

Nicotine Behavioral Sensitization in Lewis and Fischer Male Rats

Kristen R. Hamilton
Yale University School of Medicine

Amy K. Starosciak
Florida International University

Angela Chwa and Neil E. Grunberg
Uniformed Services University

Individuals with greater nicotine-reactivity may be more likely to initiate and maintain cigarette-smoking behavior than individuals with less nicotine-reactivity. In rats, behavioral sensitization reflects a progressive increase in the psychomotor response to drugs of abuse thought to result from neuroplasticity in brain regions that mediate their motivational effects. Studying nicotine behavioral sensitization in rats with differential nicotine preference and intake, such as Lewis and Fischer rats, may provide clues about the role of nicotine-reactivity in tobacco use. Rat strain differences in nicotine behavioral sensitization may contribute to strain differences in nicotine preference, sensitivity, and intake. In the present research, nicotine behavioral sensitization to multiple doses was examined in Lewis and Fischer rats. Subjects were 96 late adolescent male (48 Fischer, 48 Lewis) rats. Rats received subcutaneous injections of nicotine (0.2, 0.4, 0.7, 1.4, 2.8 mg/kg) or saline daily, and locomotor activity was measured immediately following injections on alternating days to examine sensitization. Behavioral sensitization occurred in both rat strains at the 0.2, 0.4, 0.7, and 1.4 mg/kg nicotine doses, but did not differ between Lewis and Fischer rats. The pattern of horizontal activity that occurred in response to the 2.8 mg/kg nicotine dose did not reflect behavioral sensitization. Results indicate that nicotine behavioral sensitization occurred in Lewis and Fischer rats, and did not differ between the two rat strains. It can be concluded that reported rat strain differences in nicotine intake, sensitivity, and preference do not result from rat strain differences in nicotine behavioral sensitization.

Keywords: nicotine, behavioral sensitization, Lewis rat, Fischer rat, late adolescents

As the leading cause of preventable death in the United States (Centers for Disease Control and Prevention [CDC], 2010), cigarette-smoking is a major public health problem. More than 80% of established adult smokers initiated smoking during ado-

lescence (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008). Individuals with greater reactivity to nicotine may be more likely than less nicotine-reactive individuals to initiate and maintain cigarette-smoking behavior. Comparing behavioral sensitization in rats with different levels of nicotine intake, sensitivity, and preference may provide clues about the role of nicotine reactivity in cigarette-smoking.

Lewis rats and Fischer rats are rodent models of differential nicotine proclivity, with Lewis rats demonstrating greater nicotine intake, preference, and sensitivity than Fischer rats. Lewis rats self-administered more nicotine than Fischer rats (Brower, Fu, Matta, & Sharp, 2002) and demonstrated that they are more sensitive to nicotine by discriminating lower doses of nicotine than Fischer rats (Philibin et al., 2005). Nicotine also was more appetitive and less aversive to Lewis rats than Fischer rats (Horan, Smith, Gardner, Lepore, & Ashby, 1997; Philibin et al., 2005). Specifically, Lewis rats developed conditioned place preference (CPP) to a location in which nicotine was administered previously, while Fischer rats did not (Horan et al., 1997; Philibin et al., 2005). In fact, when Horan et al. (1997) increased the number of nicotine injections in one location from five pairings to 10 pairings, Fischer rats developed conditioned place aversion, whereas Lewis rats did not develop an aversion. In addition, when Lewis and Fischer rats were injected with nicotine during saccharine consumption, Fischer rats acquired taste aversion faster and to a greater degree than did Lewis rats (Pescatore, Glowa, & Riley, 2005), indicating that nicotine is more aversive to Fischer rats than Lewis rats.

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Kristen R. Hamilton, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; Amy K. Starosciak, Department of Biomedical Engineering, Florida International University, Miami, Florida; Angela Chwa, Department of Medical and Clinical Psychology, Uniformed Services University, Bethesda, Maryland; Neil E. Grunberg, Department of Medical and Clinical Psychology, Uniformed Services University and Program in Neuroscience, Uniformed Services University, Bethesda, Maryland.

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Correspondence concerning this article should be addressed to Kristen R. Hamilton, Yale University School of Medicine, Department of Psychiatry, 1 Church Street, New Haven, CT 06510. E-mail: kristen.hamilton@yale.edu

Although differences between Lewis and Fischer rats in nicotine intake, sensitivity, and preference are robust, this is the first experiment to compare nicotine behavioral sensitization in the two rat strains.

Nicotine behavioral sensitization indexes nicotine reactivity in rats. In nicotine behavioral sensitization, a progressive and incremental increase in nicotine's effects, including locomotion, occur in response to repeated administration of nicotine (DiFranza & Wellman, 2007). Nicotine acts on the central nervous system in a neuroregulatory manner to increase the release of the catecholamines norepinephrine and epinephrine and alter the bioavailability of the catecholamine dopamine, to cause the central release of endogenous opioids, and to increase the release of adrenocorticotropin hormone, cortisol, and central acetylcholine (Pomerleau, 1992). These central effects are manifested in increased pleasure, decreased pain and anxiety, and enhanced cognition, including concentration, memory, and attention (Pomerleau, 1992).

Although to our knowledge, rat strain differences in nicotine behavioral sensitization have not previously been examined, greater nicotine behavioral sensitization in Lewis rats than Fischer rats may be related to Lewis rats' greater nicotine proclivity and sensitivity. In addition to differences in nicotine-related behaviors, Lewis and Fischer rats have differences in their nucleus accumbens-related reward circuitry, a system that is altered during the induction and expression of behavioral sensitization. Among these differences, Lewis rats have lower nucleus accumbens dopamine (DA) D2 and D3 receptor densities and levels of DA transporters (DATs) than Fischer rats (Flores, Wood, Barbeau, Quirion, & Srivastava, 1998). DA transporters are responsible for clearing DA from the synapse and terminating the DA signal, so lower levels of DAT lead to prolonged elevation of DA levels. Each of the described differences in DA neurotransmission could predispose Lewis rats to increased induction and expression of nicotine behavioral sensitization as compared with Fischer rats.

Because most adults smokers initiated smoking during adolescence (SAMHSA, 2008), nicotine behavioral sensitization to five doses of nicotine was compared in Lewis and Fischer adolescent rats. The selection of nicotine doses was based on previous research in which it was determined that 0.4–0.6 mg/kg nicotine was the optimal dose to examine nicotine behavioral sensitization (DiFranza & Wellman, 2007). A dose within this range, 0.4 mg/kg nicotine, was selected to examine nicotine behavioral sensitization in the present research. This dose was decreased by a factor of approximately 2 (0.2 mg/kg nicotine) to allow for the characterization of the ascending limb of nicotine behavioral sensitization. The 0.7 mg/kg nicotine dose was chosen because it was slightly above the optimal dose range described by DiFranza and Wellman (2007). To characterize the descending limb of nicotine behavioral sensitization, the 0.7 mg/kg nicotine dose was increased two times by a factor of 2 (1.4 and 2.8 mg/kg nicotine). Therefore, of the five doses of nicotine selected, one was in the optimal dose range previously reported to elicit nicotine behavioral sensitization, and the others were below and above the optimal dose so that a full dose-response curve of nicotine behavioral sensitization could be examined. Because greater nicotine reactivity in Lewis rats than in Fischer rats may contribute to differences in nicotine intake, preference, and sensitivity between the two rat strains, it was hypoth-

esized that nicotine behavioral sensitization would occur in both rat strains, but would be greater in Lewis rats than in Fischer rats.

Methods

Experiment Overview

The experimental design was a 2 (Lewis, Fischer) \times 6 (saline, 0.2, 0.4, 0.7, 1.4, 2.8 mg/kg nicotine) full factorial design with repeated measures, with rat strain and drug condition as between-subjects independent variables and time as a within-subject independent variable. The main dependent variable was locomotor activity, with increases in nicotine-induced locomotor activity over time revealing nicotine behavioral sensitization in Lewis and Fischer rats. The experiment was divided into two phases: saline administration, and nicotine or saline administration.

Drug or physiological saline (0.9% NaCl) was administered via 1 mL subcutaneous injections. Nicotine bitartrate was dissolved in physiological saline and nicotine dose was computed to deliver 0.2, 0.4, 0.7, 1.4, or 2.8 mg nicotine base/kg body weight to each subject. A buffer of 1.0 M Na_2HPO_4 was used to neutralize the nicotine solution, making its pH comparable to that of physiological saline. Rats were weighed daily and the nicotine doses were adjusted each day for body weight.

Drug administration occurred immediately before rats were placed into individual electronic physical activity monitoring chambers of the Accuscan/Omnitech Electronics Digiscan infrared photocell system (Test box model RXYZCM [16 TAO]) for 1 hr to measure open field locomotor activity. The 16 activity chambers were located in a designated testing room separate from the housing room; lights were turned off during data collection. In the photocell system, a grid of equally spaced infrared light beams traverse the plastic arenas (40 \times 40 \times 30 cm) from front to back and left to right. When the infrared beams were broken, movement was recorded. Horizontal activity was the parameter that was analyzed in the present experiment. In this system, horizontal activity was quantified as the number of infrared beam interruptions or beam "breaks" in the horizontal sensors during the given sample period.

Subjects and Housing

Subjects were 48 male Lewis and 48 male Fischer rats obtained from Charles River Laboratories (Wilmington, MA). Animals were pair-housed within strain and drug condition in standard polycarbonate shoebox cages (42 \times 20.5 \times 20 cm) on hardwood chip bedding (Pine-Dri) with wire mesh lids. Animals had continuous access in home cages to rodent chow (Harlan Teklad 4% Mouse/Rat Diet 7001) and water during all phases of the study. Rats' housing room was maintained at 23 °C and 50% humidity on a 12-hr reverse light/dark cycle (lights on at 2000 hours). Activity was assessed during the rats' active phase. At the beginning of the experiment (first baseline day), rats were approximately 37 days old. Nicotine or saline was administered daily from 7–9 weeks old, an age range that is analogous to late adolescence and early adulthood in humans (Spear, 2000). This experimental protocol was approved by the Uniformed Services University of the Health Sciences (USUHS) Institutional Animal Care and Use Committee

and was conducted in full compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Locomotor Acclimation Day

Prior to the beginning of the experiment, rats were acclimated to the locomotor equipment by being placed inside a locomotor activity chamber for 1 hr each. Locomotor activity data was collected during the locomotor acclimation exposure.

Baseline Day

All rats' activity was measured on Baseline Day, which occurred on the day before the beginning of the saline administration phase. All rats' activity was measured inside the locomotor activity chambers for 1 hr each.

Saline Administration Phase

For 3 days prior to the beginning of nicotine injections, all rats received daily subcutaneous 1-mL injections of physiological saline (0.9% NaCl) to acclimate them to the injection procedure and to minimize any stress that may be caused by the injection procedure. All rats were placed into locomotor activity chambers and measured immediately following injections, which were given in the locomotor activity testing room. Locomotor activity was recorded daily during the saline administration phase to provide a measure of locomotor activity after a non-nicotine injection for all rats.

Nicotine or Saline Administration Phase

The nicotine or saline administration phase lasted for 14 days. During each day of this phase, all rats received daily nicotine injections (except for the saline group, which received daily saline injections). All rats were placed immediately into locomotor activity chambers after injections on alternating days during this phase to measure activity. On the days in which locomotor activity was not measured, all rats still received injections of their respective drug dose (e.g., the 0.2 mg/kg nicotine group received an injection of 0.2 mg/kg nicotine, and the saline group received an injection of saline). Rats always were injected in the room in which locomotor activity was measured, but were returned to the home cages after injections on days when locomotor activity was not measured. On days when locomotor activity was not measured, rats remained in the locomotor activity room for 30 min after injections.

Data Analytic Strategy

Analyses of variance (ANOVAs) were used to determine whether there were strain differences on the locomotor acclimation and baseline days. The saline and drug administration phases were analyzed separately. Each phase was analyzed using repeated-measures ANOVA. The purpose of the saline administration phase was to acclimate rats to the injection procedure. Activity during the saline phase was not used as a covariate in the drug phase analyses because: (1) strain differences in activity were minimal during the saline administration phase, and (2) there was no significant strain difference on the last day of saline administration. When the

assumption of sphericity was violated, a Greenhouse–Geisser correction was used. Bonferroni's post hoc tests were used to assess nicotine-dose differences in locomotor activity. Independent samples *t* tests were used to assess strain differences in locomotor activity on individual days of nicotine administration. All statistical analyses were two-tailed, with an α level of $p < .05$. A significant drug by day interaction, or a significant effect of day within a drug dose, coupled with a pattern of locomotor activity that reflected an increase over time, indicated that nicotine behavioral sensitization had occurred.

Results

Locomotor Acclimation Day: ANOVA Results

On the locomotor acclimation day, there were no differences in activity between Lewis and Fischer rats.

Baseline Day: ANOVA Results

At the Baseline Day measurement, there were no differences in activity between Lewis and Fischer rats.

Saline Administration: Repeated-Measures ANOVA Results

During the predrug phase, there were no significant effects of strain on activity over time, although there was a between-subjects effect of strain [$F(1, 94) = 16.44, p < .001$], with Fischer rats having more activity than Lewis rats. Activity was greater in Fischer rats than Lewis rats on Saline Day 1 [$t(94) = -1.64, p < .001$] and Saline Day 2 [$t(73.15) = -2.09, p < .05$], but the activity of Fischer and Lewis rats did not differ on Saline Day 3.

Drug Administration: Repeated-Measures Analyses of Covariance Results

A significant day \times drug interaction [$F(17.49, 293.88) = 8.16, p < .001$], in combination with a pattern of activity that increased over time in the 0.2, 0.4, 0.7, and 1.4 mg/kg nicotine groups, indicated that nicotine behavioral sensitization had occurred in rats that were administered these doses of nicotine (See Figures 2b, 2c, 2d, and 2e). Significant differences in activity on the first and last days of drug administration occurred for rats that received 0.2 mg/kg nicotine (mean difference = 8510.1 total beam breaks, $p < .001$), 0.4 mg/kg nicotine (mean difference = 13,128.8 total beam breaks, $p < .001$), 0.7 mg/kg nicotine (mean difference = 17,381.8 total beam breaks, $p < .001$), and 1.4 mg/kg nicotine (mean difference = 15,410.5 total beam breaks, $p < .05$), which provides further support that nicotine behavioral sensitization occurred. By contrast, activity on the first and last days of drug administration did not differ significantly for rats that received 2.8 mg/kg nicotine or saline, indicating that nicotine behavioral sensitization did not occur in response to those doses (See Figures 2a and 2f). In addition, post hoc tests revealed that the activity of rats that were administered saline differed significantly from the drug-induced activity of rats that were administered 0.2 mg/kg nicotine (mean difference = 15,018.4 total beam breaks, $p < .001$), 0.4 mg/kg nicotine (mean difference = 20,935.7 total beam breaks, $p < .001$), 0.7 mg/kg nicotine (mean difference = 17,381.8 total beam breaks, $p < .001$), and 1.4 mg/kg nicotine (mean difference = 15,410.5 total beam breaks, $p < .05$).

.001), 0.7 mg/kg nicotine (mean difference = 21,674.9 total beam breaks, $p < .001$) and 1.4 mg/kg nicotine (mean difference = 12,591.0 total beam breaks, $p < .001$), further suggesting that nicotine behavioral sensitization occurred in those groups.

There were effects of rat strain on individual days of drug administration in rats administered 0.2, 1.4, and 2.8 mg/kg nicotine. In response to the 0.2 mg/kg nicotine dose, Fischer rats had more activity than Lewis rats on drug Day 3 [$t(14) = -2.23$, $p < .05$]. In response to the 1.4 mg/kg nicotine dose, Lewis rats had more activity than Fischer rats on drug Day 3 [$t(14) = 4.70$, $p < .001$], drug Day 5 [$t(14) = 3.05$, $p < .01$], and drug Day 7 [$t(14) = 2.11$, $p = .05$]. In response to the 2.8 mg/kg nicotine dose, Fischer rats had more activity than Lewis rats on drug Day 1 [$t(14) = -2.79$, $p < .05$].

When Lewis and Fischer rats were considered together, all rats that were administered 0.4 and 0.7 mg/kg nicotine had similar levels of activity, which was reflected by the fact that there were no significant differences in activity between the two groups. Rats administered 0.2 and 1.4 mg/kg nicotine also had similar levels of activity. The activity levels of rats that received 2.8 mg/kg nicotine and rats that received saline also did not differ. Rats administered 0.4 and 0.7 mg/kg nicotine had higher levels of activity than rats administered 0.2 (mean difference = 5,917.3 total beam breaks, $p < .001$; mean difference = 6,656.5 total beam breaks, $p < .001$) and 1.4 mg/kg nicotine (mean difference = 8,344.7 total beam breaks, $p < .001$; mean difference = 9,083.9 total beam breaks, $p < .001$). Rats administered 0.2 and 1.4 mg/kg nicotine had higher levels of activity than rats that received 2.8 mg/kg nicotine (mean difference = 14,878.9 total beam breaks, $p < .001$; mean difference 12,451.5 total beam breaks, $p < .001$) or saline (mean difference = 15,018.4 total beam breaks, $p < .001$; mean difference = 12,591.0 total beam breaks, $p < .001$). In addition, a main effect of drug on locomotor activity occurred [$F(5, 84) = 143.87$, $p < .001$], which reflects differential reactivity to different doses of nicotine.

Although there was a significant day \times drug \times strain interaction [$F(12.160, 141.872) = 2.646$, $p < .01$], there was no significant interaction of day \times strain and no main effect of strain on locomotor activity, suggesting that although some strain differences in reactivity to nicotine occurred on individual days of drug administration, nicotine behavioral sensitization did not differ between the Lewis and Fischer rat strains.

Discussion

In the present experiment, nicotine behavioral sensitization in Lewis and Fischer rats was compared. It was hypothesized that nicotine behavioral sensitization would occur in both rat strains, but would be greater in Lewis rats than in Fischer rats. There were four main findings. First, nicotine behavioral sensitization occurred in Lewis and Fischer rats in response to the 0.2, 0.4, 0.7, and 1.4 mg/kg nicotine doses, but did not occur in response to the 2.8 mg/kg nicotine dose. Second, patterns of nicotine behavioral sensitization were similar between rats that received 0.4 and 0.7 mg/kg nicotine, and between rats that received 0.2 and 1.4 mg/kg nicotine. Third, consistent with previous reports (DiFranza & Wellman, 2007), the 0.4 and 0.7 mg/kg nicotine doses were optimal for observing nicotine behavioral sensitization in Lewis and Fischer rats, as the 0.4 and 0.7 mg/kg nicotine doses produced

greater nicotine behavioral sensitization than other doses. Fourth, nicotine behavioral sensitization did not differ between Lewis and Fischer rats. Each of the main findings and its implications are discussed below.

The finding that nicotine behavioral sensitization occurred in Lewis and Fischer rats supports the first hypothesis and is consistent with previous research in which nicotine behavioral sensitization was examined in several studies using Sprague–Dawley or Lister hooded rats. The present research was the first study in which nicotine behavioral sensitization in Lewis and Fischer rats (two strains that differ in nicotine sensitivity, preference, and intake) was compared. In addition, the present research extends previous reports by comparing responses to five doses of nicotine (0.2, 0.4, 0.7, 1.4, and 2.8 mg/kg nicotine) in Lewis rats as well as Fischer rats.

Nicotine behavioral sensitization was similar in rats that received the 0.4 and 0.7 mg/kg nicotine doses and in rats that received the 0.2 and 1.4 mg/kg nicotine doses, suggesting that the range of doses used in the present research captured both the ascending and descending limbs of nicotine behavioral sensitization. When the mean activity for all rats that received each nicotine dose was depicted in a graph, an inverted-U shape function emerged, with saline and 0.2 mg/kg nicotine on the ascending limb of nicotine-induced activity, 0.4 and 0.7 mg/kg nicotine producing the highest levels of nicotine-induced activity, and 1.4 mg/kg and 2.8 mg/kg on the descending limb of nicotine-induced activity (See Figure 1). The relative levels of activity for each dose remained the same across days, and the patterns of activity reflected nicotine behavioral sensitization for the 0.2, 0.4, 0.7, and 1.4 mg/kg nicotine doses (See Figure 2).

The finding that nicotine behavioral sensitization was greater at the 0.4 and 0.7 mg/kg nicotine doses than the 0.2 and 1.4 mg/kg nicotine doses in Lewis and Fischer rats is consistent with the previously reported optimal nicotine dose for observing nicotine

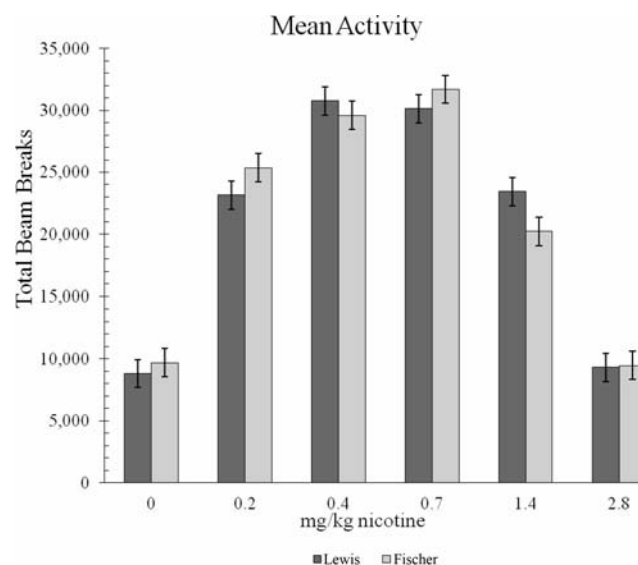


Figure 1. Mean locomotor activity [mean \pm standard error of the mean (SEM)] of Lewis and Fischer rats' mean activity averaged across all days of the drug administration phase.

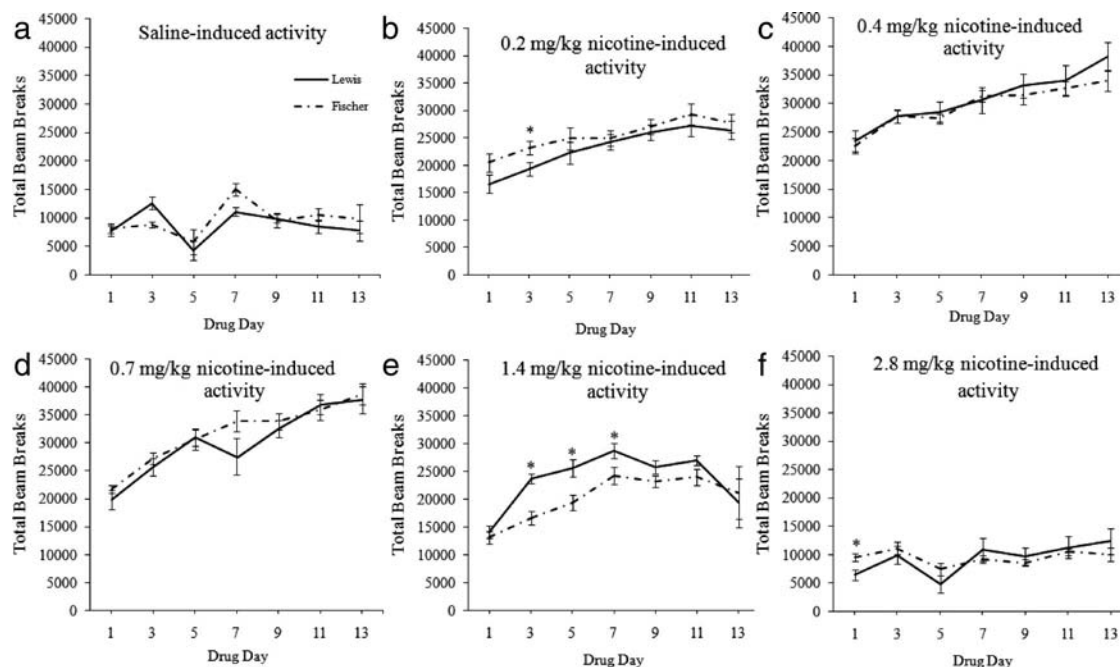


Figure 2. Mean locomotor activity (mean \pm SEM) of Lewis and Fischer rats in the saline group (2a) and each of the nicotine dose-groups (2b-2f) across all days of the drug administration phase. * Indicates a significant rat strain difference ($p < .05$).

behavioral sensitization (DiFranza & Wellman, 2007). A review of several nicotine behavioral sensitization studies concluded that 0.4 – 0.6 mg/kg nicotine is the optimal dose range for observing nicotine behavioral sensitization in rodents (DiFranza & Wellman, 2007). The optimal dose range suggested was based on nicotine behavioral sensitization studies that used Sprague–Dawley or Lister hooded rats, but no studies using Lewis and Fischer rats. These results extend previous research by suggesting that the dose range that was optimal for observing nicotine behavioral sensitization in Sprague–Dawley or Lister hooded rats also is optimal for observing nicotine behavioral sensitization in Lewis and Fischer rats.

Consistent with previous research (Collins & Izenwasser, 2004), the 2.8 mg/kg nicotine dose was too high to produce increases in horizontal activity in Lewis and Fischer rats. However, while there was no increase in horizontal activity at this high dose, it is possible that sensitization was manifested behaviorally as stereotypy, or repeated movements. Stereotypy reflects behavioral sensitization at higher doses of nicotine (DiFranza & Wellman, 2007), and increased stereotypy would have resulted in decreased horizontal locomotor activity. In addition, in previous research, high doses of nicotine (such as 1.0 mg/kg) produced anxiogenic-like effects (Ouagazzal, Kenny, & File, 1999). It is possible that the 1.0 mg/kg nicotine dose produced anxiety in the present research, which also could have resulted in decreased activity. However, neither stereotypy, nor anxiety, was assessed in this experiment, which would have allowed for the examination of these possibilities.

Overall, there were no rat strain differences in nicotine behavioral sensitization in Lewis and Fischer rats. Although nicotine sensitization did not differ between Lewis and Fischer rats, previ-

ous reports indicate that Lewis rats have greater nicotine intake, nicotine preference and sensitivity to nicotine than Fischer rats. The lack of a rat strain difference in nicotine behavioral sensitization is surprising, and raises two important issues. First, because differences in rat strain sensitivity to nicotine are not reflected in differences in behavioral sensitization, it is possible that nicotine behavioral sensitization is not involved in nicotine addiction. Second, it is possible that nicotine detection threshold and intake, for which there were strain differences in previous research, are poor indicators of vulnerability to nicotine addiction. Future research is needed that examines relationships of indicators of addiction, such as nicotine withdrawal (Hamilton et al., 2009; 2010), with nicotine behavioral sensitization, detection threshold, and intake. Furthermore, the lack of a rat strain difference in nicotine behavioral sensitization may suggest that other factors contribute to Lewis rats' greater proclivity for nicotine.

It is possible that rat strain differences in impulsivity contribute to reported differences in nicotine intake, preference, and sensitivity. Impulsivity, a tendency toward immediate action without consideration of future consequences (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), is associated with drug use (Perry & Carroll, 2008) and predicts progression through the addiction cycle in rat models. The positive association between impulsivity and nicotine self-administration has been established in clinical research, with human smokers having more impulsivity than never-smokers, and preclinical research, with impulsivity predicting rats' initiation and maintenance of nicotine self-administration, nicotine-seeking during abstinence, and relapse to nicotine self-administration upon exposure to nicotine cues (Diergaarde et al., 2008). Lewis rats are more impulsive than Fischer rats on a delay discounting task measuring impulsive choice (Anderson & Wool-

verton, 2005) and on a response inhibition task, the Five-Choice Serial Reaction Time task, which measures impulsive action (Hamilton & Grunberg, unpublished data). Future experiments should measure impulsivity and determine its relationship to nicotine intake, nicotine preference, and sensitivity to nicotine in Lewis and Fischer rats to examine whether impulsivity is related to rat strain differences in those variables.

Although there were no rat strain differences in nicotine behavioral sensitization, it is noteworthy that Lewis rats had greater nicotine-induced locomotor activity than Fischer rats on drug Days 3, 5, and 7 in response to 1.4 mg/kg nicotine, a dose on the descending limb of the nicotine behavioral sensitization curve. Because 1.4 mg/kg nicotine is on the descending limb of nicotine behavioral sensitization, it also is possible that Lewis rats have decreased sensitivity to the aversive or activity-inhibiting effects of higher doses than Fischer rats. Furthermore, effects of greater nicotine-induced activity in Lewis rats in response to the 1.4 mg/kg nicotine dose were significant on the third, fifth, and seventh days of drug administration. In the present research, the 0.4 and 0.7 mg/kg nicotine doses were optimal for observing nicotine behavioral sensitization, consistent with previous research (DiFranza & Wellman, 2007). However, the present results may suggest that a higher nicotine dose, such as 1.4 mg/kg nicotine, may be optimal for observing rat strain differences in nicotine behavioral sensitization.

In addition to rat strain, age may have contributed to levels of nicotine behavioral sensitization observed in the present experiment. The present research is limited by the use of only rats that were in late adolescence. In previous research, late adolescent Sprague–Dawley male rats had greater nicotine-induced locomotor activity than adult Sprague–Dawley male rats in response to 0.25 and 0.5 mg/kg nicotine (Belluzzi, Lee, Oliff, & Leslie, 2004). The greatest amount of nicotine-induced locomotor activity occurred in response to the 0.5 mg/kg nicotine dose (Belluzzi et al., 2004), consistent with previous research with adult rats (DiFranza & Wellman, 2007). While adult and adolescent rats were not compared in the present research, the results suggest that the optimal nicotine dose range for observing behavioral sensitization in adult Sprague–Dawley rats also is optimal for observing behavioral sensitization in Lewis and Fischer late adolescent male rats. Future research comparing nicotine behavioral sensitization in response to multiple nicotine doses in adult Lewis and Fischer rats is needed.

The present research also is limited by the examination of nicotine behavioral sensitization in male rats only, rather than a comparison of sensitization in males and females. The results of previous research investigating sex differences in nicotine behavioral sensitization are diverse, and may have been influenced by rat strain and method of nicotine administration. Greater nicotine behavioral sensitization in female than male rats has been reported in studies in which nicotine was administered intravenously in Sprague–Dawley rats (Booze et al., 1999; Harrod et al., 2004). However, in a study in which nicotine was administered through subcutaneous injections (the method used in the present study), there were no sex differences in nicotine behavioral sensitization in Wistar rats (Ericson, Norrjö, & Svensson, 2010) or in Lewis adult rats (Prus et al., 2008). The inclusion of female rats in the present study would have allowed for the determination of whether there are sex differences in nicotine behavioral sensitization in late adolescent Lewis and Fischer rats. Future research of nicotine

behavioral sensitization in adolescent Lewis and Fischer rats should include females so that sex differences can be examined.

In summary, behavioral sensitization to nicotine was compared in late adolescent Lewis and Fischer male rats in the present experiment. Nicotine behavioral sensitization occurred in both Lewis and Fischer rats in response to repeated administration of several nicotine doses. However, nicotine behavioral sensitization did not differ between the two rat strains.

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