

# Cross-Fostering Effects on the Extinction of Cocaine-Induced Taste Aversions in the Fischer and Lewis Rat Strains

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## Introduction

Inbred rodent strains provide valuable information about genetic differences and the subsequent physiological and behavioral consequences that arise. Two widely used strains, Fischer (F344) and Lewis (LEW), show dissimilar reactivity to a variety of drugs of abuse, including cocaine and morphine (Kosten & Ambrosio, 2002). For example, LEW rats will readily self-administer cocaine and morphine to a greater extent compared to F344. LEW animals also develop greater conditioned place preferences to cocaine and morphine. Furthermore, F344 rats develop stronger taste aversions to morphine and weaker aversions to cocaine compared to LEW animals. Even though these differences seem to lie in the genetic variation between these strains, salient environmental events early in development have been shown to be an important mediator of physiological, behavioral, and neurochemical responses to many stimuli.

Psychosocial stressors during the early postnatal period, such as prolonged maternal separation, have been shown to permanently alter adult biobehavioral responses to stress in outbred rats (Francis, Diorio, Plotsky, & Meaney, 2002). These alterations include increased levels of plasma corticosterone in response to stressful stimuli, heightened behavioral reactivity to stressors, and decreased levels of mGluR mRNA. Furthermore, individual differences in the quality of dams' early postnatal care correlate with differences in their pups' adult stress reactivity (Meaney, 2001).

The differences between the F344 and LEW strains have for the most part been attributed solely to genetic factors. However, Gomez-Serrano, Tonelli, Listwak, Sternberg, & Riley (2001) tested F344 and LEW rats that were reared by either dams of their own strain (in-fostered) or dams of the other strain (cross-fostered) for a number of HPA axis and stress-related measures. Significant strain differences in maternal behavior were observed, and the cross-fostering manipulation decreased the differences usually seen between the strains. Therefore, the stress response in these inbred strains is not completely genetically mediated; the maternal environment exerts some control over the HPA axis in outbred as well as inbred rat strains.

The cross-fostering experiment described above was related to HPA axis regulation and stress reactivity, not drug abuse liability *per se*. As such, it was of interest to determine what affects the postnatal environment in the form of cross-fostering may have on either of the strains' responses to drugs of abuse. To determine how early experience modulates drug acceptability, the present experiment assessed the role of genetic strain and maternal environment on expression and retention of cocaine-induced conditioned taste aversions in F344 and LEW rats.

## Method

### Subjects

Pregnant dams were obtained from Harlan Sprague-Dawley. Within 18 hours of birth, pups were randomly assigned to unrelated dams of either their own strain (in-fostered) or the other strain (cross-fostered). This manipulation created four groups: F344 pups raised by F344 dams ( $n = 12$ ), F344 pups raised by LEW dams ( $n = 12$ ), LEW pups raised by LEW dams ( $n = 12$ ), and LEW pups raised by F344 dams ( $n = 12$ ). All pups were weaned at postnatal day 22 and group housed with same-sex littermates; at 60 days they were placed in individual wire mesh cages. Testing began at 180 days.

### Apparatus

Animals were individually housed in hanging wire mesh cages with *ad-libitum* access to food. They were maintained on a 12:12 light:dark cycle (lights on at 0800 h) and at a temperature of 23°C. Graduated 50-ml Nalgene tubes were attached to the front of the cage, providing either water or saccharin during the 20-min fluid access period.

### Drugs

Cocaine HCl (generously supplied by NIDA) was prepared in a solution in saline and administered subcutaneously (sc). Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1g/L solution in tap water.

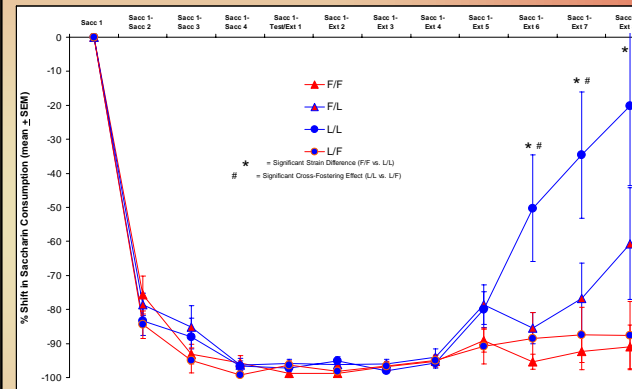
### Procedure

**Phase I: Habituation.** Following 23 hours of water deprivation, subjects were given 20-min access to water daily for 14 consecutive days.

**Phase II: Conditioning and Final Aversion Test.** On Day 1 of this phase, all subjects were given 20-min access to a novel saccharin solution during the fluid access period. Immediately following saccharin, all animals were administered 32 mg/kg dose of cocaine. (animals were not ranked on saccharin consumption due to the cross-fostering manipulation). On Days 2-4 of the cycle, all subjects received water during the fluid-access period. Days 1-4 comprised a cycle; a total of four conditioning cycles were performed. On the day immediately following the last water recovery day of the last cycle, subjects were given access to saccharin followed by a non-drug saline injection. The Final Aversion Test also served as the first Extinction trial.

**Phase III: Extinction.** Extinction was conducted identically to the Conditioning phase, except each saccharin presentation was followed by a non-drug saline injection (equivalent to cocaine). The Extinction phase was carried out for 8 cycles.

## Results



An 11 (Trial) x 2 (Pup Strain) x 2 (Dam Strain) mixed ANOVA yielded significant terms involving all three factors ( $F_s \geq 3.356$ ,  $p_s \leq .004$ ). Tukey-corrected post-hoc comparisons revealed no significant strain differences or cross-fostering effects during the acquisition or peak expression of cocaine-induced CTA; however, significant differences were found during the Extinction phase.

Specifically, the return to baseline levels of saccharin consumption over Extinction trials 6, 7, & 8 was greater in the L/L animals compared to the F/F animals ( $p_s \leq .011$ ). However, this strain difference was attenuated in the cross-fostered F344 animals during trials 7 & 8, whose consumption did not differ from their LEW counterparts also raised by LEW dams ( $p_s \geq .073$ ). Moreover, the LEW animals reared by F344 dams did not differ from the F344 animals also reared by F344 dams at any trial ( $p_s \geq .953$ ).

## Discussion

- F344 and LEW male rats did not differ in the acquisition of a cocaine-induced CTA (unlike what has been previously reported with females; Glowa, et al., 1994); however, male F344 rats displayed more resistance to extinction of the cocaine-induced aversion than LEW rats.

- These strain differences were affected by cross-fostering, specifically, LEW rats raised by F344 dams displayed resistance to extinction similar to that seen in the in-fostered F344 subjects. Further, F344 subjects raised by LEW dams showed faster extinction than their in-fostered F344 counterparts.

- That LEW rats displayed faster extinction suggests that they were less sensitive to cocaine's conditioned aversive effects, a finding consistent with LEW tendency to self-administer cocaine > F344 and show greater conditioned place preference.

- That cross-fostering had profound effects, rendering LEW rats as sensitive to cocaine's aversive effects as F344 (and weakening the F344's rats resistance to extinction), suggests that simple genetic or environmental explanations alone cannot account for the observed effects.

- Drug abuse is an extremely complex phenomenon, involving genetic predisposition, early maternal environment, and gene-environment interactions

- Understanding these interactions in the balance between reward and aversion during initial drug exposures is an important step towards understanding individual pathways to drug abuse risk and prevention.

## References

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