to respond to one lever after subcutaneous injection of nicotine and on the other lever after injection of vehicle. For half the rats, the right lever was designated as the nicotine appropriate lever, whereas the situation was reversed for the remaining rats. Two different training regimens were used based on unpublished data indicating the F-344 rat was less sensitive to the DS properties of nicotine than the LEW rat. LEW rats began training with a nicotine dose of 0.1 mg/kg. The nicotine dose was increased by 0.1 mg/kg increments for each additional eight double-alternation sessions in the LEW rat until nicotine discrimination was acquired. Dose increments for the F-344 rats were 0.2 mg/kg because of their relative insensitivity to nicotine. Learning was assessed weekly during an initial 2-min nonreinforced session followed by a 15-min training session until criterion levels of performance were established (>80% responding on the nicotine correct lever following nicotine and <20% responding on the nicotine lever following vehicle).

2.3.3. Test sessions

After rats acquired the nicotine DS, 2-min test sessions were conducted biweekly in which lever pressing on neither lever was rewarded, i.e., extinction tests. During test conditions, training sessions did not follow 2-min test sessions. Training sessions resumed on nontest days throughout the remainder of the experiment. During generalization tests, each rat was administered different doses of nicotine on different days and tested for its ability to generalize to the training dose.

2.4. Experiment 2: conditioned place preference (CPP)

2.4.1. Apparatus

Place conditioning and testing were conducted in one of four units comprised of two-compartment (Model # ENV-515 and 517) open field chambers with place preference inserts (MedAssociates, Albans, VT). Tactile (a wire mesh floor or a steel rod floor), olfactory (wood chip bedding or cardboard under the floor), and visual (three vertical or one horizontal strip of black electrical tape) cues were used to differentiate the place preference compartments. A manual guillotine door was inserted to block the arched doorway during conditioning. Activity and location data were collected by infrared beam technology connected to a PC using MedAssociates software.

2.4.2. Preexposure phase

LEW (N=24) and F-344 (N=24) rats underwent habituation/baseline exposure on the day before experimental manipulations. Half of the subjects were placed in the right-hand side of the chamber and the other half in the left-hand side for 15 min each. The side (left vs. right) each rat preferred during this preconditioning phase was recorded and used to counterbalance side preference during the testing phase. Specifically, one side was designated to be paired with drug and the other with saline, then half the rats were conditioned with nicotine in the most preferred compartment and the other half in the least preferred. No significant differences were found between time spent in the drug-paired and the saline-paired side for the preconditioning phase. Thus, this experimental design avoids any preference bias before conditioning.

2.4.3. Place conditioning phase

Unbiased conditioning began the day following the preexposure phase. Eight consecutive alternating conditioning days were used (nic-sal-nic-sal, etc.). On conditioning days, the rats received sc injections of nicotine or saline 5-min presession. Then, the rats were placed and confined via the guillotine door in the appropriate conditioning compartment (nicotine or saline) for a 12-min session.

2.4.4. Place preference tests

Test sessions were 6 min in duration and occurred in the drug-free state (i.e., no injection administered). On the test day following the last conditioning session, the rats were given free access to both compartments (that is, the manual guillotine door was removed). Using the preference data acquired during the habituation/baseline phase, side of placement for each subject was counterbalanced between the two compartments (left or right), therefore eliminating possible side preferences (i.e., biases). Time spent in each compartment was recorded.

2.5. Data analysis

For DD data, the number of responses on each lever was converted into a measure of percentage drug lever responding (%DLR) by dividing the number of responses on the reinforced lever by the total responses and multiplying by 100. The effective dose 50 (ED_{50}) values for nicotine discrimination were calculated by least squares linear regression analysis followed by calculation of confidence limits (Bliss, 1967; Tallarida and Murray, 1986). Repeated-measures one-way analysis of variance (ANOVA) was used to compare response rates (GB-STAT software; Dynamic Microsystems, Silver Spring, MD). Significant ANOVAs were followed by Newman–Keuls post hoc tests. The CPP results are expressed as time (s) spent in the drug-associated compartment compared to time spent in the saline (nondrug) compartment, using a three-way repeated measure ANOVA. Significant ANOVAs were followed by Newman–Keuls post hoc tests. In addition, differences in time spent in the nicotine-paired compartment were analyzed with ANOVAS comparing the percent change from 0.6 to the 0.9 mg/kg between strains. Percent change was calculated by subtracting the time spent in the nicotine compartment during the 0.6-mg/kg nicotine tests from the time spent in the nicotine compartment during the 0.9-mg/kg nicotine tests divided by the time spent in the nicotine compartment during the 0.6-mg/kg nicotine tests. $p<0.05$ was considered to be significantly significant.

3. Results

3.1. Experiment 1: drug discrimination (DD)

The mean %DLR and the mean responses per second for the nicotine generalization curve for the LEW rats are shown in Fig. 1A. Full nicotine generalization was obtained with the training dose (0.4 mg/kg) and the 0.8-mg/kg test dose yielding mean %DLRs of 91.2±2.1 and 100%, respectively. However, severe response rate suppression was observed at the 0.8-mg/kg dose with only 4 out of 16 animals responding. Generalization testing with nicotine yielded an ED_{50} of 0.070 mg/kg (95 % CI=0.060–0.080 mg/kg) in the LEW rats. A repeated-measures ANOVA resulted in significant differences in response rates as a function of dose [$F(15,75)=21.78$, $p<0.0001$]. Newman–Keuls tests revealed that response rates were significantly suppressed

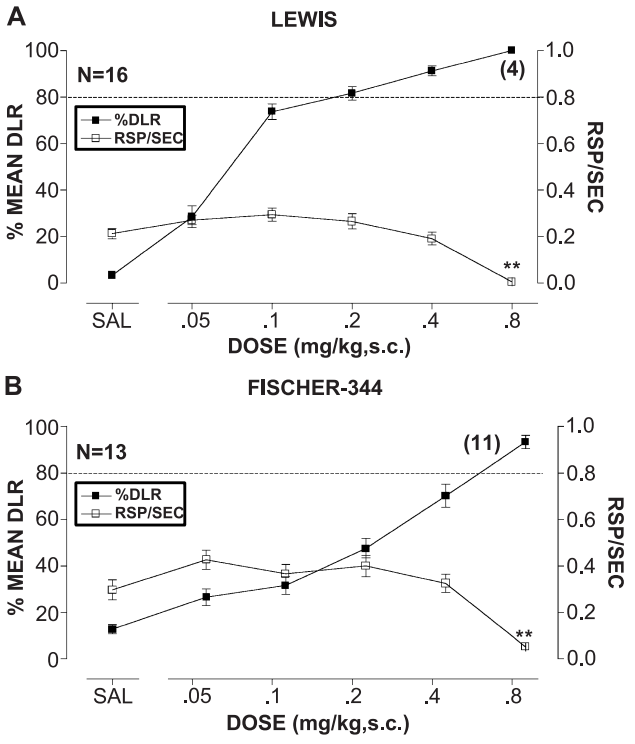

Fig. 1. Percent correct drug lever responding (%DLR,) and response rate (rsp/s, □) in (A) LEW (N=16) and (B) F-344 (N=13) rats after subcutaneous injection of various doses of nicotine. Data are presented as mean±S.E.M. The dashed line at 80% DLR indicates full generalization to the training drug. Numbers in parentheses located by the highest dose indicate the number of subjects responding at that dose. Generalization testing yielded an ED_{50}=0.070 mg/kg (95% CI=0.060–0.080 mg/kg) in the LEW rat and an ED_{50}=0.19 mg/kg (95% CI=0.17–0.23 mg/kg) in the F-344 rat. For the response rate data, significant differences are indicated by an asterisk (*p<0.01).

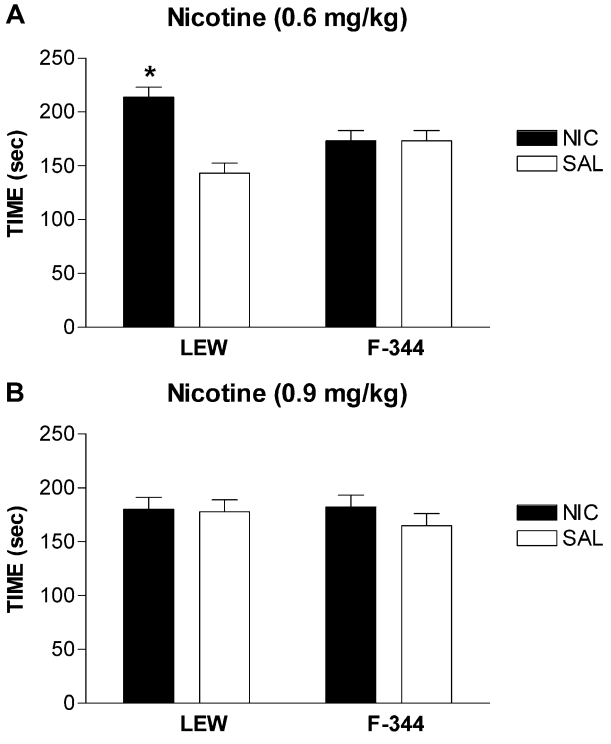

Fig. 2. Conditioned place preference (CPP) in LEW and F-344 rats after subcutaneous injection of 0.9% saline (open bars) or (A) 0.6 mg/kg or (B) 0.9 mg/kg of nicotine (filled bars). An asterisk (*) symbolizes significantly greater time (s) spent in the nicotine-paired side for the LEW compared to the F-344 rats during a 6-min test period.

by the 0.8-mg/kg dose of nicotine compared to rates of responding for all of the other doses (p<0.01).

Results from nicotine generalization testing in the F-344 rats are shown in Fig. 1B. Generalization testing yielded an ED_{50}=0.19 mg/kg (95% CI=0.17–0.23 mg/kg) in the F-344 rat. Full generalization to the nicotine cue was obtained at the 0.9 mg/kg training dose (93.3±2.9 %DLR); however, significant response rate suppression was also observed at this dose [F(12,60)=14.11, p<0.0001; p<0.01 as compared to all other doses by Newman–Keuls test].

3.2. Experiment 2: conditioned place preference (CPP)

As shown in Fig. 2A, LEW rats demonstrated preference for the 0.6-mg/kg nicotine-paired side, whereas the F-344 rats failed to exhibit preference; thus, there was a significant main effect for strain [F(1,23)=91.48, p<0.0001]. The mean time spent in the nicotine-paired compartment for the LEW and F-344 rats was 213.8±9.2 and 173.2±9.6 s, respectively. There was also a significant interaction between dose and drug [F(1,23)=5.98, p<0.05], as well as a significant interaction between strain, dose, and drug [F(1,23)=13.49, p<0.01]. As shown in Fig. 2B, the subsequent CPP test showed that neither the LEW nor the F-344 rats demonstrated preference for the 0.9-mg/kg nicotine-paired compartment. The mean time spent in the nicotine-paired compartment for the LEW and F-344 rats was 180.1±11.13 and 182.1±11.1 s, respectively. Instead of increasing preference for the nicotine-paired compartment, increasing the nicotine dose to 0.9 mg/kg in the LEW rat actually reduced the time spent in the nicotine-paired compartment by 17.6% (S.E.M.±4.9 %). On the other

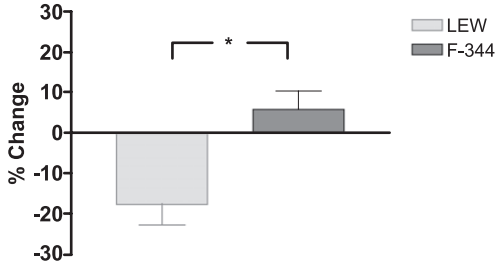

Fig. 3. Conditioned place preference for nicotine presented as a percent change in nicotine preference from 0.6 to 0.9 mg/kg nicotine in LEW and F-344 rats. An asterisk (*) symbolizes a significant difference between LEW and F-344 rats in data converted into mean percent change scores of time (s) spent in the nicotine-specific compartment at the two doses using one-way ANOVA (*p<0.001). Percent change scores are derived from the time spent (s) in the nicotine-paired side at each dose.

hand, increasing the dose of nicotine did not decrease but slightly increased the time spent by F-344 rats in the nicotine-paired compartment (Fig. 3). A one-way ANOVA revealed significant differences in percent change from 0.6 mg to 0.9 mg/kg nicotine tests as a function of strain [$F(1,46)=11.35$, $p=0.001$].

4. Discussion

Variability in the DS effects of nicotine has been observed in selectively bred rodent lines (Overstreet, 1995). In the present study, it has been demonstrated that the LEW and F-344 strains exhibit different levels of sensitivity to the DS effects of nicotine, with the LEW rats having a lower ED_{50} for the drug than the F-344 rats. Furthermore, F-344 rats required a higher training dose than the LEW rats (0.9 vs. 0.4 mg/kg) to acquire the DS.

There has been some controversy regarding the ability of nicotine to produce CPP. An interesting aspect of the studies conducted by Fudula and Iwamoto (1986) that has been overlooked was the observation that different rats exhibited a differential response to nicotine. In that study, some subjects exhibited apparent reward by choosing the nicotine compartment during test sessions, while others appeared to exhibit aversive responses to nicotine by choosing the vehicle compartment on testing. Unfortunately, there is little data on the baseline behaviors of the rats (Sprague–Dawley) used by those researchers that might offer some understanding as to why these animals exhibit a differential response to nicotine. Some of the across-laboratory inconsistencies in nicotine CPP studies may be attributed to differences in methods, i.e., using the initially less-preferred side for nicotine conditioning. This biased method of conditioning may introduce a possible confound since the drug-induced shift of preference may reflect an ability of the drug to suppress neophobia (Clarke and Fibiger, 1987; Calcagnetti and Schechter, 1994). Therefore, we used an unbiased procedure with 12-min conditioning sessions, 6-min test sessions, and a total of 8 conditioning days. These procedures are similar to nicotine CPP studies that have also used a larger number of pairing sessions and longer testing times (Horan et al., 1997; Suzuki et al., 1999). In addition, these shorter session time frames were chosen based on DS properties effects of nicotine that begin to diminish approximately 20 min after injection (unpublished observations).

Based on the DD training doses required to achieve DS control in the LEW and F-344 rat, a 0.6-mg/kg dose was chosen for the CPP procedure as this dose is intermediate between the two training doses. In the present nicotine CPP tests, place preference was induced by nicotine 0.6 mg/kg in the LEW rat but not the F-344 rat. Although there is some debate as to whether dose response curves may be obtained using CPP procedures (see Bardo and Bevins, 2000 for a review), linear correlations with respect to dosage have been obtained (reward increased and aversion decreased) (Fudala et al., 1985). In the present CPP experiments, nicotine 0.9 mg/kg was subsequently tested in an attempt to induce a greater nicotine-conditioned place preference. The LEW rats spent less time in the nicotine-paired side when a higher dose (0.9 mg/kg vs. 0.6 mg/kg) was conditioned; whereas time spent by the F-344 rats in the nicotine-paired side was unchanged compared to time spent in the nicotine-paired side after conditioning with lower dose. This may suggest that higher doses of nicotine are needed to induce nicotine-conditioned preference in the F-344. However, the probability of inducing nicotine-related toxicity did not permit testing higher doses.

Differences in sensitivity between LEW and F-344 to other drugs of abuse have been demonstrated in several studies. For example, LEW rats exhibit an increased propensity to self-administer opiates, cocaine, and ethanol compared to F-344 rats (George and Goldberg, 1988; Suzuki et al., 1992). LEW rats also exhibit greater CPP to cocaine and morphine than do F-344 rats (Kosten et al., 1994). The findings from this study suggest that the LEW rat may also be more sensitive to both the discriminative stimulus (DS) and rewarding effects of nicotine than the F-344 rat.

Different inbred strains of animals, in addition to having distinct behavioral profiles, may also differ in density and up-regulation of central nAChRs. Previous studies have shown that rats that readily desensitize to nicotine display significantly greater up-regulation of alpha-7 nAChRs but not alpha-4beta-2 nAChRs when compared to nondesensitizers, and, in vivo, the desensitizers exhibit greater hind limb rearing during initial exposure to testing chambers (Zhang et al., 2000). James et al. (1994) demonstrated differences in the ability of rats of an outbred strain to express acute tolerance to the DS effects of nicotine. The present study extended these findings to include differences in behavioral responsiveness to nicotine between two inbred strains, the LEW and F-344. Based on their responsiveness to the effects of nicotine, it is possible that the F-344 rats may readily desensitize to nicotine, whereas the LEW rats may be more resistant to nicotine desensitization. However, in vitro evidence is necessary to support the hypothesis of differential sensitivity to desensitization of nAChRs from nicotine exposure in these two rat strains. The characterization of the LEW and F-344 strains in DD and CPP provide important in vivo assays that can be compared with in vitro assays such as $^{86}Rb^{+}$ efflux to investigate strain differences at the cellular level (James et al., 2002; Robinson et al., 2003).

Thus, nicotine appears to be a neuronal modulator affecting behavior contingent on genetic background, and this may influence one's susceptibility for nicotine addiction. Analyses of strain and individual differences in responsiveness to the effects of nicotine may provide insight to the underlying mechanisms that control smoking behavior.

Acknowledgements

Supported in part by the Philip Morris External Research Program.

References

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

Bhat RV, Turner SL, Selvaag SR, Marks MJ, Collins AC. Regulation of brain nicotinic receptors by chronic agonist infusion. J Neurochem 1991;56:1932–9.

Bliss CI. Statistics in biology. New York: McGraw-Hill; 1967.

Brodkin ES, Carlezon Jr WA, Haile CN, Kosten TA, Heninger GR, Nestler EJ. Genetic analysis of behavioral, neuroendocrine, and biochemical parameters in inbred rodents: initial studies in Lewis and Fischer 344 rats and in A/J and C57BL/6J mice. Brain Res 1998;805:55–68.

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

Clarke PB, Fibiger HC. Apparent absence of nicotine-induced conditioned place preference in rats. Psychopharmacology (Berl) 1987;92:84–8.

Collins AC. Genetic influences on tobacco use: a review of human and animal studies. Int J Addict 1990;25:35–55.

Collins AC, Marks MJ. Progress towards the development of animal models of smoking-related behaviors. J Addict Dis 1991;10:109–26.

de Fiebre CM, Romm E, Collins JT, Draski LJ, Deitrich RA, Collins AC. Responses to cholinergic agonists of rats selectively bred for differential sensitivity to ethanol. Alcohol, Clin Exp Res 1991;15:270–6.

Fudala PJ, Iwamoto ET. Further studies on nicotine-induced conditioned place preference in the rat. Pharmacol Biochem Behav 1986;25:1041–9.

Fudala PJ, Teoh KW, Iwamoto ET. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 1985;22(2):237–41.

George FR, Goldberg SR. Genetic differences in responses to cocaine. NIDA Res Monogr 1988;88:239–49.

Goeders NE, Guerin GF. Effects of surgical and pharmacological adrenalectomy on the initiation and maintenance of intravenous cocaine self-administration in rats. Brain Res 1996a;22:145–52.

Goeders NE, Guerin GF. Role of corticosterone in intravenous cocaine self-administration in rats. Neuroendocrinology 1996b;64:337–48.

Hendry JS, Rosecrans JA. Effects of nicotine on conditioned and unconditioned behaviors in experimental animals. Pharmacol Ther 1982;17:431–54.

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

Iwamoto ET. Nicotine conditions place preferences after intracerebral administration in rats. Psychopharmacology (Berl) 1990;100(2):251–7.

James JR, Villanueva HF, Johnson JH, Arezo S, Rosecrans JA. Evidence that nicotine can acutely desensitize central nicotinic acetylcholinergic receptors. Psychopharmacology (Berl) 1994;114:456–62.

James JR, Gross D, Rosecrans JA. Acute tolerance to nicotine: individual differences evaluated using drug discrimination. Program No. 811.11. Abstract. Society for Neuroscience; 2002. Online.

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

Kosten TA, Miserendino MJ, Chi S, Nestler EJ. Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. J Pharmacol Exp Ther 1994;269(1):137–44.

Marks MJ, Campbell SM, Romm E, Collins AC. Genotype influences the development of tolerance to nicotine in the mouse. J Pharmacol Exp Ther 1991;259:392–402.

Overstreet DH. Differential effects of nicotine in inbred and selectively bred rodents. Behav Genet 1995;25:179–85.

Pauly JR, Marks MJ, Gross SD, Collins AC. An autoradiographic analysis of cholinergic receptors in mouse brain after chronic nicotine treatment. J Pharmacol Exp Ther 1991;258:1127–36.

Robinson SA, Lapp LE, Gross D, Philibin SD, Pehrson AL, James JR. JA Nicotine-induced 86RB+ efflux is greater in rats which fail to desensitize to nicotine in a drug discrimination paradigm. Program No. 323.9. Abstract. Society for Neuroscience; 2003. Online.

Rosecrans JA. Effects of nicotine on brain area 5-hydroxytryptamine function in male and female rats separated for differences of activity. Eur J Pharmacol 1971;16:123–7.

Rosecrans JA, Stimler CA, Hendry JS, Meltzer LT. Nicotine-induced tolerance and dependence in rats and mice: studies involving schedule-controlled behavior. Prog Brain Res 1989;79:239–48.

Russell MA. Subjective and behavioural effects of nicotine in humans: some sources of individual variation. Prog Brain Res 1989;79:289–302.

Sangster NC, Davis CW, Collins GH. Effects of cholinergic drugs on longitudinal contraction in levamisole-susceptible and-resistant *Haemonchus contortus*. Int J Parasitol 1991;21:689–95.

Schechter MD, Rosecrans JA. CNS effect of nicotine as the discriminative stimulus for the rat in a T-maze. Life Sci 1971;10:821–32.

Shiffman S. Tobacco "chippers"—individual differences in tobacco dependence. Psychopharmacology (Berl) 1989;97:539–47.

Simar MR, Saphier D, Goeders NE. Differential neuroendocrine and behavioral responses to cocaine in Lewis and Fischer rats. Neuroendocrinology 1996;63:93–100.

Suzuki T, Lu MS, Motegi H, Yoshii T, Misawa M. Genetic differences in the development of physical dependence upon diazepam in Lewis and Fischer 344 inbred rat strains. Pharmacol Biochem Behav 1992;43(2):387–93.

Suzuki T, Ise Y, Maeda J, Misawa M. Mecamylamine-precipitated nicotine-withdrawal aversion in Lewis and Fischer 344 inbred rat strains. Eur J Pharmacol 1999;369:159–62.

Tallarida RJ, Murray RB. Manual of pharmacology calculations with computer programs. New York: Springer; 1986.

Zhang X, Paterson D, James R, Gong ZH, Liu C, Rosecrans J, et al. Rats exhibiting acute behavioural tolerance to nicotine have more [125I]alpha-bungarotoxin binding sites in brain than rats not exhibiting tolerance. Behav Brain Res 2000;113:105–15.