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Strain differences in the acquisition of nicotine-induced conditioned taste aversion

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Abstract

Lewis (LEW) and Fischer (F344) rat strains differ on a variety of physiological and behavioral endpoints, including reactivity to drugs of abuse. Although they differ in drug reactivity, such assessments are generally limited to morphine and cocaine. To determine if these differences generalize to other drugs, the present study examined these strains for their reactivity to the affective properties of nicotine, specifically their sensitivity to nicotine in the conditioned taste aversion preparation. For four or five conditioning cycles given every other day, rats from both strains were allowed access to saccharin and injected with nicotine (0.1, 0.4, 0.8 mg/kg) or vehicle. On intervening days, all rats were given access to water and injected with vehicle. Under this one-bottle training and testing procedure, neither strain displayed aversions at the lowest dose of nicotine (0.1 mg/kg). Aversions were evident for both strains at 0.4 and 0.8 mg/kg, although the F344 rats acquired the aversions at 0.4 mg/kg faster and displayed a significantly greater aversion at 0.8 mg/kg than subjects from the LEW strain. For both strains, aversions were evident at all doses (and in a dose-dependent manner) when subjects were given access to saccharin and water in a two-bottle test. There were, however, no strain differences on this test. Differences between the two strains in their acquisition of nicotine-induced taste aversions were discussed in the context of aversion assessments with other compounds as well as in relation to differences in the self-administration of nicotine in the two strains.

Keywords: Nicotine; Lewis; Fischer; Conditioned taste aversion

1. Introduction

Recently, the examination of differences between the inbred LEW and F344 strains (see Brodkin et al., 1998; Karalis et al., 1995; Kosten et al., 1994; Sternberg et al., 1992) has been extended to the affective properties of drugs. For example, the LEW strain shows a greater preference for morphine than does the F344 strain in a drug-admixed food procedure (Suzuki et al., 1988a). Also, conditioned place preferences are significantly greater in LEW rats following morphine and cocaine injections (Guitart et al., 1992; Kosten et al., 1994). Additionally, LEW rats acquire cocaine self-administration significantly faster than F344 rats (Kosten et al., 1997), although F344 rats have been reported to respond significantly greater for cocaine once responding has stabilized (see Haile et al., 2005; Kosten et al., 1997). More recently, LEW rats have also been found to more readily self-administer nicotine than do F344 rats (Brower et al., 2002; Shoaib et al., 1997). Nicotine-induced conditioned place preferences have also been found in LEW (but not F344) rats (Horan et al., 1997; Philibin et al., 2005).

Although the rewarding effects of nicotine have been examined in the LEW and F344 strains, no studies have focused on the aversive properties of nicotine in these strains. Strain differences in the aversive effects of a variety of other compounds, e.g., morphine (Lancellotti et al., 2001), cocaine (Glowa et al., 1994; Grigson and Freet, 2000) and LiCl (Foynes and Riley, 2004), have been reported, suggesting that the two strains may differ with nicotine as well. Given that overall drug acceptability may be a function of the balance between these two affective properties (Cunningham et al., 2003; Gaiardi et al., 1998; Riley and Simpson, 2000; Stolerman and D'Mello, 1981; for a review see Stolerman, 1985), understanding nicotine's aversive effects in these strains may

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give insight into the basis of the differential pattern of nicotine self-administration. Accordingly, the present experiment examined nicotine-induced conditioned taste aversions in the LEW and F344 rat strains. Specifically, subjects from each strain were given access to a novel solution (saccharin) for 20 min followed by a subcutaneous (SC) injection of varying doses of nicotine (0.1, 0.4, 0.8 mg/kg) or equivolume vehicle (saline).

2. Methods

2.1. Subjects

Subjects were 66 Lewis (LEW/SsNHsd) and 66 Fischer (F344/NHsd) experimentally naïve male rats (purchased from Harlan Sprague Dawley, Indianapolis, IN). At the start of the experiment, the LEW rats weighed between 285 and 381 g and the F344 rats weighed between 230 and 304 g. All animals were approximately 90 days of age at the start of the experiment. The animals were maintained on a 12L : 12D cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Prior to habituation (see below), each animal was given food and water ad libitum. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Each animal's body weight was monitored daily. Any animals incurring weight losses greater than 10% were removed from the study and given food and water ad libitum until the 10% weight criterion was reached.

2.2. Apparatus

Subjects were individually housed in stainless-steel, wire-mesh cages. Graduated 50 ml Nalgene centrifuge tubes were attached to the front of these cages to provide 20-min access to water and/or saccharin.

2.3. Drugs and solutions

(−)-Nicotine hydrogen tartrate salt (Sigma Aldrich Co., St. Louis, Mo.) was dissolved in 0.9% saline. All doses (0.1, 0.4 and 0.8 mg/kg) are expressed as the salt and were injected SC in a volume of 1 ml/kg. Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

2.4.1. Phase I: Habituation

Following 24 h water deprivation, all subjects were given 20-min access to water in their individual home cages. This procedure was repeated daily until consumption stabilized, i.e., water consumption was no longer increasing and was within 2 ml over three consecutive days.

2.4.2. Phase II: Conditioning

On the first conditioning day, all subjects were given 20-min access to a novel saccharin solution in their home cages during their normal fluid-access period. Immediately following fluid access, subjects within each strain were ranked according to saccharin consumption, assigned to one of four groups ($n=16$–17 subjects per group) such that saccharin consumption was comparable among groups and given a SC injection of 0 (vehicle), 0.1, 0.4 or 0.8 mg/kg (−)-nicotine. This resulted in the following eight groups: L0, L.1, L.4, L.8, F0, F.1, F.4 and F.8. The letter in each group designation denotes the strain of the rat, i.e., LEW (L) and F344 (F), and the number refers to the dose of nicotine, i.e., 0, 0.1, 0.4 and 0.8 mg/kg. On the following day, the same experimental procedure was used as described above, except subjects were given 20-min access to water following which they were given a SC injection of saline. These two days constituted one conditioning cycle which was repeated for a total of four conditioning cycles.

2.4.3. Phase III: Testing

Following the final water-recovery session of the fourth conditioning cycle, all subjects were given 20-min access to saccharin in a final one-bottle test of the aversion to saccharin (Final Aversion Test). No injections were given following saccharin access on this exposure for 64 of the subjects. The remaining subjects ($n=68$) were injected with nicotine (or saline) on this exposure (Final Aversion Test) for an additional conditioning trial. A single water-recovery session followed this trial. On the following day, these subjects were given 20-min access to both saccharin and water in a two-bottle test of the aversion to saccharin. This test was run because aversions induced by nicotine are relatively weak. The two-bottle testing procedure is generally seen as a more sensitive assay and thus provides a procedure more likely to detect the aversive effects of nicotine in these two strains (Dragoin et al., 1971; Grote and Brown, 1971; Pilcher and Stolerman, 1976; Riley and Mastropaolo, 1989; van Haaren and Hughes, 1990).

3. Statistical analysis

Saccharin consumption across trials was analyzed using a $2\times4\times5$ repeated-measures analysis of variance (ANOVA) with the between-group factors of Strain (LEW and F344) and Dose (0, 0.1, 0.4 and 0.8) and the within-group factor of Trial (Trials 1–4 and Final Aversion Test). Further analyses were conducted using one-way ANOVAs with Tukey's contrasts at each trial to determine differences between groups. For the two-bottle Aversion Test, the percent of saccharin consumed was analyzed using a 2×4 ANOVA with the between-group factors of Strain (LEW and F344) and Dose (0, 0.1, 0.4 and 0.8). For all subjects, water consumption on the day prior to the initiation of conditioning as well as on the water-recovery session following each conditioning trial (Trials 1–4) was analyzed using a $2\times4\times5$ repeated-measures analysis of variance (ANOVA) with the between-group factors of Strain (LEW and F344) and Dose (0, 0.1, 0.4 and 0.8) and the within-group factor of Water Exposure (Water Baseline and Water-

Recovery Sessions 1–4). All analyses set the alpha level at 0.05. All statistical analyses were conducted using StatView Version 5.0.1 (SAS Institute Inc., 1992–1998).

4. Results

Fig. 1 presents the mean (+/− SEM) absolute saccharin consumption on Trials 1–4 and on the Final Aversion Test for LEW and F344 subjects at each dose of nicotine. Repeated-measures analysis of variance (ANOVA) revealed a significant effect of Strain ($F(1,124)=16.708$, $p<0.0001$), Dose ($F(3,124)=28.878$, $p<0.0001$) and Trial ($F(4,496)=22.701$, $p<0.0001$) as well as significant Strain × Dose ($F(3,124)=3.780$, $p=0.0123$), Trial × Strain ($F(4,496)=24.153$, $p<0.0001$), Trial × Dose ($F(12,496)=15.713$, $p<0.0001$) and Trial × Strain × Dose ($F(12,496)=3.028$, $p=0.0004$) interactions. Given the significant Trial × Strain × Dose interaction, individual factorial ANOVAs with Tukey contrasts were conducted to determine which groups differed and on what trial(s).

On Trial 1, rats from the F344 strain drank significantly less than those from the LEW strain ($F(1,124)=86.597$, $p<0.0001$); however, by Trial 2, there were no significant differences between the strains. On Trial 3, there was a significant effect of Dose ($F(3,124)=21.588$, $p<0.0001$), but no significant effect of Strain (or significant Strain × Dose interaction). Specifically, subjects injected with 0.4 and 0.8 mg/kg nicotine drank significantly less than subjects injected with saline ($p<0.05$). On Trials 4 and 5, there was a significant Strain × Dose interaction [($F(3,124)=5.215$, $p=0.0020$) and ($F(3,124)=8.037$, $p<0.0001$), respectively]. On these trials, subjects in Groups F.4 and F.8 drank significantly less than those in Groups F.1 and F0. Also, subjects in Group F.8 drank significantly less than subjects in Group F.4. On Trials 4 and 5,

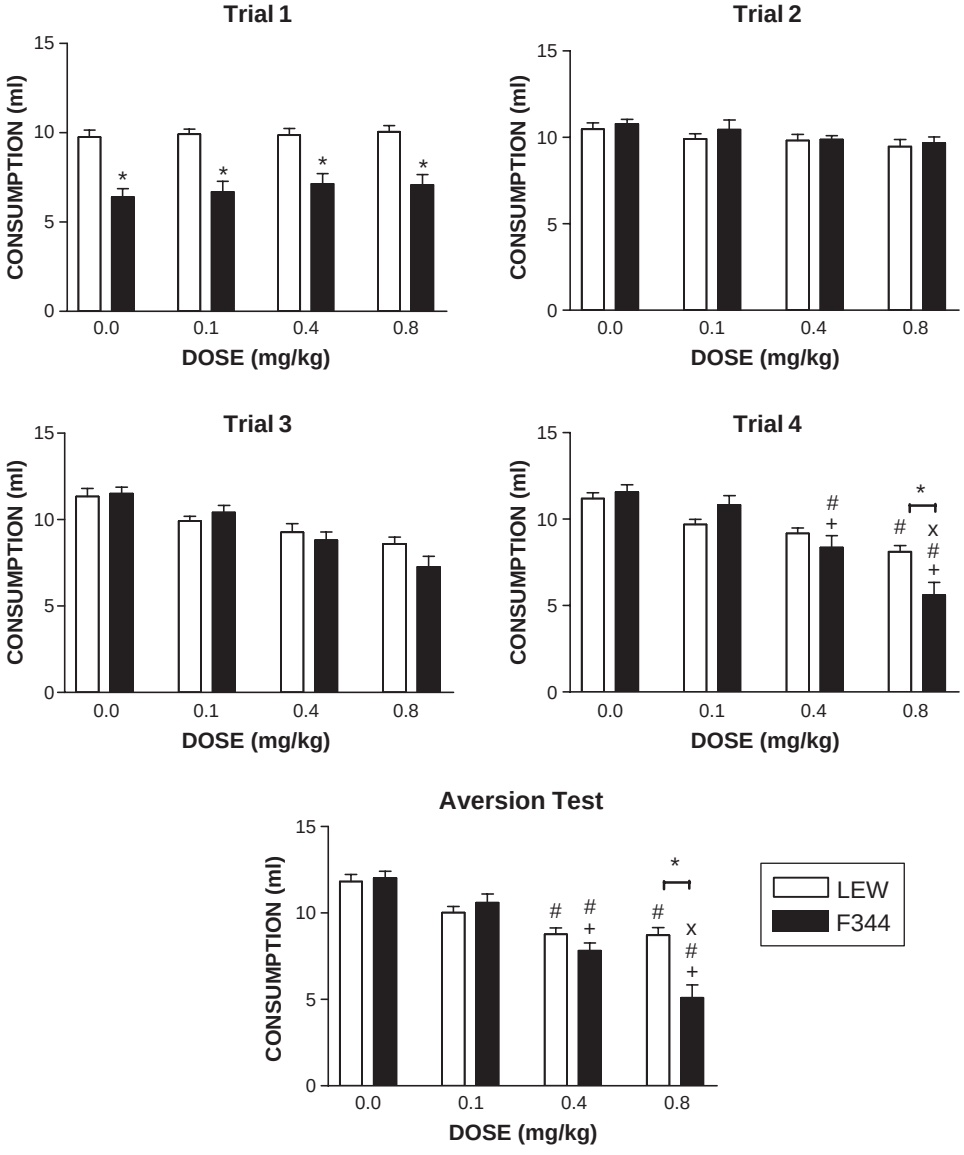

Fig. 1. Illustrates mean (+/− SEM) absolute saccharin consumption on Trials 1–4 and on the Final Aversion Test for subjects within the LEW and F344 strains for each dose of nicotine (0, 0.1, 0.4 and 0.8 mg/kg). *Indicates a significant difference between the strains for specific dose comparisons. #Indicates a significant difference from vehicle. +Indicates a significant difference from 0.1 mg/kg. xIndicates a significant difference from 0.4 mg/kg.

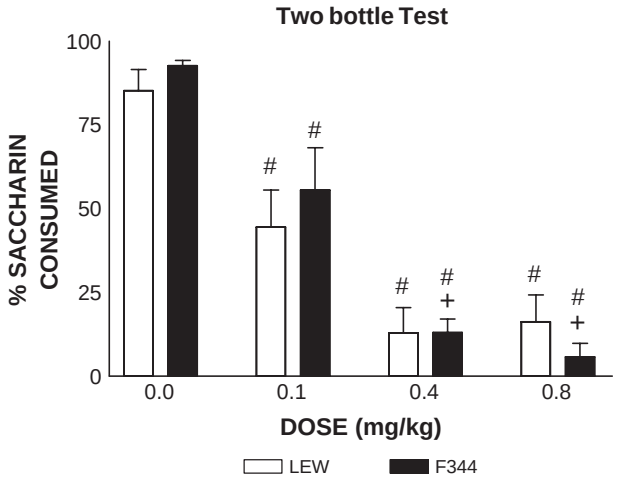

Fig. 2. Illustrates the mean (+/− SEM) percent of saccharin consumption for LEW and F344 subjects for the two-bottle Aversion Test. #Indicates a significant difference from vehicle; +indicates a significant difference from 0.1 mg/kg.

subjects in Group L.8 drank significantly less than subjects in Group L0; by Trial 5, Group L.4 also drank significantly less than Group L0. Additionally, Group F.8 drank significantly less than Group L.8 on Trials 4 and 5. No other comparisons were significant.

Fig. 2 presents the mean (+/− SEM) percent of saccharin consumption on the two-bottle Aversion Test. On this test, there was a significant effect of Dose ($F(3,60)=46.522$, $p<0.0001$), but not Strain ($F(1,60)=0.152$, $p=0.6977$). Further, there was no significant Strain × Dose interaction ($F(3,60)=0.794$, $p=0.5023$). Overall, there was a decrease in saccharin consumption as a function of Dose with the mean percent of saccharin consumed significantly less for rats injected with higher doses of nicotine (0.4 and 0.8 mg/kg) than those injected with the lowest dose (0.1 mg/kg) or with saline. No other comparisons were significant.

Fig. 3 presents the mean (+/− SEM) water consumption on the day prior to conditioning and on the water-recovery sessions following each conditioning trial for LEW and F344 subjects at each dose of nicotine. The $2\times4\times5$ repeated-measures analysis of variance (ANOVA) revealed a significant effect of Strain ($F(1,124)=28.050$, $p=0.0091$) and Water Exposure ($F(4,496)=6.337$, $p<0.0001$) with LEW rats drinking significantly less water than LEW rats. There was no main effect of Dose ($F(3,124)=0.548$, $p=0.6505$). Further, there were no significant Water Exposure × Strain ($F(4,496)=1.838$, $p=0.1202$), Water Exposure × Dose ($F(12,496)=1.756$, $p=0.0527$) or Water Exposure × Strain × Dose ($F(12,496)=0.827$, $p=0.6230$) interactions.

5. Discussion

As described, although LEW and F344 inbred rats have been shown to differ in their sensitivity to the reinforcing effects of nicotine (Brower et al., 2002; Horan et al., 1997; Philibin et al., 2005; Shoaib et al., 1997; Sziraki et al., 2001), little is known about their sensitivity to nicotine's aversive effects. To that end, the present experiment examined nicotine-induced taste aversions in these two strains. As reported, subjects from both strains acquired dose-dependent nicotine-induced taste aversions. Specifically, F344 subjects injected with 0.4 and 0.8 mg/kg nicotine drank significantly less than subjects injected with 0.1 mg/kg and vehicle. Further, F344 subjects injected with the highest dose of nicotine (0.8 mg/kg) drank significantly less than those injected with 0.4 mg/kg. LEW subjects injected with the higher doses of nicotine (0.4 and 0.8) also drank less than the vehicle-injected controls, although these groups never differed from each other or from those subjects injected with the lowest dose of nicotine (0.1). In addition to the within-strain differences, aversions did appear to be acquired faster for the F344 subjects. As noted, aversions at 0.4 mg/kg were evident by Trial 4 for the F344 strain (and Trial 5 for LEW subjects). Further, the F344 strain injected with 0.8 mg/kg nicotine drank significantly less than the LEW strain injected with the same dose on Trials 4 and 5. Under the two-bottle testing conditions, aversions for both strains were dose-dependent with aversions even at the lowest dose of nicotine, an effect consistent with prior work reporting greater sensitivity of the two-bottle procedure in detecting aversions. There were, however, no strain differences at any dose tested.

The differences in the aversions reported with nicotine in the present experiment were relatively small (evident in the rate of acquisition at 0.4 mg/kg and in the absolute differences in consumption at 0.8 mg/kg on Trials 4 and 5). Further, the two strains did not differ at any point during the two-bottle assessment. The fact that under the two-bottle testing procedure aversions were evident at the lowest dose of nicotine for both strains and that there were no longer strain differences is actually consistent with prior work using the two-bottle testing procedure. This design is generally seen as being of much greater sensitivity in detecting aversions than the one-bottle test. While this sensitivity often results in a display of aversions not evident under a one-bottle design, it can also result in a

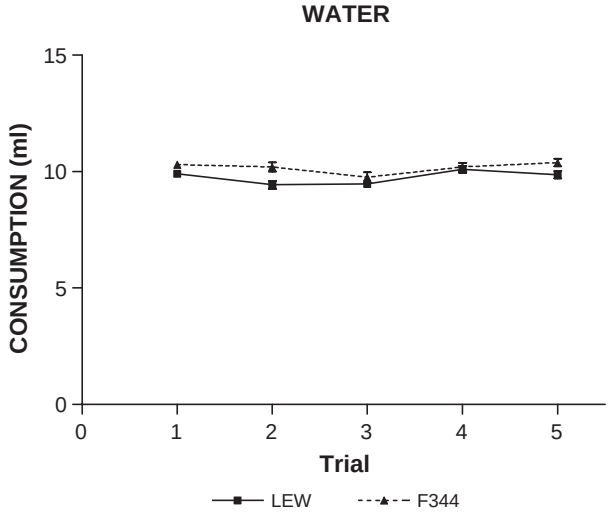

Fig. 3. Illustrates the mean (+/− SEM) water consumption on the day prior to conditioning (Pre) and on the water-recovery sessions following each conditioning trial for LEW and F344 subjects at each dose of nicotine (0, 0.1, 0.4 and 0.8 mg/kg).

failure to detect differences between groups that are seen in the one-bottle procedure (see Dragoin et al., 1971; Grote and Brown, 1971; Pilcher and Stolerman, 1976; van Haaren and Hughes, 1990). However, the increase in sensitivity unlikely mediates the failure to see a difference at the lowest dose of nicotine (0.1 mg/kg). At this dose, both strains drank approximately 50% saccharin (relative to water), i.e., there was no "basement effect" precluding further decreases in saccharin consumption. The fact that there were no strain differences at this dose under the two-bottle procedure suggests that the differences between the strains are relatively weak and evident only at specific doses and under specific conditions. It is important to note in this context that strain differences between the LEW and F344 rats are often of this nature (see Brower et al., 2002; Foynes and Riley, 2004; Glowa et al., 1994; Guitart et al., 1992; Haile et al., 2005; Kosten et al., 1994, 1997; Shoaib et al., 1997).

The differences between the F344 and LEW strain reported are being discussed as conditioned effects based on the apparent association between saccharin and the effects of nicotine. It is important to note that drugs such as nicotine may have unconditioned effects that reduce fluid consumption, and the strain differences reported at the higher doses of nicotine, i.e., 0.4 and 0.8 mg/kg, may reflect such unconditioned suppression rather than a conditioned aversion. Such a position would have to assume that there were strain differences in such unconditioned effects and that they were dose-dependent. Although the differences in the rate of acquisition (at 0.4 mg/kg) and the degree of aversions (at 0.8 mg/kg) could be a function of such unconditioned suppression, there is little evidence that there were unconditioned suppressant effects on fluid consumption. For example, comparison of water consumption both prior to conditioning and during water recovery revealed that the F344 strain drank significantly *greater* amounts of water than the LEW strain (although these differences were quite small). Thus, the fact that F344 subjects injected with 0.8 mg/kg nicotine consumed significantly less saccharin than LEW subjects injected with the same dose is not likely a consequence of some residual effect of this dose of nicotine on general fluid consumption. It might be argued that the increased consumption of water by the F344 strain reflected a compensation for the unconditioned suppression of saccharin consumption during conditioning, but this too is unlikely given that there was no Dose × Strain interaction in this analysis of water consumption, i.e., F344 subjects at all doses (including vehicle) drank more water than LEW subjects. Further, this difference in water consumption was evident even prior to conditioning (on the final day of water adaptation) when such compensation would not be expected. The fact that the suppression of saccharin consumption was still evident (and even greater) in the two-bottle test suggests that the effects seen during training reflected conditioning. The two-bottle procedure allows for an assessment of the acquisition of aversions when there may be a general decrease in overall fluid consumption (due to some unconditioned suppressant effects). The selective suppression of saccharin under this condition would argue that the suppression is a function of the association of the taste with the effects of nicotine (and not a generalized unconditioned suppression).

It is not known what mediates the relatively small differences in nicotine-induced aversions between the F344 and LEW strains. The fact that the F344 and LEW strains drank significantly different amounts on the initial exposure to saccharin makes direct comparisons between the two groups somewhat difficult. The basis for the different levels of consumption on the initial exposure to saccharin likely reflects differential neophobia in the two strains. Neophobia is a typical reaction to novel solutions in the CTA preparation (Braveman and Jarvis, 1978; Franchina and Dyer, 1985; Miller and Holzman, 1981), and it is a reaction that can be potentiated by stress (Mitchell et al., 1975). The F344 strain is known to display an exaggerated corticosterone response to stress (Baumann et al., 2000; Dhabhar et al., 1993; Glowa et al., 1992; Jongen-Relo et al., 2002; Kosten and Ambrosio, 2002; Sternberg et al., 1989, 1992; Stohr et al., 2000) which is consistent with the greater neophobic response in the taste aversion design. It is important to note in this context that by the second trial control subjects for both strains drank similar amounts of saccharin, suggestive of a waning of the neophobic response with repeated exposure to the taste (Braveman and Jarvis, 1978). The issue, however, is less that the two strains differ in the amount of saccharin consumed on the first exposure than the consequences of this difference to subsequent aversion learning. Specifically, if the amount consumed on the initial conditioning trial is associated with the degree of subsequent aversion learning, then conclusions about differences in aversion learning between groups that do differ on this exposure would be confounded by initial consumption. Interestingly, early work in taste aversion learning assessed this relationship by correlating initial consumption and subsequent aversion learning and by manipulating amount consumed and assessing the effects of these manipulations on subsequent aversions. These studies have yielded conflicting results. For example, although a meta-analysis by Kalat (1976) suggested that there was no relationship between amount consumed during conditioning and subsequent aversion learning (see also Smith and Morris, 1963), others have reported a direct relationship, i.e., the greater the amount consumed during conditioning, the stronger the taste aversion (see Archer and Sjoden, 1979; Barker, 1976; Bond and Di Giusto, 1975; Bond and Harland, 1975; see also Braveman and Crane, 1977). The fact that in the present experiment the F344 strain drank significantly less than the LEW strain on the initial conditioning trial, yet displayed stronger taste aversions, thus, is unlikely a function of the amount consumed on the initial saccharin exposure. In fact, based on the abovementioned relationships between amount consumed and taste aversions, the differences reported in the present experiment might be seen as a conservative assessment of the differences between the two strains, i.e., the differences reported may have been attenuated by the smaller amount consumed by the F344 strain on the initial exposure.

It is possible that the differences reflect metabolic differences between the two strains. For example, following a single

intravenous injection of 50 mg/kg nicotine LEW rats have been reported to have significantly higher blood nicotine levels at 15 min postinjection, whereas F344 rats have higher blood nicotine levels at 30 and 60 min postinjection (Sziraki et al., 2001). Although differences in nicotine blood levels have been found, Horan et al. have reported that following five consecutive days of daily subcutaneous injections of 0.4 mg/kg nicotine, tissue samples between LEW and F344 rats were not different in nicotine or cotinine levels (Horan et al., 1997). Although tissue samples were not analyzed in the present study, given the comparable dose and route of administration to those used in the study by Horan et al., any behavioral differences reported here are not likely a function of differences in nicotine pharmacokinetics between the two strains. There are also clear drug-induced biochemical differences between the two strains that might mediate their behavioral differences; however, it should be noted that these differences are generally associated with different reinforcing effects with recreational drugs in these animals (Guitart et al., 1992; Haile et al., 2001; Harris and Nestler, 1996; though see Grigson and Freet, 2000). It may be more parsimonious to examine differences in brain areas implicated in the aversive effects of drugs to account for differences in aversion learning between the two strains. In general, such brain areas are well-documented and include structures such as the amygdala, parabrachial nucleus (PBN), thalamus, nucleus tractus solitarus (NTS) and area postrema (AP) (Bermudez-Rattoni et al., 2004; Scalera, 2002; Yamamoto, 1993; Yamamoto et al., 1994). Although such areas have been examined in outbred rats as well as in the LEW and F344 strains (Aguero et al., 1993a,b; Bielavska and Roldan, 1996; Edmonds and Edwards, 1996; Grigson et al., 1997; Grabus et al., 2004), these areas have not been examined with nicotine in these strains. Such an examination would be useful in elucidating the extent to which the effects of nicotine differ in these areas and the relationships of these differences to aversion learning between the two strains.

Data from other assessments of drugs of abuse suggest that the LEW and F344 strains differ in their response to the affective (both aversive and rewarding) properties of these compounds. Given that the affective properties of recreational drugs contribute to drug acceptability (Cunningham et al., 2003; Gaiardi et al., 1998; Riley and Simpson, 2000; Stolerman and D'Mello, 1981), these strains might be expected to show differences in drug acceptability. In fact, such differences are evident with morphine, ethanol and nicotine self-administration (Ambrosio et al., 1995; Brower et al., 2002; Suzuki et al., 1988b). The fact that the differences between the F344 and LEW strains in the aversive effects of nicotine were small and evident only under specific dose and testing conditions suggests that the role of nicotine's aversive effects in mediating the reported differences in self-administration of nicotine between these two strains may be minimal. Again, however, because the differences between these two strains (both in reward and aversion assessments) are parameter-dependent, it remains to be determined what role the aversive effects of nicotine may play in nicotine self-administration or in the differences between the LEW and F344 strains.

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