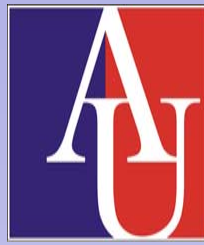




Genetic Strain, Maternal Environment, and Biological Sex Interact to Affect Cocaine-Induced Taste Aversions in Fischer and Lewis Rats



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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, and 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-related behaviors, the present experiment assessed the role of genetic strain and maternal environment in both female and male F344 and LEW rats on cocaine-induced conditioned taste aversions.

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 eight groups: F344 pups raised by F344 dams (F/F, 12 male and 12 female), F344 pups raised by LEW dams (F/L, 12 male and 12 female), LEW pups raised by LEW dams (L/L, 12 male and 12 female), and LEW pups raised by F344 dams (L/F, 12 male and 12 female). Litters were culled to 8 per dam (4 male, 4 female). 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

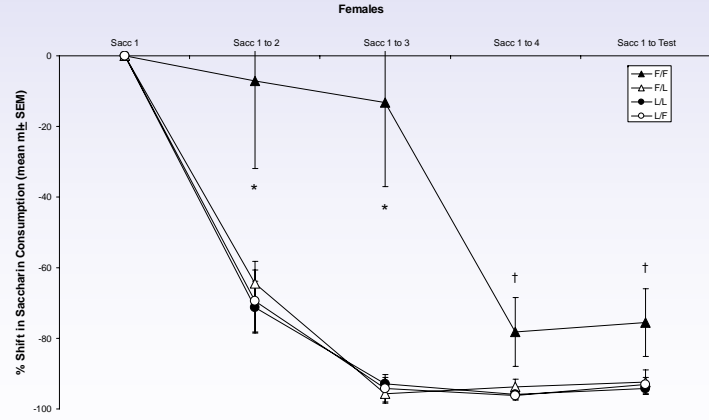
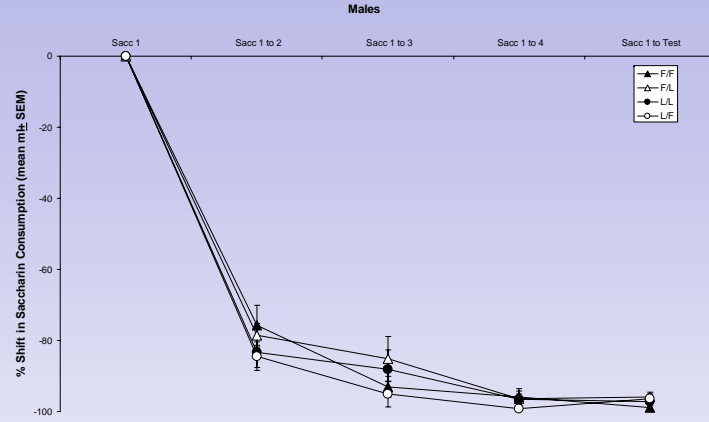
Animals were individually housed in hanging wire mesh cages with *ad-libitum* access to food. They were maintained on a 12:12 light:dark cycle (lights on at 0800 h) and at a temperature of 23°C. Graduated 50-ml Nalgene tubes were attached to the front of the cage, providing either water or saccharin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

Drugs

Cocaine HCl (generously supplied by NIDA) was prepared in a 50 mg/ml solution in saline, 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 without a subsequent injection, providing a drug-free saccharin test day.



Asterisk indicates significant difference between the females in Group F/F and every other group ($p \leq .05$). Dagger indicates significant difference between Group F/F females and every other group except females in Group F/L ($p \leq .05$).

Results

- 4 x 2 x 2 x 2 mixed ANOVA with repeated-measures factor of Trial (Trial 1 to 2, 3, 4, and Test) and between-groups factors of Pup Strain (F344 and LEW), Dam Strain (F344 and LEW) and biological Sex (Male and Female) performed with percent shift from Trial 1 as dependent variable.
- Significant Trial x Pup Strain x Dam Strain X Sex interaction $F(3,264) = 3.10$, $p = .027$ was found.
- Post-hoc comparisons (Tukey's HSD) revealed that female rats in Group L/L significantly decreased saccharin consumption over trials to a greater extent than female rats in Group F/F, an effect consistent with previously reported differences between the two strains (Glowa, Shaw, & Riley, 1994).
- Females in Group F/F displayed significantly less of an aversion than all other groups.
- Cross-fostering reversed acquisition of aversions in the Group F/L females, in which they resembled females in Group L/L.
- Females in Group L/F and males in Groups F/L and L/F were unaffected by cross-fostering.

Conclusions

- Intrinsic and environmental factors can interact to affect drug acceptability.
- Cocaine-induced taste aversions in F344 females can be modulated by changes in the maternal environment.
- LEW males and females were unresponsive to the cross-fostering manipulation.
- Drug abuse is an extremely complex phenomenon, involving genetic predisposition, early maternal environment and biological sex.
- Understanding these interactions is an important step in understanding individual pathways to drug abuse risk and prevention.

References

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