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The effects of cocaine preexposure on cocaine-induced taste aversion learning in Fischer and Lewis rat strains

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Abstract

The Fischer (F344) and Lewis (LEW) inbred rat strains differ on a number of behaviors, including those induced by a variety of drugs of abuse. Although a number of physiological and biochemical differences between the strains have been reported following both single and repeated drug administration, studies assessing changes in the affective properties of drugs after repeated exposure are limited. To that end, using the F344 and LEW strains, the present study examined the effects of repeated exposure to cocaine on the subsequent acquisition of cocaine-induced conditioned taste aversions, a preparation often used in assessing the development of tolerance to the drug's aversive effects. Specifically, separate groups of male F344 and LEW rats received five injections of 32 mg/kg cocaine (or vehicle) prior to taste aversion conditioning with 32 mg/kg cocaine (or vehicle). Vehicle-preexposed subjects of both strains acquired aversions to the cocaine-associated taste with no differences in the strength of the aversions. Further, cocaine-preexposed subjects displayed significantly attenuated aversions, an effect consistent with prior work with outbred animals. There was no difference between the two strains in this attenuation, suggesting that there were no genotype-specific differences in tolerance to cocaine's aversive effects. The data were discussed in relation to genetic/environmental interactions in the vulnerability to drugs of abuse.

Keywords: F344; LEW; Drug preexposure; CTA; Genetic differences; Aversion; Cocaine

1. Introduction

The inbred Fischer (F344) and Lewis (LEW) rat strains differ on a variety of physiological and behavioral endpoints (DeCarolis et al., 2003; Gomez-Serrano et al., 2001, 2002; Sternberg et al., 1992; Stohr et al., 2000; for a review see Kosten and Ambrosio, 2002). Although not selectively bred for responses to drugs of abuse, these strains show differential behavioral and neurochemical reactivity to such drugs, prompting their use as a model to investigate vulnerabilities to substance abuse (Ambrosio et al., 1995; Brower et al., 2002; Horan et al., 1997; Kosten et al., 1994; Martin et al., 1999, 2003; Pescatore et al., 2005; Philibin et al., 2005; Roma et al., 2006; Roma et al., 2007; see Kosten and Ambrosio, 2002; Riley et al., in press). The majority of work done with these strains has focused on their responsivity to acute drug administration, characterizing the LEW animals as being more sensitive to the rewarding effects of drugs compared to F344 rats (Ambrosio et al., 1995; Kosten et al., 1994; Philibin et al., 2005; Suzuki et al., 1988a,b; Suzuki et al., 1992; Werme et al., 1999, 2000). Although these differences to acute drug administration are well documented, little is known about the changes in the affective properties of drugs following repeated drug administration in these strains, effects that may provide information about neuroplastic changes that modulate drug taking behaviors (see Hyman et al., 2006).

Although such effects have not been investigated with F344 and LEW rats, Risinger and Cunningham (1995) have addressed this issue in other inbred rodent strains, specifically, C57BL/6J and DBA/2J mice (see also Camarini and Hodge, 2004; Cunningham et al., 2002; Meyer et al., 2004). In their report, they examined tolerance to the aversive effects of ethanol in the C57 and DBA mouse strains using the conditioned taste aversion preparation (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Rozin and Kalat, 1971; see CTAlearning.com). Specifically, C57 and DBA mice were exposed to ethanol prior to pairings of a NaCl solution and ethanol (see Experiment

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2), a manipulation that generally attenuates aversion learning in outbred rats and mice (see Riley and Simpson, 2001 for a review). In the Risinger and Cunningham investigation, the ethanol-preexposed C57 strain displayed weaker ethanol-induced aversions than the DBA strain (with vehicle-preexposed subjects of both strains displaying comparable aversions), suggesting that greater tolerance to ethanol's aversive effects had developed in the C57 mice (for a discussion of the effects of drug preexposure in the conditioned taste aversion design, see Riley and Simpson, 2001). The differential effects of ethanol preexposure indicated genotype-specific differences in tolerance to ethanol's aversive effects.

Although little is known about the effects of drug history on the affective properties of drugs in the LEW and F344 rat strains, previous investigations report differential effects of repeated cocaine administration on a variety of behavioral and neurochemical responses in these strains, suggesting genotypic differences in adaptations to cocaine exposure (see Beitner-Johnson et al., 1991; Haile et al., 2001). For example, F344, but not LEW animals, exposed repeatedly to cocaine show protein level changes in the nucleus accumbens (NAcc), ventral tegmental area (VTA), lateral caudate putamen and cingulate cortex, areas important for behavioral responding to drug administration (Haile et al., 2001; Werme et al., 2000). Moreover, repeated cocaine administration increases locomotor activity in the LEW strain, while decreasing this activity in the F344 rats, suggesting sensitization and tolerance to cocaine's activating effects in each strain, respectively (Haile et al., 2001). Given these reported differences to repeated cocaine administration and the prior report of Risinger and Cunningham (1995) demonstrating genotypic differences in the development of tolerance to the affective properties of ethanol, the present study examined the effects of repeated cocaine exposures (preexposure) on taste aversions induced by cocaine in the F344 and LEW strains. Specifically, male F344 and LEW rats were given an intraperitoneal (ip) injection of cocaine (32 mg/kg) or equivolume vehicle every other day for 10 days, followed by conditioning with this dose of cocaine or vehicle. The dose of cocaine employed has been reported to induce comparable aversions in outbred (and male F344 and LEW; see Roma et al., 2007) rats and preexposure to this dose of cocaine is effective in attenuating the subsequent acquisition of cocaine-induced taste aversions in outbred subjects (see Riley and Diamond, 1998; Riley and Simpson, 1999). Given that overall drug acceptability may be a balance of the drug's rewarding and aversive effects (see Cunningham et al., 2003; Gaiardi et al., 1991; Mayer and Parker, 1993; Riley et al., in press; Risinger and Cunningham, 1995; Simpson and Riley, 2005; Stolerman and D'Mello, 1981), understanding the impact drug history has on the aversive effects of cocaine in these two strains may help in the understanding of the interaction of genetic and environmental factors in drug vulnerability.

2. Methods

2.1. Subjects

The subjects were male F344/N ($n=34$) and LEW/N ($n=33$) rats obtained from Harlan–Sprague Dawley, Indianapolis, IN. The average weight of the subjects at the initiation of the study was 277.4 g + 7.7 g (F344) and 331.9 g + 7.8 g (LEW), a weight difference [$F(1, 66)=25.910$, $p<0.05$] characteristic of these strains (see Glowa et al., 1994; Gomez-Serrano et al., 2001, 2002; Lancellotti et al., 2001; Pescatore et al., 2005; Riley et al., in press; Roma et al., 2006). Procedures recommended by the National Research Council (1996), Committee on Guidelines for the Care and Use of Animals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Apparatus

Animals were individually housed in hanging wire-mesh cages (24 × 19 × 18 cm) with ad libitum access to food. They were maintained on a 12:12 light/dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Graduated 50-ml Nalgene tubes were attached to the front of the cages, providing either water or saccharin during the 20-min fluid access period (see below).

2.3. Drugs and solutions

Cocaine hydrochloride (generously supplied by NIDA) was prepared as a 10 mg/ml solution in physiological saline (drug vehicle). Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/L solution in tap water. All doses of cocaine are expressed as the salt.

2.4. Procedure

2.4.1. Phase I: habituation

After 23 h of water deprivation, rats were given 20-min access to water daily, beginning at 1000 h, until they were approaching and drinking from the tube within 2 s of its presentation. Once this criterion was reached, the preexposure manipulation began.

2.4.2. Phase II: preexposure

Water consumption for all subjects was recorded and averaged over the last 3 days of habituation. Within each strain, animals were ranked on average water consumption and assigned to a preexposure condition (cocaine or vehicle). Five hours following their regular 20-min access to water, animals within each strain were injected intraperitoneally (ip) with drug or vehicle (see below) every other day for 10 days (five total drug or vehicle injections). Vehicle injections were given to all animals on intervening days. All preexposure injections were given between 1600–1700 h. Fluid intake was monitored throughout the preexposure phase.

2.4.3. Phase III: CTA conditioning

On Day 1 of this phase, animals were given 20-min access to a novel saccharin solution. After saccharin access, animals were serially ranked by saccharin consumption depending on strain and preexposure condition (to enable matching of fluid consumption). These procedures yielded eight experimental

groups: CCF ($n=8$), CVF ($n=9$), VCF ($n=9$), VVF ($n=8$), CCL ($n=8$), CVL ($n=8$), VCL ($n=8$) and VVL ($n=9$), with the first letter denoting the preexposure drug, the second letter denoting the conditioning drug and the third letter representing the strain. Subjects were then given ip injections of cocaine or vehicle. On the next day of the cycle, animals received 20-min access to water, followed by equivolume vehicle injections. This alternating procedure of conditioning and water recovery was repeated until all subjects had received four complete cycles.

2.4.4. Phase IV: Final Aversion Test

Two days after the last conditioning cycle, all animals were given a final 20-min one-bottle aversion test. No injections were given following this test.

3. Data analysis

3.1. Preexposure

A 2×2×10 repeated measures ANOVA with the between-subjects factors of Strain (F344 and LEW) and Dose (0 vs. 32 mg/kg cocaine) and the within-subjects factor of Preexposure Days (1–10) was run to compare the amount of water consumed among groups over preexposure.

3.2. Conditioning

Given that the two strains differed in the amount of saccharin consumed on the initial exposure to saccharin [$F(1, 66)=23.084$, $p<0.05$], consumption data for each strain was converted to a percentage of control levels to allow between-strain comparisons. Specifically, for each animal within each strain the amount consumed on each trial was divided by the average consumption of the control subjects in that strain. A 2×2×5 repeated measures ANOVA with the between-subjects factors of Strain (F344 and LEW) and Preexposure Dose (0 vs. 32 mg/kg) and the within-subjects factor of Trials (1–4; Final Aversion Test) was then run on the percentage of control consumption over conditioning.

4. Results

4.1. Preexposure

The 2×2×10 repeated-measures ANOVA on water consumption over the cocaine preexposure period revealed significant effects of Strain [$F(1, 63)=33.776$, $p<0.05$] and Preexposure Day [$F(9, 567)=6.793$, $p<0.05$]. Overall, LEW animals displayed greater water consumption than the F344 animals throughout preexposure and all subjects increased consumption over the multiple preexposure sessions (see Table 1). There was no effect of Preexposure Dose, indicating that cocaine exposure had no effect on water intake during this phase. No interactions were significant.

Table 1
Mean water consumption (±SEM) for F344 and LEW rats during the cocaine preexposure period

	Group	F344	LEW
Day 1	Cocaine	9.53±0.36	10.84±0.36
	Vehicle	9.32±0.26	10.53±0.27
Day 10	Cocaine	9.47±0.41	11.13±0.44
	Vehicle	9.65±0.32	10.88±0.39
	Total mean consumption (Days 1–10)[a]	9.29±0.16	10.64±0.17

[a] Total mean consumption (Days 1–10) represents the average water intake over the 10-day preexposure period for each strain, regardless of preexposure group.

Table 2
Mean saccharin consumption (±SEM) for all F344 and LEW rats on Trial 1 of cocaine taste aversion conditioning (regardless of preexposure or conditioning group) and control group consumption on Trials 2 through the Final Test

		F344	LEW
Trial 1		10.19±0.29	12.22±0.30
	Control groups only		
Trial 2	Cocaine–vehicle	12.22±0.68	12.63±0.35
	Vehicle–vehicle	11.69±0.72	12.11±0.51
Trial 3	Cocaine–vehicle	13.39±0.96	13.06±0.50
	Vehicle–vehicle	12.50±0.37	12.06±1.0
Trial 4	Cocaine–vehicle	12.00±0.77	13.44±0.42
	Vehicle–vehicle	12.19±0.82	12.06±0.46
Final Test	Cocaine–vehicle	13.72±0.62	13.56±0.33
	Vehicle–vehicle	12.31±0.66	13.22±0.42

4.2. Conditioning

As noted above, because F344 and LEW rats differed in saccharin consumption on the initial conditioning trial (see Table 2), consumption for each experimental group was converted to a percentage of control consumption. Although by the second conditioning trial control subjects in each strain no longer differed, given the initial difference between strains consumption for all conditioning trials were compared using the percentage transformation. The 2×2×5 repeated-measures ANOVA on the transformed percentage shift from controls revealed significant effects of Trial [$F(3, 84)=84.565$, $p<0.05$] and Preexposure Dose [$F(1, 28)=18.465$, $p<0.05$]. There was no effect of Strain or any interaction with Strain as a factor

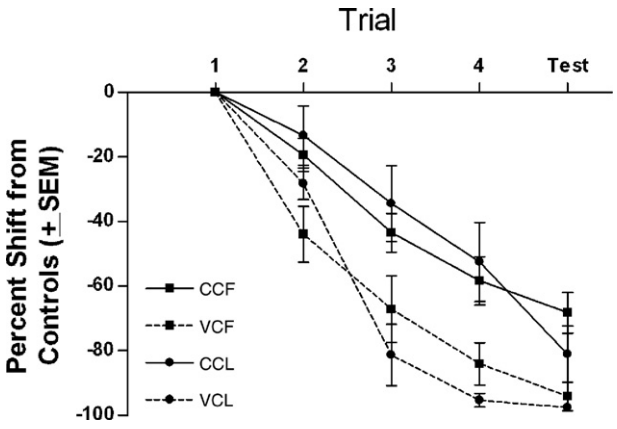

Fig. 1. Percent difference (±SEM) in saccharin consumption from controls for F344 and LEW animals over taste aversion conditioning with cocaine. Significant differences ($p<0.05$) were found between groups that were preexposed with vehicle (groups VCF and VCL; dashed lines) and groups preexposed with cocaine (groups CCF and CCL; solid lines).

[Strain: $F(1, 28)=0.013$, $p=0.912$; Strain × Preexposure: $F(1, 28)=0.164$, $p=0.689$]. All subjects injected with cocaine during conditioning decreased consumption (relative to controls) over repeated trials. This decrease was significantly less in subjects receiving cocaine during preexposure, and there was no difference between the two strains in the degree of attenuation. Fig. 1 illustrates these percentage shifts in saccharin consumption.

5. Discussion

The current study assessed how cocaine history would impact the aversive effects of cocaine in the LEW and F344 rat strains. Given the use of these strains as animal models of drug use and abuse (Ambrosio et al., 1995; Glowa et al., 1994; Haile and Kosten, 2001; Kosten et al., 1994; Kruzich and Xi, 2006a,b; Riley et al., in press; Roma et al., 2006; Werme et al., 1999, 2000), this examination may aid in understanding the interaction of genetic (strain) and environmental (drug history) factors in drug vulnerability.

As described, cocaine induced comparable taste aversions in the two strains, an effect previously reported in comparisons of cocaine-induced taste aversions between F344 and LEW rats (Kosten et al., 1994; Roma et al., 2007; although see Glowa et al., 1994; Grigson and Freet, 2000). Further, preexposure to cocaine (five exposures every other day) comparably attenuated the acquisition of cocaine-induced aversions in these strains. The attenuation reported here is similar to the previously reported effects of cocaine preexposure on cocaine-induced aversions in outbred rats (see Riley and Diamond, 1998; Riley and Simpson, 1999). Also, similar to these reports with outbred rats, after repeated conditioning trials, preexposed subjects of both strains eventually avoided the cocaine-associated solution at levels similar to nonpreexposed subjects. Although the bases for the effects of cocaine preexposure in the taste aversion preparation have not been established (for outbred rats or inbred strains), the effects of drug history on aversion learning are generally discussed in terms of tolerance (or adaptation) to the aversive effects of the drug during preexposure (see Riley and Diamond, 1998; Simpson and Riley, 2005; though see de Brugada et al., 2003). The fact that aversions were attenuated in both strains is consistent with the position that tolerance occurred to cocaine's aversive effects during preexposure and that this tolerance was comparable for the F344 and LEW rats. These data suggest that there was no strain (gene) by drug history (environment) interaction for cocaine within this preparation (for a comparison with alcohol in DBA and C57 mice, see Risinger and Cunningham, 1995).

Although cocaine preexposure had no differential effect on the induction of cocaine taste aversions between the F344 and LEW strains, it is possible that differences might emerge with preexposure to other drugs. In this context, additional groups of male F344 and LEW rats were preexposed to morphine (5 mg/kg) and then conditioned with morphine (5 mg/kg) under the same parameters used for cocaine. F344 animals preexposed to and conditioned with morphine displayed complete attenuation of the morphine-induced aversion, suggesting tolerance to morphine's aversive effects. However, the lack of morphine-induced taste aversions in vehicle-preexposed LEW animals (an effect previously reported by Lancellotti et al., 2001) prevented the assessment of the effects of morphine preexposure in this strain as well as any determination of a strain × history interaction with morphine. Thus, until morphine-induced taste aversions can be demonstrated in the LEW strain, assessing genotype-specific tolerance to morphine's aversive effects with these inbred animals remains difficult.

The basis for the current series of investigations was to assess if there were genotype (strain)/environment (drug history) interactions in taste aversion learning. As we report, this did not appear to be the case with cocaine, as both strains displayed comparable attenuating effects of drug exposure on cocaine-induced aversions. Further work with the F344 and LEW strains with other drugs of abuse is needed to determine the extent (if any) to which these strains display differential changes in drug-induced behaviors (including conditioned taste aversions) following experience with the drug. The interest in assessing the interaction of strain and drug history stems in part from trying to predict abuse liability. Given that drug use and abuse may be a function of the balance of the rewarding and aversive effects of drugs, understanding the various factors (and their interaction) impacting this balance may be useful in predicting vulnerability to drug abuse.

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