Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2007) 1 – 8
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Cross-fostering and the extinction of cocaine's conditioned aversive effects: Evidence for gene-environment interaction

Peter G. Roma *, Anthony L. Riley

Psychopharmacology Laboratory, Department of Psychology, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016, USA

Received 21 February 2007; received in revised form 28 May 2007; accepted 19 June 2007
Available online 28 June 2007

Abstract

Although genetic and early environmental factors interact to affect drug abuse in humans, surprisingly few tractable laboratory animal models have been developed. Using reciprocal cross-fostering of the inbred Fischer and Lewis rat strains, we recently reported significant gene-environment interaction effects on responses to the aversive properties of 32 mg/kg subcutaneous cocaine, but only in females [Roma PG., Davis CM, Riley AL. Effects of cross-fostering on cocaine-induced conditioned taste aversions in Fischer and Lewis rats. Dev Psychobiol 2007;49:172–9]. The present study describes a follow-up analysis tracking the extinction of the equally acquired cocaine aversions in the adult male Fischer and Lewis rats raised by either Fischer or Lewis dams (n=11–12/group). Based on mean consumption, after eight saccharin–saline pairings, the in-fostered Fischer rats never extinguished while the Lewis animals fully extinguished; however, the cross-fostered Fischer rats partially extinguished, while extinction was completely suppressed in the cross-fostered Lewis animals. Based on documented strain differences in avoidance behavior and stress reactivity, the data were interpreted in terms of differential sensitivity to conditioned aversive stimulation. These data join other examples of cross-fostering effects on physiology and behavior in these strains and further support the use of the Fischer–Lewis model for exploring gene-environment interaction in drug-induced phenotypes.

Keywords: Fischer; Lewis; Cocaine; Conditioned taste aversion; Extinction; Avoidance; Gene-environment interaction

1. Introduction

When considering the etiology of psychiatric disorders, compelling demonstrations of the interplay between genetic and early environmental factors have left little room for the conventions of the nature *versus* nurture debate (Meaney, 2001; McClearn, 2004; Moffitt et al., 2006; Robinson, 2004; Rutter et al., 2006). In addition to anxiety and depression, the conceptual framework of gene-environment interaction has also been valuable for understanding the etiology of drug abuse in humans (Cloninger et al., 1982; Dick et al., 2006; Kendler et al., 2005; National Institute on Drug Abuse [NIDA], 1996). In the laboratory, researchers utilize a variety of innovative animal models to explore genetic (Crabbe, 2002) and environmental (Lu et al., 2003) influences on responses to drugs of abuse, but despite acknowledgement of the interactive nature of these factors (Enoch and Goldman, 2001), surprisingly few explicit experimental demonstrations of gene-environment interactions within a developmental framework have been published.

Some notable examples come from the primate literature. For example, female rhesus monkeys that are heterozygous with both long and short allelic variants (l/s) of the serotonin transporter gene promoter region (rh5HTTPLR) show an increased preference for self-administered alcohol compared to their homozygous l/l counterparts. However, the effect of genotype is only evident in l/s animals that were reared in peer-only groups throughout infancy; mother-reared monkeys of both genotypes exhibit identical alcohol preferences (Barr et al., 2004). A similar pattern was also observed with acute intoxication scores in response to intravenous ethanol administration (Barr et al., 2003). Other behavioral pharmacological research directed towards gene-environment interaction comes from Ellenbroek, Cools and colleagues, who, in addition to

* Corresponding author. Tel.: +1 202 885 1721; fax: +1 202 885 1081.
E-mail address: PeteRoma@gmail.com (P.G. Roma).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.06.005

assessing acute stress effects in adulthood (van der Kam et al., 2005a,b, 2006), have explored the effects of specific neonatal manipulations on their selectively bred apomorphine susceptible (APO-SUS) and unsusceptible (APO-UNSUS) lines of Wistar-derived rats (see Ellenbroek and Cools, 2002). Within this presumably genetic model, a single 24-h episode of early maternal deprivation led to increased apomorphine-induced gnawing responses in adult UNSUS rats relative to their non-separated controls, while SUS rats reared by UNSUS dams were significantly less responsive than SUS rats reared by SUS dams (Ellenbroek et al., 2000).

In recent years, our laboratory has begun exploring gene-environment interaction effects with a focus on the aversive properties of abused drugs in the inbred Fischer and Lewis rat strains (Riley et al., in press). Using reciprocal cross-fostering (Ressler, 1962; cf. Gomez-Serrano et al., 2001, 2002) followed by conditioned taste aversion (CTA) training in adulthood, established strain differences in sensitivity to the aversive effects of morphine and cocaine have been shown to be influenced by both genotype and maternal environment. Specifically, Lewis rats are virtually immune to morphine-induced CTA (Lancellotti et al., 2001), yet male Lewis animals reared by Fischer dams developed stronger CTAs to 10 mg/kg morphine than their in-fostered counterparts, with a similar pattern observed in females at 32 mg/kg (Gomez-Serrano, 2005; see Riley et al., in press). Regarding stimulant drugs, although cross-fostering appears not to influence amphetamine-induced locomotor activity in these strains (Wood et al., 2001), the aversive properties of cocaine do appear subject to gene-environment interaction effects. Fischer females acquire weaker cocaine-induced CTAs than do Lewis females (Glowa et al., 1994); however, we recently reported that female Fischer rats reared by Lewis dams acquired aversions induced by 32 mg/kg cocaine equally robust as their counterparts of the Lewis genotype (Roma et al., 2007).

Unlike with morphine, sensitivity to the aversive effects of 32 mg/kg cocaine among Fischer and Lewis males did not vary by genotype or maternal environment, as all groups acquired equally strong CTAs. Nonetheless, this lack of effect during acquisition provided a unique opportunity to assess gene-environment interaction in the extinction of cocaine's conditioned aversive effects. Despite its name, extinction of a learned response is generally recognized as an active learning process rather than the simple loss of an existing association (Rescorla, 2001), and monitoring the extinction of an avoidance response such as drug-induced CTA may reveal differences between groups that are not apparent during acquisition (e.g., Kunin et al., 2001). The following report presents supplementary CTA extinction data from the in-fostered and cross-fostered adult male Fischer and Lewis subjects previously reported to acquire equivalent aversions to 32 mg/kg cocaine (Roma et al., 2007). Given that male Fischer and Lewis rats acquired cocaine-induced aversions at identical rates, this assessment provides a view of strain differences in response to the removal of cocaine's unconditioned aversive effects within a CTA preparation, while the cross-fostering manipulation permits evaluation of gene-environment interactions therein.

2. Method

2.1. Subjects

A total of 60 rats served in the experiment (12 dams and 48 pups); 6 dams and 24 pups were of the Fischer strain (F344/SsNHsd), and 6 dams and 24 pups were of the Lewis strain (LEW/NH). Within 18 h of birth, the pups were assigned to unrelated dams of either their own strain (in-fostered) or of the other strain (cross-fostered). This manipulation created four experimental groups: Fischer pups raised by Fischer dams (F/F), Fischer pups raised by Lewis dams (F/L), Lewis pups raised by Lewis dams (L/L) and Lewis pups raised by Fischer dams (L/F). Animal housing rooms operated on a 12-h light/dark schedule (lights on at 0800 h) and were maintained at an ambient temperature of 23 °C; all CTA procedures were conducted between 0900 h and 1300 h. For additional details of the cross-fostering, rearing and housing conditions for these animals, see Roma et al. (2007). All procedures described in this report were in compliance with the US Animal Welfare Act and National Research Council guidelines (1996, 2003) and were approved by the Institutional Animal Care and Use Committee at American University.

2.2. Drugs and solutions

Cocaine hydrochloride (generously supplied by NIDA) was prepared in a 50 mg/ml solution in saline and administered via subcutaneous (SC) injection at a dose of 32 mg/kg. All non-drug saline injections were also administered SC and were equivolume to cocaine. Sodium Saccharin (Sigma) was prepared as a 1 g/L (0.1%) solution in tap water.

The cocaine dose and concentration profile was intended to replicate Glowa et al. (1994); however, SC cocaine under these conditions is known to produce necrotic lesions at the injection site. Although the strains did not visibly differ in lesion severity, in order to minimize discomfort, each cocaine injection was administered at a different site along each rat's dorsum during acquisition; necrotic sites were also avoided during extinction, with no injections administered at an unhealed site.

2.3. CTA training

2.3.1. Acquisition

As adults, the individually housed animals were maintained on *ad libitum* food, but were acclimated to 20-min per day water access prior to CTA training. During the Acquisition phase, the rats received access to the saccharin solution followed immediately by cocaine injection. The following three days consisted of water access and no injections; this cycle was repeated for a total of five cycles (CTA 1–5). Additional details of the habituation and acquisition procedures conducted in these subjects are described in Roma et al. (2007).

2.3.2. Extinction

The final saccharin presentation of the CTA Acquisition phase described above also served as the first day of the CTA

Extinction phase (EXT), where saccharin consumption was followed by injection of SC saline instead of cocaine. All procedures and conditioning cycles during Extinction were identical to that of Acquisition except 1) saccharin presentations were followed by saline injections, and 2) the Extinction phase was carried out for a total of eight consecutive cycles. The Extinction phase culminated in a final saccharin presentation after the last day of the 8th conditioning cycle.

2.4. Data analysis

The data in this report describe the behavior of 11–12 animals per group. Mean (±SD) saccharin consumption on CTA 1 (Baseline) was 7.47±2.74 ml in animals of the Fischer genotype and 10.54±2.15 ml in animals of the Lewis genotype. A preliminary analysis of variance (ANOVA) revealed that this pre-conditioning difference in consumption was significant ($F(1,42)=18.28$, $p<.001$); therefore, in order to facilitate comparisons across groups, individual data at each trial were expressed as a percent of baseline consumption (i.e., percentage of the amount of saccharin consumed on CTA 1). Formal statistical analysis was accomplished via mixed ANOVA, and post-hoc analyses were conducted via Tukey-corrected comparisons and paired-samples *t*-tests. Statistical significance for all analyses was set at $\alpha=.05$ (two-tailed when applicable).

3. Results

A 12×2×2 mixed ANOVA with a repeated-measures factor of Trial (CTA 1–4, CTA 5/EXT 1, and EXT 2–8) and between-groups factors of Genotype (Fischer or Lewis) and Rearing environment (In-Fostered or Cross-Fostered) was performed with percent of CTA 1 consumption as the dependent variable. The ANOVA yielded a significant main effect of Trial ($F(11,462)=79.86$, $p<.001$) and significant Trial×Genotype ($F(11,462)=3.13$, $p<.001$) and Genotype×Rearing ($F(1,42)=8.77$, $p<.01$) interactions. The main effects of Genotype and Rearing, as well as the Trial×Rearing interaction, were not significant ($Fs<1.72$, $ps>.06$); however, the analysis did reveal a significant Trial×Genotype×Rearing interaction ($F(11,462)=7.10$, $p<.001$). Given the significant interaction of all three factors, Tukey-corrected comparisons were performed in order to determine specific between-groups differences at each trial. Response patterns within each group across the experiment were evaluated by paired-samples *t*-tests at consecutive trials (except where noted).

3.1. CTA acquisition

As previously reported in these subjects (Roma et al., 2007), there were no between-groups differences in the strength of the CTA response through CTA 5/EXT 1 ($ps>.40$). For all groups, consumption decreased from CTAs 1 to 2 ($ts>12.45$, $ps<.001$), but consumption on CTAs 3 and 4 did not differ in any group ($ts<1.84$, $ps>.09$).

3.2. CTA extinction

Saccharin consumption did not differ between groups from CTA 5/EXT 1 through EXT 5 ($ps>.10$). However, as seen in Fig. 1, the variations in within-group patterns of extinction produced both strain differences and cross-fostering effects.

3.2.1. Strain differences

Significant decreases in consumption by the in-fostered Fischer animals (F/F) ceased by CTA 3, and no two subsequent consecutive trials differed through EXT 8 ($t(10)s<2.04$, $ps>.06$). The F/F group's failure to extinguish was also evident in their significantly lower consumption on EXT 8 compared to CTA 1 ($t(10)=12.90$, $p<.001$). In contrast, the in-fostered Lewis animals (L/L) reached their maximum aversion at CTA 2, but began to emerge from their avoidance response by the 5th

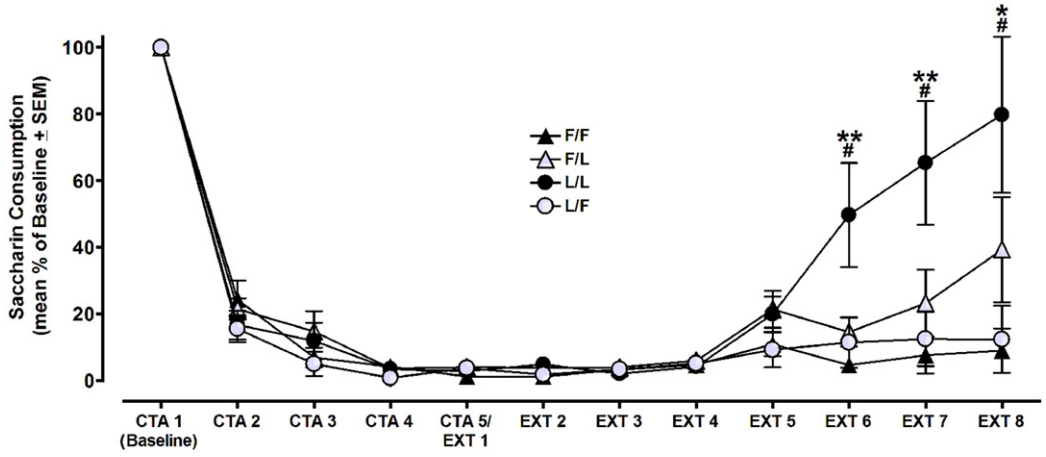

Fig. 1. Acquisition and extinction of conditioned taste aversions induced by 32 mg/kg SC cocaine in adult male Fischer and Lewis rats reared by Fischer or Lewis dams. F/F=Fischer rats raised by Fischer dams (in-fostered), F/L=Fischer raised by Lewis (cross-fostered), L/L=Lewis raised by Lewis, L/F=Lewis raised by Fischer ($n=11–12$ per group). All groups acquired equally robust aversions; however, pronounced strain differences and gene-environment interaction effects emerged during extinction. Significant strain differences in mean saccharin consumption (F/F vs. L/L) are indicated by * ($p<.05$) and ** ($p<.01$); significant cross-fostering effect (L/L vs. L/F) is indicated by # ($p<.05$). Acquisition data (CTA 1-CTA 5) redrawn from Roma et al. (2007).

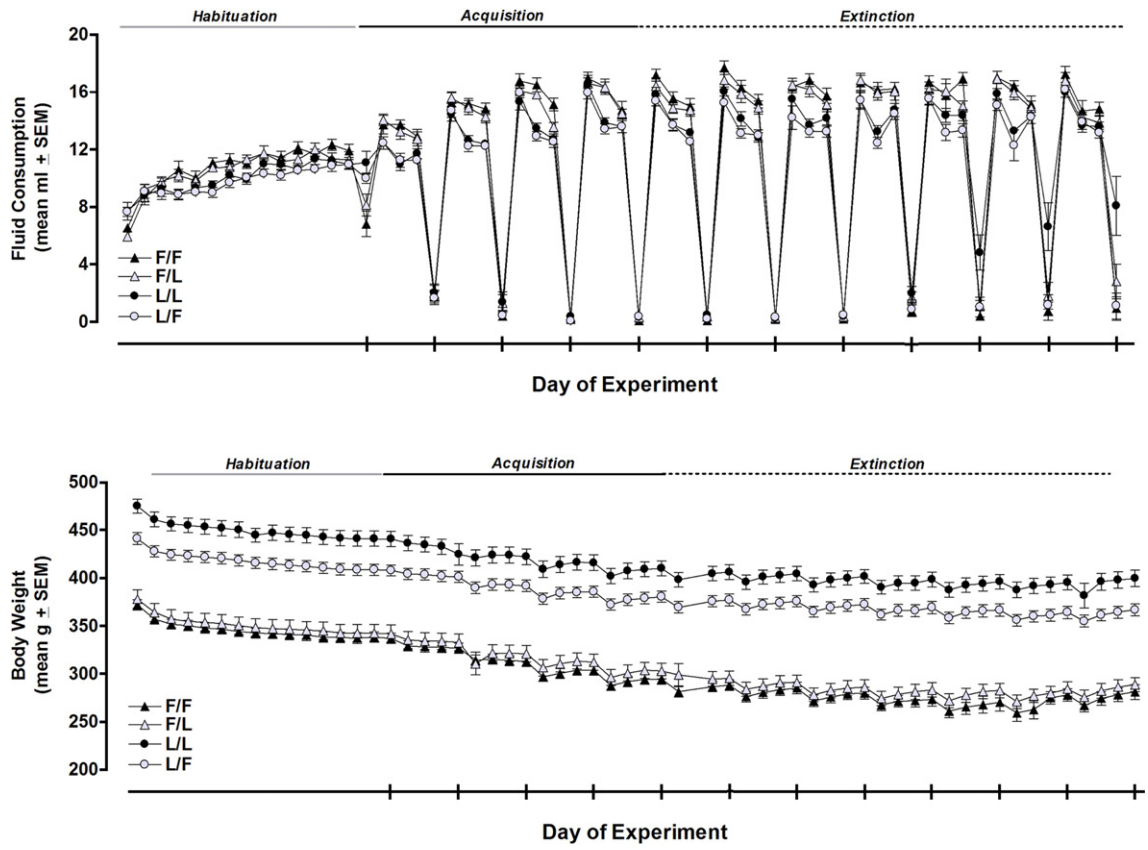

Fig. 2. Raw daily mean fluid consumption (top panel) and body weights (bottom panel) across the entire CTA procedure. Within each panel, the days comprising each phase of the experiment are indicated by the horizontal overhead lines: Habituation = solid gray, Acquisition = solid black and Extinction = broken black. Tick-marks along the *x*-axis denote the presentation of saccharin during the daily fluid-access period; all other days were water. F/F = Fischer rats raised by Fischer dams (in-fostered), F/L = Fischer raised by Lewis (cross-fostered), L/L = Lewis raised by Lewis, L/F = Lewis raised by Fischer (n = 11–12 per group).

extinction trial (EXT 4 vs. EXT 5: $t(11) = 2.97$, $p < .05$). Saccharin consumption then increased on consecutive trials from EXT 4 through EXT 8 ($t(10)$s < 2.44, ps $< .05$), and by the 7th extinction trial, mean consumption did not differ from pre-conditioning baseline ($t(11) = 1.86$, $p > .08$). Significant differences in mean consumption between the F/F and L/L groups were confirmed at extinction trials 6, 7, and 8 (ps $< .05$).

3.2.2. Cross-fostering effects

Like their in-fostered F/F counterparts, significant decreases in consumption by the F/L animals ceased by CTA 3; however, consumption did increase significantly from EXT 4–5 ($t(10) = 2.30$, $p < .05$), but despite this partial extinction, mean consumption did not differ between the F/F and F/L groups at any trial (ps $> .30$). The most striking cross-fostering effects were observed among the animals of the Lewis genotype. Specifically, mean consumption in the cross-fostered Lewis group (L/F) was identical to that of the in-fostered Fischer rats (F/F), with maximum suppression at CTA 3 and no sequential increases in consumption through EXT 8 (absolute $t(10)$ s < 2.03, ps $> .06$). Indeed, there were no differences between the L/F and F/F groups at any trial (ps $> .40$). Direct comparison between the in-fostered Lewis animals (L/L) and their cross-fostered L/F counterparts confirmed that the L/L animals consumed significantly more saccharin on EXT 6, EXT 7 and EXT 8 (ps $< .05$). For reference, mean body weights and raw fluid consumption values for all groups across the entire experiment are presented in Fig. 2.

4. Discussion

The present study revealed significant strain differences and cross-fostering effects on the extinction of cocaine-induced conditioned taste aversions in male Fischer and Lewis rats. As previously reported (Roma et al., 2007), the saccharin avoidance response was acquired at comparable rates in these subjects; however, the follow-up data described here revealed marked differences in the extinction of cocaine's conditioned aversive effects. A basic strain difference in mean consumption was observed between the F/F and L/L animals, with full extinction in the L/L group but no extinction in the F/F group. In terms of cross-fostering, unlike their in-fostered F/F counterparts, the F/L rats significantly increased saccharin consumption during extinction, although they never returned to pre-conditioning levels. However, the most profound gene-environment interaction effect was seen in the Lewis animals. Specifically, the in-fostered L/L rats consumed significantly more saccharin on average than all other groups during the last three extinction trials, whereas their cross-fostered L/F counterparts exhibited no signs of extinction throughout the procedure,

mimicking the strain difference produced by the similarly reared F/F group.

Although other parametrically diverse assessments of cocaine-induced CTA in male Fischer and Lewis rats have been made (Grigson and Freet, 2000; Kosten et al., 1994), to the best of our knowledge, this is the only published report directly comparing the strains' extinction of CTA induced by any compound. As a learning phenomenon, extinction is generally viewed as distinct from acquisition, even in aversively motivated designs, because of the inherent invocation of inhibitory processes that counter the previously conditioned behavior (Myers and Davis, 2002; Rescorla, 2001). In CTA, this is complicated by the fact that the avoidance response conditioned during acquisition is itself an inhibition of a consummatory drive. Although the theoretical implications of these considerations remain to be explored, an extensive body of empirical literature indicates a clear difference between the two procedures, where group differences (or lack thereof) during CTA acquisition do not necessarily correspond to differences during extinction (e.g., Chambers, 1985; Chambers and Hayes, 2002; Kunin et al., 2001). Regarding the present study's focus on the extinction of cocaine-induced CTA, the lack of similar assessments in these strains presents an obvious challenge for data interpretation; however, a number of motivational and physiological explanations may be informative, especially when viewed in light of other avoidance preparations tested in these strains as well as work done specifically on CTA extinction outside the Fischer–Lewis model.

Before entertaining more complex interpretations of the data, plausible simpler alternatives must first be considered. Principal among them is the possibility of differential effects of the fluid restriction inherent to the CTA procedures. Although other fluid access designs are also effective (e.g., Grigson, 1997; Smith et al., 2004), the relatively conservative method employed in our laboratory could have exerted an undue influence on consumption, in this case, a unique susceptibility of the L/L animals leading to increased saccharin consumption despite equal resistance to extinction. Such an account is parsimonious, but is not supported by the mean raw consumption values and body weight data presented in Fig. 2. While absolute body weights paralleled the extinction data, with the L/L rats weighing significantly more than all other groups (statistics not shown; cf. Gomez-Serrano et al., 2002), all four groups still exhibited identical patterns of weight loss and gain across conditioning cycles. Also, despite the differences in saccharin consumption, animals of the Lewis genotype actually consumed *less* than the Fischer rats during intervening water-recovery days, suggesting, if anything, reduced sensitivity to fluid restriction and less need to consume the cocaine-associated saccharin. Moreover, even if the fluid deprivation data could account for the strain difference between the F/F and L/L groups, water consumption varied only by genotype, thereby rendering these data incapable of explaining the cross-fostering effects on saccharin consumption. Another possibility is that of a generally stronger preference for saccharin in the L/L animals, which could have led to increased consumption relative to the other groups despite equal persistence of the conditioned aversion. This hypothesis appears supported by the higher levels of saccharin consumption on CTA 1; however, every CTA experiment conducted in our laboratory with exclusively vehicle-treated control groups of these strains has shown equivalent absolute saccharin consumption either at baseline or from the second trial onward, if not significantly greater increases in consumption among the initially neophobic Fischer rats (Foynes and Riley, 2004; Glowa et al., 1994; Lancellotti et al., 2001; Pescatore et al., 2005; Roma et al., 2006). This suggests at least an equal preference for the saccharin solution under the conditions imposed during CTA (and no differential sensitivity to injection), if not a greater preference among the smaller Fischer animals if the equivalent absolute consumption values are transformed to ml consumed per kg of body weight. A final consideration is that of strain differences in basic learning ability. Although we are not aware of any explicit tests of passive avoidance extinction in these strains, differential learning ability still seems an unlikely mechanism since previous research comparing Fischer and Lewis rats has shown comparable performances in acquisition of operant responding for food (Haile and Kosten, 2001; Kearns et al., 2006) as well as in LiCl-induced CTA (Foynes and Riley, 2004; Grigson and Freet, 2000). Most damning to a purely learning account is the fact that all groups in the present study acquired the aversion equally in terms of rate, suggesting that the strain differences and cross-fostering effects that emerged during extinction were not dependent upon the conditioning parameters employed; however, the possibility of a "floor effect" in the peak aversion at CTA 5 should be considered.

Even if one dismisses simple physiological alternative hypotheses and accepts equivalent underlying learning ability in these groups of Fischer and Lewis rats, there were still obvious differences in behavior that call for interpretation. Although consensus has not been reached on the exact nature of the avoidance response seen in CTAs induced by drugs of abuse (Broadbent et al., 2002; Ettenberg, 2004; Grigson, 1997; Parker, 1995; Riley and Tuck, 1985; Stolerman and D'Mello, 1981), aversive subjective effects during initial exposures are often reported in the human drug abuse literature (Baker and Cannon, 1982; Evans and Levin, 2004; Griffiths et al., 2003; Zacny and Gutierrez, 2003), and this is the interpretation we favor, with the CTA assay as an animal model inherently biased towards conditioning to the aversive effects of compounds with bivalent stimulus properties paired with novel flavors. Assuming that there is indeed something aversive about SC cocaine in rats, known strain differences in aversively motivated conditioning and biobehavioral stress reactivity may produce a reasonable, albeit speculative, account of the extinction data presented here.

Regardless of sex, Fischer rats tend to show stronger responses than Lewis rats in conventional shuttle-box shock escape experiments, as well as greater suppression of drinking in a conditioned emotional response design (Katzev and Mills, 1974; Stöhr et al., 2000, 1998b). In addition, male Fischer rats habituate less than male Lewis rats during tests of acoustic startle reactivity (Varty and Geyer, 1998), while locomotor responses to repeated exposures to a novel environment actually increase (sensitize) in Fischer rats, but decrease (habituate) in the Lewis strain (Stöhr et al., 1998a). Although Fischers engage in less freezing behavior than Lewis during tone-shock pairings in the acquisition phase of a conditioned

fear preparation, they show markedly more freezing than Lewis subjects when subsequently tested without tone or shock in the conditioning chamber or when tested in a neutral chamber with continuous exposure to the tone alone (Pryce et al., 1999). Taken together, these data suggest greater emotionality in response to conditioned aversive stimulation in Fischer rats relative to Lewis counterparts. Although the strength of the cocaine dose administered during CTA acquisition may have produced equal avoidance in all groups, in terms of extinction, the F/F group's resistance to accept the saccharin as no longer predictive of cocaine's aversive effects (Chambers, 1985) is consistent with the US-free tests of conditioned fear described above.

A number of neurobiological systems are also known to be involved in CTA extinction, for example, estradiol and vasopressin generally accelerate whereas testosterone generally retards extinction of LiCl-induced aversions (Brownson et al., 1994; Hayes and Chambers, 2005; Yuan and Chambers, 1999). Unfortunately, and unlike the mesolimbic dopamine system so crucial for drug reward (see Kosten and Ambrosio, 2002), these systems have not received much systematic attention in Fischer and Lewis rats (Inaguma et al., 2003), and their relevance to CTAs induced by drugs of abuse such as cocaine awaits exploration. However, additional support for a motivational hypothesis of differential sensitivity to aversive stimuli may actually be drawn from the extensive body of work on physiological stress reactivity in these strains. It is well-documented that adult Fischer animals show greater stress-induced hypothalamic-pituitary-adrenal (HPA) axis activation than Lewis (see Kosten and Ambrosio, 2002; Grakalic et al., 2006). This is particularly interesting given the positive correlation between ACTH and corticosterone and resistance to extinction of LiCl-induced CTA, with higher levels of these stress hormones associated with more protracted avoidance (Chambers, 1982; Levine et al., 1977; Smotherman, 1985). If the extinction of cocaine-induced CTA operates under similar mechanisms, then at least the lack of recovery in the F/F groups versus the L/L animals may be explained.

Whatever the endogenous processes mediating the basic strain differences in cocaine CTA extinction may be, we consider the most compelling aspect of the data presented here to be the cross-fostering effects. As with the acquisition of morphine-and cocaine-induced CTAs in Fischer and Lewis rats, genotype alone simply cannot account for the drug-conditioned phenotypes observed in the present study. Even as mature adults, rearing in the Lewis maternal environment produced partial extinction in rats of the Fischer genotype, yet rearing in the Fischer maternal environment completely prevented extinction in rats of the Lewis genotype. This gene-environment interaction effect was thus bidirectional (i.e., both strains were affected by cross-fostering) but asymmetrical (i.e., the cross-fostering effect was stronger in the Lewis strain). This pattern differs from the body weight data, where only the Lewis animals were affected by cross-fostering, although the direction of the effect was the same as in the behavioral data. Also intriguing is the fact that in our initial report of cocaine CTA acquisition (Roma et al., 2007), cross-fostering only affected Fischer females, whereas both sexes and strains were affected in some way by cross-fostering during acquisition of morphine-induced CTAs (Gomez-Serrano, 2005; see Riley et al., in press). Although this presentation is the only known published report of CTA extinction directly comparing these strains, the males did not appear affected by cross-fostering during acquisition, but only during extinction. Even without sex differences superimposed, these data suggest a rather complex interaction between drug, dose and assay, and regardless of the specific patterns observed, further underscore the profound and enduring nature of epigenetic influences on physiology and behavior in Fischer and Lewis rats.

In conclusion, fostering rats of the Fischer and Lewis genotypes into Fischer or Lewis maternal environments revealed strain differences and produced significant gene-environment interaction effects on the extinction of cocaine-induced conditioned taste aversions in mature adult males. Fischer animals raised by Fischer dams failed to extinguish their avoidance response, whereas mean consumption in Lewis animals raised by Lewis dams returned to baseline levels. Cross-fostering produced partial extinction in the Fischer animals and completely suppressed extinction in the Lewis. The strain differences data are consistent with documented differences in avoidance responding and conditioned fear and indicate a crucial role of the pre-weaning environment in the development of sensitivity to conditioned aversive stimulation. Given the hypothesized balance between aversion and reward in predicting a drug's abuse potential or an individual's abuse liability (see Riley et al., in press), the more rapid extinction of cocaine's conditioned aversive effects in the L/L versus F/F rats may render the in-fostered Lewis animals more susceptible to relapse or reinstatement of drug-seeking behavior. Although not directly tested in the present study, this idea is tentatively supported by recent self-administration work in Fischer and Lewis rats (see Kruzich and Xi, 2006, Figs. 2 and 4), while the cross-fostering effects in both strains reveal considerable plasticity in this particular aspect of genetically influenced vulnerability to addiction. It is not known exactly what features of the Lewis maternal environment facilitate cocaine CTA extinction or drug abuse vulnerability in general, or exactly what features of the Fischer genotype confer resistance (see Roma et al., 2007 for a discussion). However, the data presented here further demonstrate the utility of systematically comparing Fischer and Lewis rats' responses to early environmental manipulations for assessing genetic and environmental contributions to adult biobehavioral phenotypes (Gomez-Serrano et al., 2001, 2002; Ellenbroek and Cools, 2000; Varty and Geyer, 1998) and further support the viability of cross-fostering within the Fischer–Lewis model for assessing gene-environment interaction effects in assays of the motivational properties of drugs.

Acknowledgements

We thank Elizabeth Lawrence for her assistance with the cross-fostering procedures. This research was supported by a grant from the Mellon Foundation to A.L.R.

References

Baker, TB, Cannon, DS. Alcohol and taste-mediated learning. Addict Behav 1982;7:211–30.

Barr, CS, Newman, TK, Becker, ML, Champoux, M, Lesch, KP, Suomi, SJ, et al. Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress. Alcohol Clin Exp Res 2003;27:812–7.

Barr, CS, Newman, TK, Lindell, S, Shannon, C, Champoux, M, Lesch, KP, et al. Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. Arch Gen Psychiatry 2004;61:1146–52.

Broadbent, J, Muccino, KJ, Cunningham, CL. Ethanol-induced conditioned taste aversion ini 15 inbred mouse strains. Behav Neurosci 2002;116:138–48.

Brownson, EA, Sengstake, CB, Chambers, KC. The role of serum testosterone in the accelerated extinction of a conditioned taste aversion in fluid deprived male rats. Physiol Behav 1994;55:273–8.

Chambers, KC. Failure of ACTH to prolong extinction of a conditioned taste aversion in the absence of the testes. Physiol Behav 1982;29:915–9.

Chambers, KC. Sexual dimorphisms as an index of hormonal influences on conditioned food aversions. Ann N Y Acad Sci 1985;443:110–25.

Chambers, KC, Hayes, UL. Exposure to estradiol before but not during acquisition of LiCl-induced conditioned taste avoidance accelerates extinction. Horm Behav 2002;41:297–305.

Cloninger, RC, Sigvardsson, S, Bohman, M, von Knorring, A-L. Predisposition to petty criminality in Swedish adoptees II: Cross-fostering analysis of gene-environment interaction. Arch Gen Psychiatry 1982;39:1242–7.

Crabbe, JC. Genetic contributions to addiction. Ann Rev Psychol 2002;53: 435–62.

Dick, DM, Agrawal, A, Shuckit, MA, Bierut, L, Hinrichs, A, Fox, L, et al. Marital status, alcohol dependence, and GABARA2: evidence for gene-environment correlation and interaction. J Stud Alcohol 2006;67:185–94.

Ellenbroek, BA, Cools, AR. The long-term effects of maternal deprivation depend on the genetic background. Neuropsychopharmacology 2000;23: 99–106.

Ellenbroek, BA, Cools, AR. Apomorphine susceptibility and animal models for psychopathology: genes and environment. Behav Genet 2002;32:349–61.

Ellenbroek, BA, Sluyter, F, Cools, AR. The role of genetic and early environmental factors in determining apomorphine susceptibility. Psychopharmacology (Berl) 2000;148:124–31.

Enoch, M-A, Goldman, D. The genetics of alcoholism and alcohol abuse. Curr Psychiatry Rep 2001;3:144–51.

Ettenberg, A. Opponent process properties of self-administered cocaine. Neurosci Biobehav Rev 2004;27:721–8.

Evans, SM, Levin, FR. Differential response to alcohol in light and moderate female social drinkers. Behav Pharmacol 2004;15:167–81.

Foynes, MM, Riley, AL. Lithium-chloride-induced conditioned taste aversions in the Lewis and Fischer 344 rat strains. Pharmacol Biochem Behav 2004;79: 303–8.

Glowa, JR, Shaw, AE, Riley, AL. Cocaine-induced conditioned taste aversions: comparisons between effects in LEW/N and F344/N rat strains. Psychopharmacology (Berl) 1994;114:229–32.

Grakalic, I, Schindler, CW, Baumann, MH, Rice, KC, Riley, AL. Effects of stress modulation on morphine-induced conditioned place preferences and plasma corticosterone levels in Fischer, Lewis, and Sprague-Dawley rat strains. Psychopharmacology (Berl) 2006;189:277–86.

Griffiths, RR, Bigelow, GE, Ator, NA. Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend 2003;70:S41–54.

Grigson, PS. Conditioned taste aversions and drugs of abuse: a reinterpretation. Behav Neurosci 1997;111:129–36.

Grigson, PS, Freet, CS. The suppressive effects of sucrose and cocaine, but not lithium chloride, are greater in Lewis than in Fischer rats: evidence for the reward comparison hypothesis. Behav Neurosci 2000;114:353–63.

Gomez-Serrano, MA. The effects of cross-fostering on morphine-induced conditioned taste aversion in fischer and lewis rats (Doctoral dissertation, American University, 2004). Dissertation Abstracts International 2005;65 (7-B): 3692.

Gomez-Serrano, M, Tonelli, L, Listwak, S, Sternberg, E, Riley, AL. Effects of cross fostering on open-field behavior, acoustic startle, lipopolysaccharide-induced corticosterone release, and body weight in Lewis and Fischer rats. Behav Genet 2001;31:427–36.

Gomez-Serrano, MA, Sternberg, EM, Riley, AL. Maternal behavior in F344/N and LEW/N rats: Effects on carrageenan-induced inflammatory reactivity and body weight. Physiol Behav 2002;75:493–505.

Haile, CN, Kosten, TA. Differential effects of D1-and D2-like compounds on cocaine self-administration in Lewis and Fischer 344 inbred rats. J Pharmacol Exp Ther 2001;299:509–18.

Hayes, UL, Chambers, KC. Peripheral vasopressin accelerates extinction of conditioned taste avoidance. Physiol Behav 2005;84:147–56.

Inaguma, S, Takahashi, S, Ohnishi, H, Suzuki, S, Cho, Y-M, Shirai, T. High susceptibility of the ACI and spontaneously hypertensive rat (SHR) strains to 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) prostate carcinogenesis. Cancer Sci 2003;94:974–9.

Katzev, RD, Mills, SK. Strain differences in avoidance conditioning as a function of the classical CS-US contingency. J Comp Physiol Psychol 1974;87: 661–71.

Kearns, DN, Gomez-Serrano, MA, Weiss, SJ, Riley, AL. A comparison of Lewis and Fischer rat strains on autoshaping (sign-tracking), discrimination reversal learning and negative auto-maintenance. Behav Brain Res 2006;169: 193–200.

Kendler, KS, Gardner, C, Jacobson, KC, Neale, MC, Prescott, CA. Genetic and environmental influences on illicit drug use and tobacco use across birth cohorts. Psychol Med 2005;35:1–8.

Kosten, TA, Ambrosio, E. HPA axis function and drug addictive behaviors: insights from studies with Lewis and Fischer 344 inbred rats. Psychoneuroendocrinology 2002;27:35–69.

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

Kruzich, PJ, Xi, J. Different patterns of pharmacological reinstatement of cocaine-seeking behavior between Fischer 344 and Lewis rats. Psychopharmacology (Berl) 2006;187:22–9.

Kunin, D, Gaskin, S, Borjas, MB, Smith, BR, Amit, Z. Differences in locomotor response to an inescapable novel environment predict sensitivity to aversive effects of amphetamine. Behav Pharmacol 2001;12:61–7.

Lancellotti, D, Bayer, BM, Glowa, JR, Houghtling, RA, Riley, AL. Morphine-induced conditioned taste aversions in the LEW/N and F344/N rat strains. Pharmacol Biochem Behav 2001;68:603–10.

Levine, S, Smotherman, WP, Hennessy, JW. Pituitary-adrenal hormones and learned taste aversion. In: Miller LH, Sandman CA, Kastin AJ, editors. Neuropeptide influences on the brain and behavior. New York: Raven Press; 1977. p. 163–77.

Lu, L, Shepard, JD, Hall, FS, Shaham, Y. Effect of environmental stressors on opiate and psychostimulant reinforcement, reinstatement and discrimination in rats: a review. Neurosci Biobehav Rev 2003;27:457–91.

McClearn, GE. Nature and nurture: interaction and coaction. Am J Med Genet B Neuropsychiatr Genet 2004;124:124–30.

Meaney, MJ. Nature, nurture, and the disunity of knowledge. Ann N Y Acad Sci 2001;935:50–61.

Moffitt, TE, Caspi, A, Rutter, M. Measured gene-environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. Perspect Psychol Sci 2006;1:5–27.

Myers, KM, Davis, M. Behavioral and neural analysis of extinction. Neuron 2002;36:567–84.

National Institute on Drug Abuse. Individual differences in the biobehavioral etiology of drug abuse (No. 96-4034). Washington, DC: Government Printing Office; 1996.

National Research Council. Guide for the care and use of laboratory animals. Washington, DC: National Academy Press; 1996.

National Research Council. Guidelines for the care and use of mammals in neuroscience and behavioral research. Washington, DC: National Academy Press; 2003.

Parker, LA. Rewarding drugs produce taste avoidance, but not taste aversion. Neurosci Biobehav Rev 1995;19:143–51.

Pescatore, KA, Glowa, JR, Riley, AL. Strain differences in the acquisition of nicotine-induced conditioned taste aversion. Pharmacol Biochem Behav 2005:751–7.

Pryce, CR, Lehmann, J, Feldon, J. Effect of sex on fear conditioning is similar for context and discrete CS in Wistar, Lewis and Fischer rat strains. Pharmacol Biochem Behav 1999;64:753–9.

Rescorla, RA. Experimental extinction. In: Mowrer RR, Klein SB, editors. Handbook of contemporary learning theories. Mahwah, NJ: Erlbaum; 2001. p. 119–54.

Ressler, RH. Parental handling in two strains of mice reared by foster parents. Science 1962;137:129–30.

Riley, AL, Tuck, DL. Conditioned taste aversions: a behavioral index of toxicity. Ann N Y Acad Sci 1985;443:272–92.

Riley AL, Davis CM, Roma PG. Strain differences in taste aversion learning: Implications for animal models of drug abuse. In: Reilly S, Schachtman TR, editors. Conditioned taste aversion: Behavioral and neural processes. New York: Oxford University Press; in press.

Robinson, GE. Beyond nature and nurture. Science 2004;304:397–9.

Roma, PG, Flint, WW, Higley, JD, Riley, AL. Assessment of the aversive and rewarding effects of alcohol in Fischer and Lewis rats. Psychopharmacology (Berl) 2006;189:187–99.

Roma, PG, Davis, CM, Riley, AL. Effects of cross-fostering on cocaine-induced conditioned taste aversions in Fischer and Lewis rats. Dev Psychobiol 2007;49: 172–9.

Rutter, M, Moffitt, TE, Caspi, A. Gene-environment interplay and psychopathology: multiple varieties but real effects. J Child Psychol Psychiatry 2006;47: 226–61.

Smith, ME, Norgren, R, Grigson, PS. A mixed design reveals that glucose moieties facilitate extinction of a conditioned taste aversion in rats. Learn Behav 2004;32:454–62.

Smotherman, WP. Glucocorticoid and other hormonal substrates of conditioned taste aversion. Ann N Y Acad Sci 1985;443:126–44.

Stöhr, T, Wermeling, DS, Weiner, I, Feldon, J. Rat strain differences in open-field behavior and the locomotor stimulating and rewarding effects of amphetamine. Pharmacol Biochem Behav 1998a;59:813–8.

Stöhr, T, Wermeling, DS, Szuran, T, Pliska, V, Domeney, A, Welzl, H, et al. Differential effects of prenatal stress in two inbred strains of rats. Pharmacol Biochem Behav 1998b;59:799–805.

Stöhr, T, Szuran, T, Welzl, H, Pliska, V, Feldon, J, Pryce, CR. Lewis/Fischer rat strain differences in endocrine and behavioural responses to environmental challenge. Pharmacol Biochem Behav 2000;67:809–19.

Stolerman, IP, D'Mello, GD. Oral self-administration and the relevance of conditioned taste aversions. In: Thompson, PB, Dews,, McKim, WA, editors. Advances in behavioral pharmacology. Hillsdale, NJ: L. Erlbaum; 1981. p. 169–214.

van der Kam, EL, Coolen, JCM, Ellenbroek, BA, Cools, AR. The effects of stress on alcohol consumption: mild acute and sub-chronic stressors differentially affect apomorphine susceptible and unsusceptible rats. Life Sci 2005a;76:1759–70.

van der Kam, EL, Ellenbroek, BA, Cools, AR. Gene-environment interactions determine the individual variability in cocaine self-administration. Neuropharmacology 2005b;48:685–95.

van der Kam, EL, Coolen, JCM, Ellenbroek, BA, Cools, AR. Expression of cocaine-induced conditioned place preference in apomorphine susceptible and unsusceptible rats. Behav Pharmacol 2006;17:331–40.

Varty, GB, Geyer, MA. Effects of isolation rearing on startle reactivity, habituation, and prepulse inhibition in male Lewis, Sprague-Dawley, and Fischer 344 rats. Behav Neurosci 1998;112:1450–7.

Wood, GK, Marcotte, ER, Quirion, R, Srivastava, LK. Strain differences in the behavioural outcome of neonatal ventral hippocampal lesions are determined by the postnatal environment and not genetic factors. Eur J Neurosci 2001;14:1030–4.

Yuan, DL, Chambers, KC. Estradiol accelerates extinction of a conditioned taste aversion in female and male rats. Horm Behav 1999;36:1–16.

Zacny, JP, Gutierrez, S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. Psychopharmacology (Berl) 2003;170:242–54.