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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

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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

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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