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Morphine-induced conditioned taste aversions in the LEW/N and F344/N rat strains

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Abstract

Previous reports have shown that the LEW/N and F344/N inbred rat strains display a differential sensitivity to cocaine in a number of preparations, with the LEW/N rats displaying an increased sensitivity to both the reinforcing and aversive effects of cocaine (relative to the F344/N rats). Given that the LEW/N rats are also more sensitive to the reinforcing effects of morphine than the F344/N strain, the present experiment examined the ability of morphine to condition taste aversions in the LEW/N and F344/N strains to determine if the general sensitivity to cocaine generalizes to another drug of abuse. Specifically, on four conditioning trials, 35 LEW/N and 33 F344/N female rats were allowed access to a novel saccharin solution and then injected with varying doses of morphine (0, 10, 32 and 56 mg/kg). On intervening recovery days, subjects were allowed 20-min access to water. Following the fourth trial, a final aversion test was administered. The F344/N rats, but not the LEW/N rats, rapidly acquired morphine-induced taste aversions at all doses of morphine. Pharmacokinetic differences between the strains were also assessed. Specifically, 10 mg/kg morphine (or vehicle) was administered to subjects of both strains and plasma morphine levels were analyzed at 0.5, 2 and 4 h postinjection. No differences in plasma levels between the strains were observed. Unlike with cocaine, the LEW/N rats do not seem generally sensitive to morphine (relative to the F344/N rats). Rather, the differential sensitivity of the two strains to these compounds seems to be preparation dependent. Possible mechanisms underlying the differential sensitivity evident in the strains were discussed.

Keywords: LEW/N; F344/N; Morphine; Conditioned taste aversion; Rats

1. Introduction

Previous studies have shown that the behavioral and neurochemical profiles of Lewis (LEW/N) and Fischer (F344/N) inbred rodent strains differ considerably. In particular, the strains seem to differ on a variety of physiological and behavioral measures including responses to immune and inflammatory challenges (Sun et al., 1999), aging (Sternberg et al., 1989), stress (Sternberg et al., 1992; Stohr et al., 1998a), startle reaction (Glowa et al., 1992; Varty and Geyer, 1998) and open-field behavioral (Chauloff et al., 1995; Paulus et al., 1998).

In addition to these differences, the strains also differ in their behavioral responses to drugs of abuse (Ambrosio et al., 1995; Kosten et al., 1994, 1997; Suzuki et al., 1988a,b, 1992a). For example, in a report by Kosten et al. (1997) assessing intravenous cocaine self-administration in these strains, the LEW/N rats acquired cocaine self-administration after fewer training sessions and at lower doses than F344/N rats. In addition to self-administration, differences between the strains are evident when utilizing the conditioned place preference procedure. Specifically, Kosten et al. (1994) reported that cocaine-induced conditioned place preference was greater in LEW/N rats at 15 and 30 mg/kg cocaine relative to F344/N rats (see also Guitart et al., 1992).

Interestingly, not only do the strains display a differential sensitivity to the reinforcing effects of cocaine, but they also differ in their response to the aversive effects of this compound (Glowa et al., 1994; Grigson and Freet, 2000).

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For example, utilizing the conditioned taste aversion procedure Glowa et al. (1994) demonstrated that low (18 mg/kg) and intermediate (32 mg/kg) doses of subcutaneous injections of cocaine induced stronger taste aversions in the LEW/N rats (relative to F344/N rats). Both strains exhibited strong and comparable taste aversions at the 50 mg/kg dose of cocaine. Similarly, Grigson and Freet (2000) reported that the LEW/N strain drank significantly less than the F344/N strain of a saccharin solution paired with 10 mg/kg of cocaine. Thus, it appears that the LEW/N rats are more sensitive to the aversive effects of cocaine than the F344/N rats (though see Kosten et al., 1994). Combined with the work on self-administration and conditioned place preferences (see above), these results suggest that the LEW/N strain may be more sensitive to the effects of cocaine in general (for assessments of LEW/N and F344/N differences with cocaine in other designs, see Camp et al., 1994; George et al., 1991; Guitart et al., 1992; Kosten et al., 1994; Ortiz et al., 1995).

It is unknown to what extent this general sensitivity to the effects of cocaine in these strains generalizes to other drugs of abuse. As cited above, LEW/N and F344/N rats are differentially sensitive to the reinforcing effects of a variety of drugs of abuse, including cocaine, opioids, nicotine, THC and ethanol (Ambrosio et al., 1995; George and Goldberg, 1989; Kosten et al., 1994, 1997; Suzuki et al., 1988a,b, 1992a). One drug that has received considerable attention in these analyses is morphine. Like those with cocaine, studies examining the reinforcing effects of morphine generally show that LEW/N rats self-administer (both intravenously and orally) more drug than F344/N rats (Ambrosio et al., 1995; Martin et al., 1999; Suzuki et al., 1988b, 1992a). In addition to self-administration studies, differences between the LEW/N and F344/N rats are found when utilizing the conditioned place preference procedure (Guitart et al., 1992). That is, although both LEW/N and F344/N rats develop place preferences with morphine, the LEW/N rats display more than a twofold increase in sensitivity to dose relative to the F344/N rats. Thus, the LEW/N strain seems more sensitive to the reinforcing effects of both morphine and cocaine.

Although studies have established the differential sensitivity to the reinforcing effects of morphine in the LEW/N and F344/N rats, no studies have examined the aversive effects of morphine in the two strains. However, a number of studies have demonstrated morphine-induced aversions in outbred rat strains (Berger, 1972; Cappell et al., 1973; Hutchinson et al., 2000; Mucha and Herz, 1985; Riley et al., 1978; Siegel et al., 1995). Given that the LEW/N and F344/N strains appear differentially sensitive to the reinforcing effects of morphine and that morphine has been reported to induce aversions in other rat strains, morphine may provide a test of whether the general sensitivity to the effects of cocaine in the strains generalizes to other drugs of abuse. To that end, the present study assessed whether the LEW/N and F344/N rats were differentially sensitive to the aversive effects of morphine utilizing the conditioned taste aversion preparation.

2. General method

2.1. Experiment 1: conditioned taste aversion

2.1.1. Subjects

Subjects were 35 LEW/N and 33 F344/N drug-naive female rats (Harlan Sprague–Dawley), weighing approximately 140 and 185 g at the start of the experiment, respectively.

2.1.2. Apparatus

Subjects were housed individually in stainless-steel, wire mesh cages on the front wall of which a single 50-ml graduated Nalgene tube could be placed for presentation of either water or saccharin. Subjects were maintained on a 12-h light/12-h dark cycle (lights on at 0800 hours) in a room that was maintained at approximately 23°C. Rat chow (Agway) was available ad libitum.

2.1.3. Drug administration

Morphine sulfate (generously supplied by NIDA) was prepared in a 10-mg/ml solution in distilled water. Morphine and vehicle control injections were administered subcutaneously (sc). Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1-g/l solution in distilled water.

2.1.4. Procedure

2.1.4.1. Phase 1: habituation. Following 23 2/3 h of water deprivation, all subjects were given 20-min access to water daily for 19 consecutive days.

2.1.4.2. Phase 2: conditioning. On Day 1 of this phase, all subjects were given access to a novel saccharin solution during the scheduled 20-min fluid access period. Immediately following this exposure, the 35 subjects from the LEW/N strain were ranked on saccharin consumption and assigned to four groups such that mean saccharin consumption was comparable among groups ($n = 8–10$ per group). Subjects were then injected with either morphine sulfate or the vehicle (distilled water). Specifically, subjects in Groups L10, L32 and L56 were given 10, 32 and 56 mg/kg morphine sulfate, respectively, while subjects in Group L0 were given distilled water equivolume to that given with the highest dose of morphine sulfate (56 mg/kg). Subjects in the F344/N strain ($n = 33$) were treated similarly on Day 1 of this phase, i.e., they were ranked on saccharin consumption and assigned to four groups such that mean saccharin consumption was comparable among groups ($n = 8–9$ per group). Subjects in Groups F10, F32 and F56 were given 10, 32 and 56 mg/kg morphine sulfate, respectively, while subjects in Group F0 were given distilled water equivolume

to that given with the highest dose of morphine sulfate (56 mg/kg). For the 3 days following conditioning, all subjects were given 20-min access to water. This sequence of alternating a single conditioning day with three water-recovery days was continued for an additional three cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin. No injections were given following this session.

2.2. Experiment 2: plasma morphine levels

Thirty-three days following the final morphine injections of Experiment 1, six randomly selected rats from each of the four conditioning groups from each strain were given a single 10 mg/kg (sc) injection of morphine sulfate ($n=18$ per strain) or the distilled water vehicle ($n=6$ per strain) (the remaining 20 rats were used in an unrelated study). Morphine-treated animals were then sacrificed by decapitation either 0.5, 2 or 4 h postinjection. Vehicle-control animals were sacrificed by decapitation at 2 h postinjection. To determine morphine content in rat plasma, trunk blood was collected and placed in tubes pretreated with heparin. The blood was centrifuged at 2500 rpm for 25 min at 4°C. The samples were frozen until assayed.

Assays were performed with a kit used to measure plasma morphine (Coat-A-Count Serum Morphine, Diagnostic Products, Los Angeles, CA 90045). Iodinated morphine and each plasma sample were added to a tube containing antibodies to morphine. After the tubes remained for 1 h at room temperature, the tubes were decanted and radioactivity was counted on a gamma counter. Since the morphine radioimmunoassay (RIA) is used to determined human levels of plasma morphine, a separate set of standards was made for each strain of rat. The standards were made from vehicle-injected rats for each strain.

2.3. Statistical analysis

In Experiment 1, mean saccharin consumption for each group was analyzed using a $2 \times 4 \times 5$ repeated-measures analysis of variance (ANOVA) with the between-subjects variables of Strain (LEW/N and F344/N) and Dose (control, 10, 32 or 56 mg/kg morphine) and the within-subjects variable of Trial (1–5). Post hoc assessments were conducted using Scheffe comparisons. Mean water consumption for the LEW/N and F344/N rats on days intervening between each conditioning trial was analyzed using a one-way ANOVA. An α=.05 was used for determining significance throughout.

In Experiment 2, mean plasma levels of the two strains were compared using a $2 \times 3 \times 4$ one-way ANOVA with the between-subjects variables of Strain (LEW/N and F344/N), Time (0.5, 2 and 4) and History (previous injections of vehicle, 10, 32 or 56 mg/kg morphine). Post hoc assessments were analyzed using Scheffe comparisons. α was set at .05 throughout. All data analyses were conducted using the Statistical Package for the Social Sciences, Base 8.0 (SPSS, 1998).

3. Results

3.1. Experiment 1: conditioned taste aversion

On the initial exposure to saccharin (Conditioning Day 1), there were no significant differences in saccharin consumption among the various groups with the mean saccharin consumption ranging from 7.72 to 8.94 ml (all P's > .953). Fig. 1 illustrates mean saccharin consumption on this and subsequent conditioning trials and on the final aversion test for the LEW/N and F344/N strains for each dose of morphine (and for the vehicle control). Repeated-measures ANOVA revealed significant Trial [$F(4, 60)=56.012$, $P<.0001$], Strain [$F(1, 63)=99.206$, $P<.0001$] and Dose [$F(3, 63)=27.979$, $P<.0001$] effects and significant Strain × Trial [$F(4, 60)=13.748$, $P<.0001$] and Dose × Trial [$F(4, 62)=12.444$, $P<.0001$] interactions. Post hoc assessments using Scheffe comparisons yielded the following results. On Conditioning Trial 2 (the first aversion test), Groups F10, F32 and F56 drank significantly less saccharin than Group F0 (vehicle control) (all P's < .0001), indicating an aversion to the saccharin solution. There were no significant differences in saccharin consumption among Groups F10, F32 and F56 (all P's > .669). Similar results were found on subsequent conditioning trials and on the final test. That is, subjects in Groups F10, F32 and F56 continued to drink significantly less saccharin than control subjects (Group F0) (all P's < .001), but did not differ among themselves (all P's > .476). In contrast to the results with the F344/N strain, on Conditioning Trial 2, there were no significant differences in saccharin consumption among Groups L10, L32 and L56 relative to Group L0 (vehicle control) (all P's > .204), indicating that aversions to saccharin were not acquired in the LEW/N strain. Further, there were no significant differences in saccharin consumption among Groups L10, L32 and L56 (all P's > .478). Similar results were found on subsequent conditioning trials and on the final test. That is, over repeated conditioning trials Groups L10, L32 and L56 did not drink significantly less sacccharin than control subjects (Group L0) (all P's > .211) and did not differ among themselves (all P's > .079).

Although at no point during conditioning did saccharin consumption differ between the F344/N and LEW/N control subjects (Groups F0 and L0) (all P's > .993), on Conditioning Trials 2, 3, 4 and on the final test subjects in Groups F10, F32 and F56 differed from those in Groups L10, L32 and L56, respectively (all P's < .001).

Fluid intake on intervening water-recovery days was assessed using a general factorial ANOVA. This analysis revealed a significant Strain [$F(4, 57)=2.885$, $P=.03$] effect but failed to reveal a significant Dose [$F(4, 59)=1.227$, $P=.309$] effect or Strain × Dose [$F(4,$

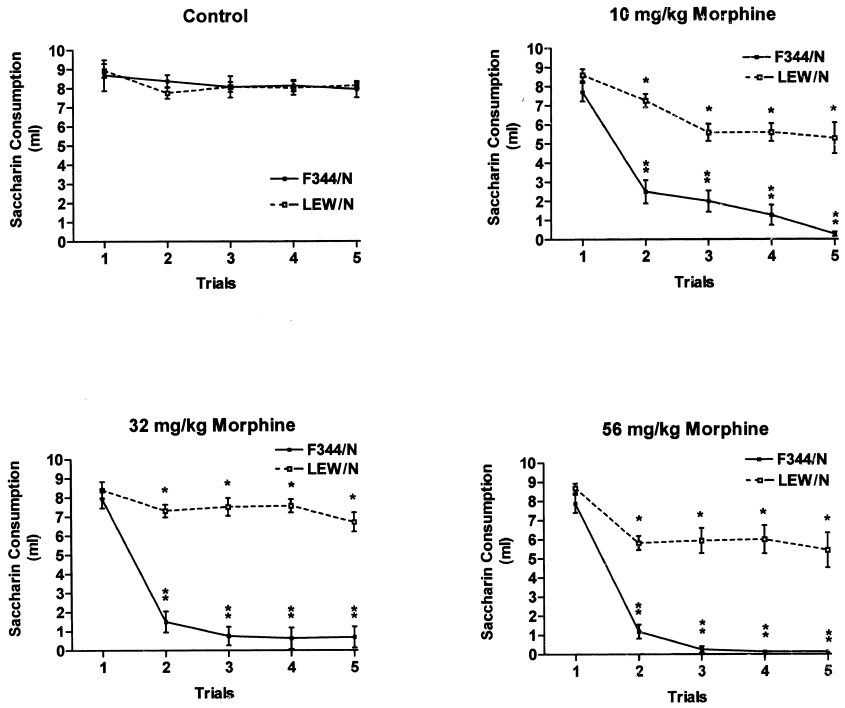

Fig. 1. Mean saccharin consumption (±S.E.M.) over repeated conditioning trials for LEW/N and F344/N strains injected with vehicle (a, Groups L0 and F0), 10 mg/kg morphine (b, Groups L10 and F10), 32 mg/kg morphine (c, Groups L32 and F32) and 56 mg/kg morphine (d, Groups L56 and F56). The LEW/N strain is noted by the open square symbol and dashed line; the F344/N strain is noted by the closed square and solid line. * Significant differences between the LEW/N and F344/N Groups. ** Significantly different from Trial 1.

59) = 1.10, P = .365] interaction. That is, the F344/N rats drank significantly more water than LEW/N rats on the days prior to Conditioning Trial 2 (P=.037) and the final aversion test (P=.016). This elevation in water consumption seen in the F344/N strain may be due to the fact that these animals displayed suppressed fluid consumption on conditioning days (relative to the LEW/N rats).

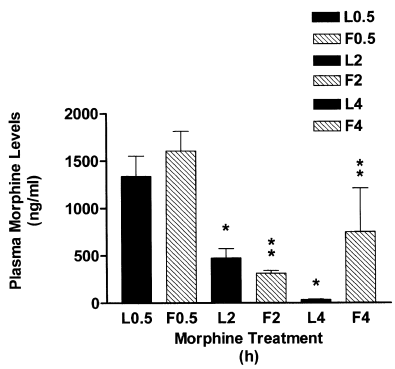

Fig. 2. Mean morphine plasma levels (±S.E.M.) 0.5, 2 and 4 h postinjections of 10 mg/kg morphine in the LEW/N and F344/N strains. The LEW/N strain is noted by the black bar; the F344/N strain is noted by the striped bar. * Significantly different from L0.5. ** Significantly different from F0.5.

3.2. Experiment 2: plasma morphine levels

Fig. 2 illustrates mean plasma morphine levels 0.5, 2 and 4 h postinjections of 10 mg/kg morphine in the LEW/N and F344/N rats. A general factorial ANOVA revealed a significant Time [F(2, 33) = 17.240, P = .001] effect but failed to reveal a significant Strain [F(1, 33) = 2.488, P = .146] or History [F(3, 33) = 1.779, P = .215] effect. There was no significant Strain × Time [F(2, 33) = 2.381, P = .143], History × Time [F(6, 33) = 1.272, P = .351] or Strain × Time × History [F(6, 33) = 1.355, P = .319] interaction. Post hoc assessments using Scheffe comparisons yielded the following results. At 0.5 h, mean plasma levels were significantly elevated compared to both the 2 and 4 h levels postinjection (P < .001). Further, mean plasma levels did not differ at 2 and 4 h postinjection (P = .986). Plasma morphine levels did not differ between the LEW/N and F344/N rats at any time point (0.5, 2 and 4 h). At 4 h, the F344/N strain had one extreme value (4548 ng/ml) that was excluded from the analysis based on an outlier's test (1385.33 ± 1803.44 ng/ml).

4. Discussion

Previous studies have indicated that the LEW/N rats are more sensitive to a variety of behavioral effects of cocaine

(relative to the F344/N rats). For example, LEW/N rats display an increased sensitivity to both the reinforcing and aversive effects of cocaine, with the LEW/N rats self-administering cocaine at a more rapid rate (Kosten et al., 1997), displaying a greater conditioned place preference for cocaine (Guitart et al., 1992; Kosten et al., 1994) and acquiring cocaine-induced taste aversions at lower doses (Glowa et al., 1994; Grigson and Freet, 2000) than F344/N rats. Given that the strains display differential reinforcing patterns with morphine (see above for review) and morphine-induced taste aversions have been reported in outbred rats (see above), the current study evaluated the role of strain in morphine-induced conditioned taste aversions to determine whether the general sensitivity found with cocaine generalizes to another drug of abuse. As described, in the present assessment rats from the F344/N strain rapidly acquired morphine-induced taste aversions, displaying marked reductions in saccharin consumption following only a single conditioning trial and near total suppression of consumption after repeated conditioning. Such effects were evident at all doses of morphine (10, 32 and 56 mg/kg). Conversely, no significant decreases in saccharin consumption were evident in the LEW/N rats (relative to vehicle-injected controls), indicating that aversions to morphine were not acquired in this strain.

It is unlikely that the strain-dependent differences in morphine-induced taste aversions were a function of pharmacokinetic differences between the two strains. As described, both LEW/N and F344/N strains displayed significantly elevated plasma morphine levels 0.5 h postinjection (10 mg/kg morphine, sc) that decreased significantly at the 2 and 4 h assessments. At no time period did the two strains differ in plasma levels. These findings are similar to those reported by Gosnell and Krahn (1993) and Guitart et al. (1992) who demonstrated that there were no differences in serum levels between the two strains following subcutaneous injections of 3 and 4 mg/kg morphine, respectively (see Guitart et al., 1992 and Kosten et al., 1997 for similar pharmacokinetic analyses with cocaine). Although there were no differences in plasma levels between the two strains in the present experiment, it is possible that morphine brain levels did differ for the LEW/N and F344/N rats. Brain morphine levels were not assessed in the present experiment; however, Gosnell and Krahn (1993) did examine morphine levels in the brain in their analysis of the effects of morphine on food consumption in the LEW/N and F344/N strains. In their report, they noted that 30 min postinjection F344/N rats had significantly higher brain levels than LEW/N rats. This effect was not evident at 3 h. Although suggestive that the greater aversions in the present experiment could be a result of more rapid movement of morphine into the brain of the F344/N rats, it should be noted that increasing the dose of morphine from 10 to 32 to 56 mg/kg had no effect on the acquisition of aversions in the LEW/N strain (i.e., aversions were not evident at any dose). Further, aversions were evident at the lowest dose of 10 mg/kg for the F344/N strain, again an effect that did not vary with increases in the dose. If aversions were a function of a rapid (and large) movement of morphine into the brain following injection, it might be expected that the LEW/N strain would show aversions with increasing doses and that the aversions evident in the F344/N strain would be dose dependent. Further, although work on the central basis of taste aversion learning is limited, the central administration of the opioids is generally ineffective in inducing taste aversions. For example, Amit et al. (1977) have reported that infusions of morphine into the hippocampus or caudate nucleus did not produce aversions (whereas infusions of THC into the hippocampus was effective). Similarly, Stapleton et al. (1979) noted that the intracerebroventricular administration of morphine or the delta peptidergic agonist D-ala^2-methionine enkephalin was ineffective in the aversion design (see also Bechara et al., 1987). Thus, the differential effects noted here was not likely a function of pharmacokinetic differences, e.g., metabolic or distribution, between the two strains.

Another possibility for the differential aversions induced by morphine between the two strains is related to reports demonstrating biochemical differences between the strains. To date, research into the biochemical differences between the LEW/N and F344/N rats has focused primarily on biological systems thought to mediate the differential sensitivity to the reinforcing effects of drugs of abuse. Such analyses have demonstrated a variety of biochemical differences between the strains in the mesolimbic dopaminergic system (for review, see Di Chiara et al., 1992; Guitart et al., 1992; Mark et al., 1991; Nestler, 1992). Interestingly, studies have also shown biochemical differences in the locus coeruleus, an area implicated in drug withdrawal (Guitart et al., 1993; Nestler, 1994) in the LEW/N and F344/N rats. This latter difference may be particularly important when looking at aversion learning in that a number of studies have demonstrated that withdrawal is sufficient to condition aversions in drug dependent animals (Parker and Radow, 1974; Pournaghash and Riley, 1991; Zellner et al., 1984). Although not yet examined, differences in the brain areas involved in taste aversion learning may also differ between the strains. Possible brain structures that have been implicated in aversion learning include the parabrachial nucleus (Bechara et al., 1993; Nader et al., 1996; Sakai and Yamamoto, 1998, 1999; for review, see Reilly, 1999), nucleus tractus solitarius (Houpt et al., 1996, Sakai and Yamamoto, 1997; though see Grigson et al., 1997), area postrema (Sakai and Yamamoto, 1997) and the amygdala (Morris et al., 1999; Nachman and Ashe, 1974; Sakai and Yamamoto, 1999; Yamamoto and Fujimoto, 1991; Yamamoto et al., 1995). Although these areas have been implicated, it is important to note that lesions to these sites do not affect aversion learning to all drugs equally (Bechara et al., 1993). Further, activity within these sites (e.g., as measured by c-*fos* levels) differs for various aversion-inducing compounds (Sakai and Yamamoto, 1997;

Yamamoto et al., 1992), demonstrating that the basis for aversions may differ for different drugs. Even if specific sites were well defined and their role in aversion learning to specific drugs established, the fact that the physiological basis of aversion learning in the two strains has not been examined limits any discussion regarding the biochemical basis of their differences.

Independent of the basis for the differential sensitivities to the aversive effects of morphine reported in the present experiment, it is clear that these differential sensitivities are in contrast to those reported in the assessment of the reinforcing properties of morphine in which the LEW/N rats appear more sensitive than the F344/N strain. Thus, unlike with cocaine, the LEW/N rats do not appear to be generally sensitive to morphine (relative to the F344/N rats) (for assessments of LEW/N and F344/N differences with morphine in other designs, see Gosnell and Krahn, 1993; Morgan et al., 1999; Suzuki et al., 1988c; Woolfolk and Holtzman, 1995). From this analysis, it is clear that such drug sensitivity is preparation dependent. In this context, it is important to note that the majority of the reports assessing the reinforcing properties of morphine in the LEW/N and F344/N rats have used male subjects. On the other hand, the present study assessed the aversive properties of morphine in female LEW/N and F344/N rats (see also Glowa et al., 1994). The failure to find a general sensitivity of the LEW/N strain to both the reinforcing and aversive properties of morphine (or a general insensitivity of the F344/N strain), thus, may be due in part to gender differences in the aversive and reinforcing effects of morphine in the two strains. Interestingly, gender differences in outbred rats have been reported in preparations assessing the reinforcing (Lynch and Carroll, 1999, 2000) and aversive (Chambers, 1985; Dacanay et al., 1984) properties of drugs. In such assessments, female rats generally show a greater sensitivity to the reinforcing effects of the drug, while male rats show a greater sensitivity to its aversive effects. Studies directly assessing gender differences in the LEW/N and F344/N strains are somewhat limited and have found no consistent gender differences in the two strains, i.e., in some cases, the gender differences are evident in the LEW/N strain only (Suzuki et al., 1992b), in the F344/N strain only (Sircar and Kim, 1999), in neither strain (Stohr et al., 1998b) or in both strains (Pryce et al., 1999). In relation to the reinforcing properties of drugs, Stohr et al. (1998b) reported no gender differences in the acquisition of amphetamine-induced place preferences for the two strains. Given that no consistent gender differences have been reported and that there are no direct assessments of gender differences in aversion learning in the two strains, it remains unknown to what extent gender differences contribute to the sensitivity differences reported here with morphine between the two strains.

It is apparent that the differential sensitivity of the LEW/N and F344/N rat strains is both preparation and drug (and perhaps gender) dependent, limiting the generalizability of strain-dependent differences to various compounds. Perhaps, examining a broad range of psychoactive compounds may give insight into the nature of the differences. To that end, future research designed to further delineate the differences between the LEW/N and F344/N rat strains is necessary to provide insight into genetic and environmental factors mediating various behaviors including both aversion learning and the use and abuse of various compounds.

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