Shelby Towers, Josiah Comstock, Nick Paige, Price Dickson, and Deranda Lester

Environmental Enrichment Alters Mesolimbic Dopamine Release in Mice

Faculty Sponsor

Dr. Deranda Lester

Abstract

Social isolation in rodents is often used to model early life stress, increasing the occurrence of behaviors related to substance use disorder. Given that the rewarding properties of abused drugs are associated with increased dopamine release, the present study aimed to determine how various housing conditions affect dopamine functioning. Mice spent 10-12 weeks in one of three housing conditions: environmentally enriched (EE, including physical and social stimuli), socially enriched (SE, including only social stimuli), or isolation. *In vivo* fixed potential amperometry was used to quantify dopamine release in the nucleus accumbens before and after cocaine administration. Isolated mice showed an increased dopaminergic response to cocaine relative to both EE and SE mice. No differences were observed between EE and SE mice, suggesting social stimuli may be driving the protective effects of EE more so than physical stimuli. Identifying such factors may be important for prevention and treatment of substance use disorder.

Introduction

A survey from the National Institute on Drug Abuse (NIDA) in 2013 reported that approximately 24.6 million Americans 12 years or older used illicit drugs such as marijuana, cocaine, prescription drugs, hallucinogens, and heroin in a month span. According to Dr. Volkow, Director of NIDA, drug addiction is defined as "drug seeking that is compulsive, or difficult to control, despite harmful consequences." However, some drugs are more addictive than others, and not everyone may become addicted to the same drug. Factors affecting the risk of addiction are both biological and environmental. Age of first exposure, genes, and preexisting mental disorders affect probability of becoming addicted to drugs as well as social pressure and relationships, feelings of stress and anxiety, and low cost and high availability of drugs (NIDA, 2018). Adolescents are at an even greater risk of abusing drugs relative to adults (Wagner & Anthony, 2002). Furthermore, adolescents who lack strong parental supervision and/or come from low socioeconomic status are even more likely to fall victim to drug addiction compared to adolescents with supportive, involved parental monitors from middle and/or upper socioeconomic statuses (Guo, Hawkins, Hill, & Abbott, 2001). Findings from animal studies further support that environmental factors such as reduced social and physical stimuli can have detrimental effects on the developing adolescent brain.

Rearing rodents in social isolation models an early life stressor; it has been shown to enhance the rewarding effects of drugs and increase the occurrence of behaviors related to psychological disorders such as depression and anxiety (Czoty, Gould, Gage, & Nader, 2017; Laviola, Hannan, Macri, Solinas, & Jaber, 2008; Yorgason et al., 2016). On the opposite spectrum, adding stimulating objects to cages such as toys with complex textures and running wheels create an enriched environment that mimics positive life experiences. Enriched environments (EE) reduce the occurrence of behaviors associated with substance use disorder, such as drug seeking, liking, and self-administration (Stairs, Prendergast, Bardo, 2011; Stairs & Bardo, 2009; Solinas, Chauvet, Thiriet, El Rawas, & Jaber, 2008). Furthermore, Nader et al. (2012) and Solinas et al. (2008) found that switching mice from standard group-housed conditions (aka social enrichment: SE) to EE cages for 30 days provides preventative effects against conditioned place preference for cocaine. Conditioned place preference is a common preclinical test for drug preference or liking. Thus, mice exposed to EE for more than 30 days displayed reduced cocaine preference or liking compared to SE mice. In the other direction, mice raised in EE and then switched to SE showed an increased cocaine preference compared to control (SE only) mice 7 and 30

days after the switch. Overall, the more time spent in EE the greater the positive effects regarding vulnerability to the rewarding effects of drugs.

As mentioned, EE generally consists of toys, climbing objects, running wheels, and cage mates. It is not fully understood whether one of these aspects of EE is more beneficial than others. Aarde, Miller, Creehan, Vanderwater, and Taffe (2015) and Cosgrove, Hunter, and Carroll, (2002) found that exposure to a running wheel led to an immediate decrease in self-administration of psychostimulants. Other studies indicate social interaction may be the driving force behind altered behaviors related to drug reinforcement (Gibson, Beckman, El-Maraghi, Marusich, & Bardo, 2011; Morse, Erwin, & Jones, 1993).

Reinforcing stimuli such as natural rewards and most drugs of abuse increase dopamine release in the mesolimbic dopamine pathway. This pathway originates in cell bodies in the ventral tegmental area (VTA) which project to and release dopamine in the nucleus accumbens (NAc) (Le Moal & Simon, 1991; Kalat, 2013). Previous studies regarding dopamine differences related to housing differences have not been consistent. For example, El Rawas et al. (2009) found similar drug-induced dopamine levels in the NAc of EE and SE, but Bardo et al. (1999) found increased drug-induced dopamine release in EE mice relative to SE mice. While some studies have found no differences in amphetamine-induced extracellular dopamine across EE, SE, and isolated rats using microdialysis (Meyer & Bardo, 2015), clear differences have been detected between isolated and SE rats using fast-scan cyclic voltammetry (Yorgason, Espana, Konstantopoulos, Weiner, & Jones, 2013). Differences are likely related to time spent in EE conditions, route of drug administration, and techniques used to measure dopamine.

The aim of the present study was to determine how these housing conditions alter mesolimbic dopamine transmission related to substance use disorder, in hopes of parsing the value of social and physical stimuli in protecting against the impact of isolation. In the present study, mice spent 10-12 weeks in one of the three housing conditions: EE, SE, and isolation. Following this time period, we used *in vivo* fixed-potential amperometry to quantify dopamine release before and after an injection of cocaine. Based on behavioral findings in previous studies, we hypothesized that mice in the isolated housing condition would have a greater dopaminergic response to cocaine relative to the mice in the SE and EE conditions, meaning we expected isolated mice to be more susceptible to the rewarding effects of

cocaine, thus providing a neurochemical basis for the protective ability of group and EE housing conditions towards behaviors related to drug reward.

Methods

These experiments have been approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Memphis and were also aligned with those outlined in The Public Health and Service Policy on Humane Care and Use of Laboratory Animals (National Institutes of Health, 2015) and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003).

Subjects

Fifteen male C57Bl/6J mice were acquired from Jackson Laboratory (Bar Harbor, ME, USA) at 3 weeks of age. Upon arrival, mice were immediately and randomly separated into one of three housing conditions: EE (n = 6), SE (n = 6), or isolated (n = 3). Cages were kept in a temperature-controlled room (21 ± 1° C) with a 12:12 light-dark cycle (lights on at 0600). Food and water were available ad libitum.

Apparatus and Materials

In vivo fixed potential amperometry coupled with carbon fiber microelectrodes has been confirmed as a valid technique for real-time monitoring of stimulation-evoked NAc dopamine release (Forster & Blaha, 2003; Lester, Rogers, & Blaha, 2010). There are 3 amperometry set-ups in the Psychology building at the University of Memphis. An amperometry set-up consists of a large faraday cage to block electrical noise, a stereotaxic frame with electrode carriers (David Kopf Instruments, CA, USA), a programmable stimulator (Iso-Flex/Master-8; AMPI, Israel), and an electrometer to measure oxidation currents of dopamine (e-corder 401 and Picostat, eDAQ Inc., CO, USA) connected to a computer. All chemicals were purchased from Sigma-Aldrich. Standard operating procedures for urethane (U2500 Sigma-Aldrich), dopamine (H8502 Sigma-Aldrich), and cocaine (C5776 Sigma-Aldrich) were approved by the Environmental Health and Safety department at our university.

Procedures

Housing Conditions

Mice in the environmentally enriched (EE) housing condition were housed 3-5 per cage in large cages with running wheels, nesting materials, and

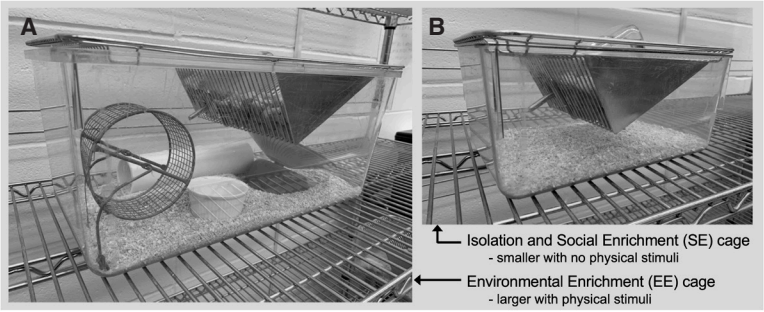

Figure 1. Experimental housing conditions. Mice in the environmentally enriched (EE) condition had access to running wheels, tunnels, and cage mates in a larger cage. Mice in the socially enriched (SE) and isolated conditions were in standard cages with no EE objects.

tunnels (Figure 1). EE items were obtained from Bio Serve. Mice in the SE condition were housed 3-5 per cage in standard cages without EE items. Mice in the isolated housing condition were housed individually in standard cages without EE items. Cages from all conditions were housed in the same room of the animal-care facility. Consequently, the isolated mice were housed without direct contact to social or physical stimuli, but auditory and visual social stimuli was present. Mice were housed in one of these conditions for 10-12 weeks.

Fixed Potential Amperometry

Mice were deeply anesthetized using two urethane i.p. injections totaling 1.5 g/kg. Foot and tail pinch and eye blink induced reflexes fifteen minutes after second injection guaranteed proper anesthetization. Mice were then placed under a stereotaxic frame that included a warming pad to ensure body temperature remained at 38 ± 1° C. Stereotaxic carriers were used to guide all electrodes. A stimulating electrode (SNE-100 outer diam. 100 um; Rhodes Medical Co., CA, USA) was placed into the left VTA (coordinates in mm from bregma: AP -3.3, ML +0.3, and DV -4.0 from dura; Paxinos & Franklin, 2001). A carbon fiber dopamine recording electrode (7 µm o.d. and 500 µm long, Thornel Type P, Union Carbide, PA, USA) was positioned into the left NAc (coordinates in mm from bregma: AP +1.5, ML +1.0, and DV -4.0 from dura; Paxinos & Franklin, 2001). A silver-chloride reference and auxiliary electrode combination was placed in contact with the surface of the parietal cortex contralateral to the stimulating electrode (-3.0 mm from bregma) as shown in Figure 2. A fixed +8.0 V current was continuously applied to the recording electrode via an electrometer (ED401 e-corder 401 and

EA162 Picostat, eDAQ inc., Colorado Springs, CO). Changes in dopamine release in the NAc were monitored continuously in response to brief chains of electrical stimulation (20 pulses at 50 Hz every 30 sec for five minutes) applied to the VTA as a baseline recording. After five minutes, the mice received an i.p. injection of cocaine (10 mg/kg) to measure the dopaminergic system's transporter function and its psychostimulant response allowing us to examine the impact of housing conditions. Dopamine recordings continued 1-hour post cocaine injection.

In vitro electrode calibrations were performed after all experiments enabling dopamine oxidation currents (nAmp) to be converted to dopamine concentrations (μM). Each carbon fiber electrode was exposed to varying known dopamine concentrations (0.2, 0.4, 0.8, and 1.2 μM) via a flow injection system while recording oxidation current change (Dugast, Suaud-Chagny, & Gonon, 1994).

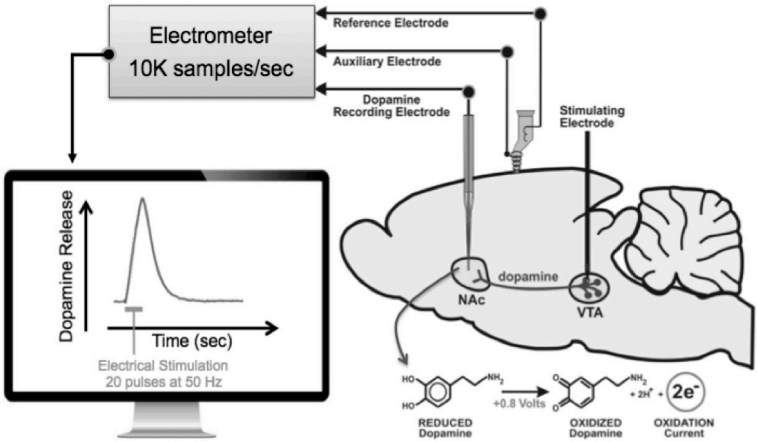

Figure 2. Experimental design. *In vivo* fixed potential amperometry with carbon fiber recording electrodes quantified nucleus accumbens (NAc) dopamine release evoked by stimulation of dopamine cell bodies within the ventral tegmental area (VTA).

Results

Baseline Dopamine Efflux

A one-way ANOVA was used to compare mean dopamine release before cocaine administration. There was a significant effect of housing on baseline dopamine release [$F(2, 19) = 4.16$, $p = .032$; Figure 3 and 4]. Post hoc com-

parisons using Tukey HSD test indicated that the mean dopamine release (in μM) for the EE condition (M = 0.117, SD = 0.105) was significantly lower than the isolated condition (M = 0.280, SD = 0.130; Figure 3). However, the SE condition (M = 0.252, SD = 0.119) did not significantly differ from the EE or isolated conditions.

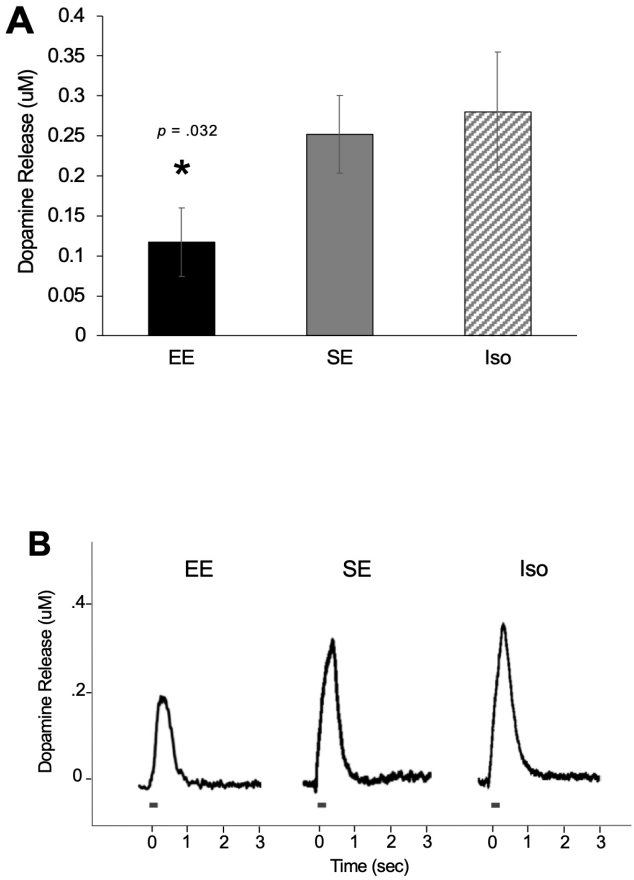

Figure 3. Baseline (pre-cocaine) dopamine release presented as (A) mean ± SEM and (B) representative stimulation-evoked responses from each housing group. *Mice in the environmentally enriched (EE) condition had significantly reduced dopamine release relative to isolated mice.

Dopamine Efflux following Cocaine

Percent change in stimulation-evoked dopamine release following cocaine administration was compared in 10 min increments post injection. A two-way mixed ANOVA revealed a nearly significant effect of housing (between-subject IV) on dopamine release over time (the 60 min recording period, within-subject IV), $F(12, 72) = 1.835$, $p = 0.058$, $np2 = 0.23$ (Figure 4). One-way ANOVAs showed a nearly significant difference in percent change in dopamine release between experimental groups at 10 min ($p = 0.059$)

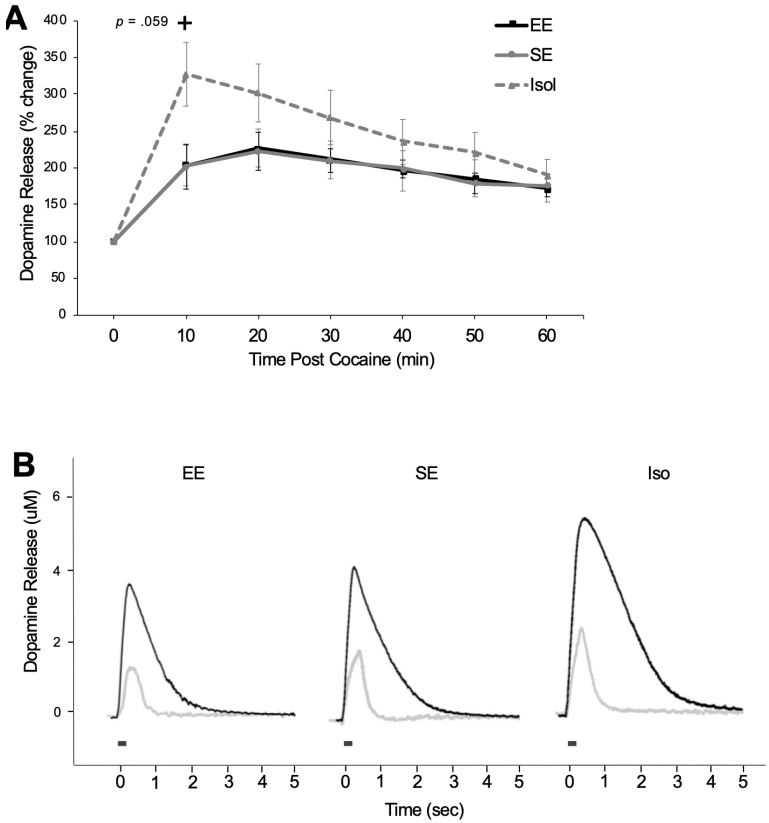

Figure 4. Dopamine release following cocaine administration presented as (A) mean ± SEM and (B) representative stimulation-evoked responses from each housing group, with the light line depicting the pre-cocaine response and the black line depicting the response 10 min post cocaine. + There was a near significant effect of housing conditions on dopaminergic response to cocaine, indicating an increased response by the isolated mice compared to both EE and SE groups.

but no differences at any other time points. At the 10 min post-cocaine time point, Tukey's HSD post hoc analyses revealed a trend in the data in which the isolated mice had near significant increases in percent change dopamine release relative to EE ($p = 0.075$) and SE ($p = 0.071$).

Discussion

The rewarding effects of abused drugs are strongly associated with increased activity in the mesolimbic dopamine system (Le Moal & Simon, 1991). The purpose of the present study was to determine how housing conditions can alter NAc dopamine functioning and the response of this pathway to the well-known dopamine agonist cocaine. Mice were housed in either EE (physical and social stimuli), SE (social stimuli), or isolated (lacking both physical and social stimuli) conditions for 10-12 weeks prior to dopamine quantification using *in vivo* fixed potential amperometry.

Baseline dopamine release, as measured by the magnitude of the VTA stimulation-evoked response, was significantly lower in EE mice relative to isolated mice, with SE mice not differing from either of the other 2 groups. These findings suggest that the combination of the physical and social stimuli are more influential on the dopamine system relative to social stimuli alone, at least in mice. These effects may be species dependent. Recently, using a similar dopamine recording technique in brain slices, Karkhanis et al. (2018) found that isolated rats displayed increased stimulation-evoked dopamine release relative to group housed rats. Furthermore, exposure to chronic and intermittent social defeat stress also results in augmented stimulated dopamine release in rats (Deal et al., 2018). Social interaction is more rewarding for rats than mice, and social isolation has been shown to be more anxiety-provoking for rats than mice (see Ellenbroek & Youn, 2016).

Our results demonstrate that social interaction, or lack thereof, also impacts the response of this dopamine system to the psychostimulant cocaine. As expected, dopamine release was significantly increased following cocaine in mice from all housing groups. However, a strong trend in the data indicated that cocaine increased dopamine release to a greater degree in isolated mice relative to the enriched mice (both EE and SE) at 10 min post injection. At the time points following 10 min post injection, the cocaine-induced increases in dopamine release were similar in all experimental groups, but the observed increased dopaminergic response at the 10 min mark may have implications towards the rewarding effects of dopamine agonists. The sooner an increase in dopamine efflux occurs following a drug administration, the more rewarding potential that drug has (Volkow and Morales, 2015). Thus, these findings indicate cocaine may have greater reinforcing properties in

the isolated mice relative to the EE and SE groups.

EE mice had decreased dopamine release to begin with, but following cocaine, the findings showed the percent change in dopamine release did not differ from SE mice. Behavioral studies have shown that EE reduces responses to psychostimulants compared to isolation (Stairs, Prendergast, Bardo, 2011; Staires & Bardo, 2009; Solinas, Chauvet, Thiriet, El Rawas & Jaber, 2008). Regarding the isolated mice, these findings are consistent with the previously mentioned results on dopamine release post cocaine. Thus, while baseline (pre-cocaine) dopamine release was altered more by physical stimuli (EE group showing decreased release), the dopaminergic effect of cocaine was altered to a greater degree by social factors (isolated group showing increased response to cocaine). These findings provide neurochemical support for related behavioral studies.

The relative influence of physical and social stimuli on dopamine and drug reinforcement is not clear in the literature. While Gipson et al. (2011) indicate social interaction is the driving force behind altered behaviors related to drug reinforcement, others propose physical activity is important to reducing self-administration (Creehan, Vanderwater, & Taffe, 2015; Cosgrove, Hunter, & Carroll, 2002). Our findings are consistent with the former. No differences were observed between EE and SE groups post cocaine, indicating that social interaction may be the environmental stimuli providing the psychostimulant-related protective effect in both conditions.

There are numerous directions the present topic could be expanded for future research. Some of the most important include describing strain and sex differences. For example, DBA2J mice are another inbred strain commonly used in addiction studies and differ behaviorally from C57BL/6J mice (Voikar, Polus, Vasar, & Rauvala, 2005). They may be more susceptible to the effects of isolation. In addition, it is unknown whether female responses will match the male patterns. Adolescent social isolation has been shown to induce increased stress hormones and anxiety-related behaviors to a greater extent in male rats compared to females (Pisu et al., 2016).

In conclusion, the present findings extend our understanding of how the social and physical environment contributes to the development and functioning of the dopaminergic reward system and vulnerability to drug abuse. Further, we provide neurochemical support for behavioral studies showing isolated mice are more likely to self-administer cocaine. This information can help guide prevention and treatment programs for drug abuse. Ensuring positive environmental factors like social relationships and interactions may be beneficial additions to current therapies and prevention programs.

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