Behavioural Brain Research 332 (2017) 23–31

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Altered reward sensitivity in female offspring of cocaine-exposed fathers

Delaney K. Fischer[a,1], Richard C. Rice[a,1], Arlene Martinez Rivera[a,b], Mary Donohoe[b,c,d], Anjali M. Rajadhyaksha[a,b,*]

[a] Pediatric Neurology, Pediatrics, USA
[b] Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY, USA
[c] Burke Medical Research Institute, White Plains, NY, USA
[d] Department of Cell and Developmental Biology, Weill Cornell Medical College, New York, NY, USA

ARTICLE INFO

Keywords:
Cocaine
Female
Intergenerational
Male
Mice
Reward

ABSTRACT

Recent rodent studies have demonstrated that parental cocaine exposure can influence offspring behavior, supporting the idea that environmental insults can impact subsequent generations. However, studies on the effects of paternal cocaine exposure are limited and multiple inconsistencies exist. In the current study, we behaviorally characterize the effects of paternal cocaine exposure in a C57BL/6J intergenerational mouse model. Male sires were administered cocaine hydrochloride (20 mg/kg) or saline (0.01 mL/g) once a day for 75 days, and bred with drug naïve females twenty-four hours after the final injection. Offspring, separated by sex, were tested in a battery of behaviors. We found that paternal cocaine exposure altered sensitivity to the rewarding and stimulant effects of psychostimulants and natural reward (sucrose) in female offspring; female cocaine-sired offspring showed blunted cocaine preference using cocaine conditioned place preference (CPP) at a low dose (5 mg/kg), but displayed similar preference at a higher dose (10 mg/kg) compared to saline-sired controls. Additionally, cocaine-sired female offspring exhibited higher psychomotor sensitivity to cocaine (10 mg/kg) and amphetamine (2 mg/kg) and consumed more sucrose. Cocaine-sired males exhibited increased psychomotor effects of cocaine and amphetamine. Male offspring also displayed an anxiety-like phenotype. No effect of paternal cocaine exposure was observed on depressive-like, learning and memory or social behavior in male or female offspring. Collectively, our findings show that paternal, chronic cocaine exposure induces intergenerational behavioral effects in male and female offspring with greatest impact on sensitivity to psychostimulants and sucrose in females.

1. Introduction

Substance abuse and addiction, both highly comorbid with mood disorders, are prevalent problems in today's society. Genetic and environmental factors, in part, contribute to addictive behavior and mood disorders [1]. Furthermore, multiple studies suggest an additional contribution of familial genetic and epigenetic mechanisms, an idea that is supported by the observation of higher likelihood of drug abuse amongst individuals with a family history of substance abuse [2–4]. Indeed, recent studies using animal models identify parental drug exposure as a contributing factor to behavioral, physiological, and molecular phenotypes in offspring [5,6]. Even though males appear to abuse numerous drugs more frequently than females [7], the effects of maternal drug exposure have been investigated at greater lengths compared to paternal drug exposure.

Although there is compelling evidence for the intergenerational effects of parental cocaine exposure to subsequent generations using rat and mouse models, studies examining the behavioral consequences of paternal cocaine administration on offspring are sparse with varying results [5,6]. For example, cocaine-sired male, but not female, rats displayed reduced reinforcing effects of cocaine using self-administration [8] whereas in cocaine-sired mice there was no difference in the stimulant effects of cocaine [9]. Similarly, investigating the cognitive impact of paternal cocaine exposure has provided conflicting results: one study indicated female offspring display learning and memory deficits [10] while another (not separated by sex), failed to show learning deficits [9]. Additionally, multiple studies have suggested that cocaine use in humans leads to the comorbidity of neuropsychiatric phenotypes such as anxiety and depression [11]. However, as with reports on drug sensitivity and cognition, there have been varying reports on the effects of parental drug exposure on depression-like phenotypes [9,12] in animal models, suggesting further examination of

* Corresponding author at: Pediatric Neurology, Pediatrics, Weill Cornell Medicine, 1300 York Avenue, Box 91, New York, NY 10065, USA.
E-mail address: amr2011@med.cornell.edu (A.M. Rajadhyaksha).
[1] Equally contributed as co-first authors.

http://dx.doi.org/10.1016/j.bbr.2017.05.054
Received 7 March 2017; Received in revised form 23 April 2017; Accepted 24 May 2017
Available online 26 May 2017

neuropsychiatric phenotypes is necessary.

Thus, we sought to investigate the behavioral implications of chronic, paternal cocaine administration on the subsequent generation of male and female offspring. We aimed to comprehensively characterize the behavioral phenotype of cocaine-sired offspring with regards to responsivity to reward, affective behavior, cognition, and social behavior.

2. Methods

2.1. Breeding scheme

Adult male C57BL/6J mice (Jackson Labs, Bar Harbor, ME) were treated with cocaine (20 mg/kg, intraperitoneal (i.p.)) starting at postnatal day 56, once a day for 75 days. Control mice received saline injections (0.01 mL/g body weight) for the same number of days. Twenty-four hours after the last cocaine or saline injection, cocaine- and saline-exposed males (designated as F0 generation) were mated with drug naïve, primiparous C57BL/6J female mice (Jackson Labs, Bar Harbor, ME). All breeding cages housed one male and one female breeder. Females were removed from breeding cage once they were plug positive to eliminate the effect of male behavior on offspring. All offspring (F1 generation) were weaned at 21 days of age (P21) and male and female offspring were separated. Female mice bred with cocaine-exposed sires relative to controls were monitored for maternal behavior. Behavioral testing was performed on adult (> P60) male and female offspring. All procedures were conducted with approval from the Weill Cornell Medicine Institutional Animal Care and Use Committee and conducted in accordance with the National Institute of Health guidelines.

2.2. Behavioral tests

To ensure no one litter was over represented, two independent cohorts of mice were behaviorally tested, with each cohort consisting of mice from at least four different litters (2–3 mice per litter per cohort), Behaviors in offspring involving drug treatment were conducted last. All other behaviors were conducted in a semi-random fashion and data revealed that order of testing had no impact of the phenotypes reported. Behavioral tests were separated by a minimum of 48 h.

2.2.1. Basal locomotor activity

Basal locomotor activity was performed as previously described [13]. For each test session, animals were placed in the chamber, and distance traveled was recorded for 1 h without interruption.

2.2.2. Cocaine conditioned place preference (CPP)

A three-chamber place preference protocol (Med Associates Inc., St. Albans, VT, USA) was used as previously described [14]. On Day 1, mice were allowed to freely explore all three chambers (20 min). On Day 2–4 (conditioning sessions), a biased procedure was used wherein mice were paired with cocaine (5 mg/kg, i.p. or 10 mg/kg, i.p.) for 20 min in the morning on the less preferred side, and paired with saline (0.01 mL/g body weight) for 20 min in the afternoon on the opposite side. On Day 5, mice were allow to freely explore the CPP box for 20 min. Time spent in the cocaine-paired chamber minus saline-paired chamber was calculated for post-conditioning (day 5) and pre-conditioning (day 1) and is referred to as CPP score.

2.2.3. Cocaine- and amphetamine-induced locomotor activity

Animals were injected with cocaine (10 mg/kg, i.p.) or amphetamine (2 mg/kg, i.p.), immediately placed in the chamber, and distance traveled was recorded for 1hr without interruption as previously described [15].

2.2.4. Sucrose consumption test

Mice were single housed for the duration of the sucrose consumption assay. The water bottle from each cage was removed and replaced with two smaller bottles (50 mL Falcon tubes, Corning, Tewksbury, MA), one containing drinking water and the other containing 1% sucrose dissolved in drinking water. A hole was drilled into each small bottle, allowing the mice to lick the solution from the drilled hole. Body weights and the mass of water and sucrose consumed were monitored once a day for four days. The first two days were considered habituation days and not used in analyses. Sucrose consumption (averaged over days 3 and 4) was calculated as (sucrose consumed (g)/water consumed (g)).

2.2.5. Forced swim test

The test was performed in a 2L beaker containing 1800 mL of 26 °C water, for 10 min. Each mouse was video-recorded using a camera directed to the front of the beaker, as well as a camera above the beaker. Time spent immobile was scored by an experimenter blind to the conditions using the computer assisted software ButtonBox v5.1 (Behavioral Research Solutions, Madison, WI).

2.2.6. Elevated plus maze

Elevated plus maze test was performed as previously described [13]. Mice were placed in the center of a cross-shaped maze elevated 38 cm above the floor and consisting of two open and two closed arms (arm: 50.0 cm × 6.4 cm, height of closed arm: 15.2 cm). All trials were recorded with a video camera mounted above the maze. Time spent in the open and closed arms was obtained using the ANY-maze software (Stoelting Co., Wood Dale, IL).

2.2.7. Three-Chambered social interaction

Social interaction was conducted as previously published [16] in a rectangular plastic apparatus (67.3 cm × 41.9 cm × 22.9 cm) containing three separate chambers that could be divided by plastic walls (40.6 cm × 15.2 cm). Following habituation, the experimental mouse was given access to all three chambers for five minutes. The experimental mouse was then contained in the center chamber for 1 min while a pencil cup containing a novel object and a pencil cup containing an aged-matched stranger mouse (C57BL/6J) were placed in opposite chambers of the apparatus. The experimental mouse was then allowed to explore the full chamber for five minutes, and the total time spent with each cup was recorded. A virtual three-inch contact zone was created around each pencil cup. Sociability was assessed by comparing the amount of time spent within the stranger contact zone versus the novel object contact zone. All trials were recorded using a video camera mounted above the plastic apparatus and mouse position and interaction time was recorded using ANY-maze software (Stoelting Co., Wood Dale, IL).

2.2.8. Morris water maze

A modified version of the Morris water maze was utilized [17]. A black plastic pool with a radius of 48.3 cm and height of 36.8 cm was used. The maze was filled with water (25–26 °C) and clouded with non-toxic, white tempura paint to conceal the position of an underwater escape platform submerged 1–1.5 cm beneath the surface. Four different starting points labeled North, East, South, and West were designated, and four distal cues (27.9 cm × 21.6 cm) were scattered on the walls surrounding the maze at a height of 49.5 cm. The maze was virtually split into triparts, with one tripart containing the platform (goal), and the other two containing nothing (lures). Mice were first habituated to the pool and allowed to swim freely for 60 s. Following habituation, animals underwent training, wherein 12 training trials were administered over the span of three days (four trials/day). During training, mice were released from different starting points on the maze and allowed to find the escape platform, which remained stationary throughout the experiment. The latency (secs) to locate the hidden