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Effects of adolescent social defeat on adult amphetamine-induced locomotion and corticoaccumbal dopamine release in male rats

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ABSTRACT

Maturation of mesocorticolimbic dopamine systems occurs during adolescence, and exposure to social stress during this period results in behavioral dysfunction including substance abuse disorders. Adult male rats exposed to repeated social defeat in adolescence exhibit reduced basal dopamine tissue content in the medial prefrontal cortex, altered dopamine tissue content in corticoaccumbal dopamine regions following acute amphetamine, and increased amphetamine conditioned place preference following repeated amphetamine treatment. Such changes may reflect altered amphetamine-induced extracellular dopamine release in the corticoaccumbal regions. Therefore, we used *in vivo* microdialysis to measure extracellular dopamine simultaneously within the medial prefrontal cortex and nucleus accumbens core of previously defeated rats and controls, in response to either acute or repeated (7 daily injections) of amphetamine (1.0 mg/kg). Locomotion responses to acute/repeated amphetamine were also assessed the day prior to taking dopamine measurements. Adolescent defeat potentiated adult locomotion responses to acute amphetamine, which was negatively correlated with attenuated amphetamine-induced dopamine release in the medial prefrontal cortex, but there was no difference in amphetamine-induced accumbal dopamine release. However, both locomotion and corticoaccumbal dopamine responses to repeated amphetamine were equivalent between previously defeated rats and controls. These data suggest adolescent defeat enhances behavioral responses to initial amphetamine exposure as a function of diminished prefrontal cortex dopamine activity, which may be sufficient to promote subsequently enhanced seeking of drug-associated cues. Interestingly, repeated amphetamine treatment appears to normalize amphetamine-elicited locomotion and cortical dopamine responses observed in adult rats exposed to adolescent social defeat, providing implications for treating stress-induced dopamine dysfunction.

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1. Introduction

Adolescent bullying victimization is associated with increased substance misuse (Nelson et al., 1995; Rossow and Lauritzen, 2001; Sullivan et al., 2006; Tharp-Taylor et al., 2009; Topper et al., 2010), which suggests alterations to reward pathways in the brain. Adolescent male rats exposed to repeated social defeat, as a model of adolecent bullying (Bjorkqvist, 2001; Watt et al., 2009), exhibit decreased basal medial prefrontal cortex (mPFC) dopamine (DA) tissue content as adults (Watt et al., 2009). Rats defeated in adolescence also show blunted mPFC DA tissue content in response to acute amphetamine in adulthood, while nucleus accumbens (NAc) core DA tissue content responses are enhanced (Burke et al., 2010). Adolescent defeat also increases adult amphetamine conditioned place preference (CPP) and locomotion in a novel environment (Watt et al., 2009; Burke et al., 2010, 2011). Rats that naturally exhibit high novelty-induced locomotion, which predicts psychostimulant self-administration and sensitization (Piazza et al., 1990; Hooks et al., 1991), show blunted basal mPFC DA activity and exaggerated NAc DA responses to cocaine (Piazza et al., 1991; Hooks et al., 1992). Collectively, this implies that enhanced adult behavioral responses to amphetamine following adolescent defeat may be a function of altered mPFC and NAc core DA activity.

Dopamine transmission in the NAc core during initial psychostimulant exposure is implicated in development of conditioned responses to associative cues (Ito et al., 2000; Sellings and Clarke, 2006; Everitt et al., 2008; Meredith et al., 2008). As such, enhanced

Abbreviations: CPP, conditioned place preference; DA, dopamine; DAT, dopamine transporter; HPLC, high-performance liquid chromatography; ip, intraperitoneal; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; P, postnatal day.

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CPP for amphetamine exhibited by adult rats exposed to adolescent defeat (Burke et al., 2011) suggests potentiated NAc core DA responses to drug-associated cues. Furthermore, reward-elicited NAc DA release can be further enhanced by mPFC DA depletion (Mitchell and Gratton, 1992; Ventura et al., 2004), as increased mPFC DA activity functionally dampens NAc DA activity (Deutch et al., 1990; Doherty and Gratton, 1996; Pascucci et al., 2007; Del Arco and Mora, 2008). Given that rats defeated in adolescence show reduced mPFC DA tissue content (Watt et al., 2009), it is possible that heightened adult behavioral responses to amphetamine following adolescent defeat are a result of augmented NAc core DA levels in response to amphetamine via reduced DA release in the mPFC. In support of this, acute amphetamine-induced increases in *ex vivo* DA tissue content within the NAc core of adult rats are heightened following adolescent defeat exposure (Burke et al., 2010), but it is not known whether this reflects increased *in vivo* extracellular DA concentrations in response to either acute or repeated administration of amphetamine. Also, it is unknown whether naturally decreased mPFC DA activity, such as that seen following adolescent defeat, results in potentiated extracellular NAc DA to acute or repeated amphetamine as has been shown in rats with pharmcologially-induced mPFC DA lesions (Mitchell and Gratton, 1992; Ventura et al., 2004). Therefore, we measured amphetamine-induced locomotion and amphetamine-induced DA release simultaneously in the mPFC and NAc core using *in vivo* microdialysis. Responses following either acute or repeated amphetamine were measured to determine whether adolescent defeat-induced alterations to amphetamine responses differ with increased amphetamine exposure.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Animal Resource Center, University of South Dakota, Vermillion, SD) used as experimental subjects were pair-housed according to treatment (social defeat or control) under a reverse light cycle (lights off from 10:00–22:00 h) from postnatal day (P) 21 onwards. Resident adult male Sprague-Dawley rats (300–400 g) for social defeat experiments were housed singly prior to assessment of their aggressive behavior. Food and water were available *ad libitum* to all rats. All behavioral procedures were conducted between 11:00 and 15:00 in a dark room under red lighting. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of South Dakota, and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals used and their suffering.

2.2. Adolescent social defeat

Social defeat of adolescent male rats followed previously established procedures (Watt et al., 2009; Burke et al., 2010). Briefly, an adolescent male rat (P35) was introduced into a resident adult male's home cage. The adolescent subject was considered socially-defeated when it exhibited a minimum of 3 submissive postures in response to separate resident attacks (Watt et al., 2009). Following this, a mesh barrier was used to separate the resident and the adolescent for 35 min to prevent further physical attacks, but still allowing further visual, auditory and olfactory intimidation from the resident (Watt et al., 2009; Burke et al., 2010). Adolescents ($N = 71$) were exposed to social defeat each day for 5 days (P35–39) and were confronted with a different resident male each day to control for individual variance in defeat intensity. Age-matched controls ($N = 67$) experienced no social defeat but instead were placed in empty novel cages at matched times to control for handling and novel environment stress (Watt et al., 2009; Burke et al., 2010). Rats were returned to their home cages (pair-housed according to treatment) after each daily trial. Following the final social defeat conditioning, subjects and controls were left in their original pairs in their home cages and allowed to mature undisturbed into early adulthood (P56) when adult behavioral testing commenced.

2.3. Adult behavioral testing

In early adulthood (P56+), equivalent numbers of previously defeated and control rats were assigned to either acute or repeated amphetamine (1.0 mg/kg, ip., $N = 16–20$/group) or saline groups ($N = 13–19$/group). The repeated amphetamine administration involved either amphetamine or saline injection once per day for five consecutive days prior to any behavioral testing, and mimicked the dosing regimen that revealed enhanced amphetamine conditioned place preference following adolescent social defeat (Burke et al., 2011). Locomotion responses to amphetamine in both acute (no previous amphetamine treatment) or repeated amphetamine groups were assessed as follows. Rats were first placed in an opaque plastic open field (45 cm × 30 cm × 39 cm) for 60 min to acclimate to the environment. Immediately following this, rats were administered either amphetamine or saline of equivalent volume and returned to the testing environment for 90 min. Rats already exposed to amphetamine or saline for the previous five days received the same injection on the behavioral test day. Distance moved (cm) in the open field was measured by Ethovision XT v5.1 (Noldus Information Technology, Inc., Leesburg, VA, USA).

2.4. Microdialysis procedures

For the acute amphetamine experiment, three days were allowed between behavioral testing and microdialysis sampling to avoid any carry-over effect of the amphetamine administered on the behavioral testing day (Forster et al., 2002; Miller et al., 2002; Burke et al., 2010). For the repeated amphetamine experiment, rats were injected once daily for five consecutive days, followed 24 h later by an injection for behavioral testing (day six), with a final injection upon microdialysis testing on day seven.

Consistent with our previous methodology (Forster et al., 2008; Lukkes et al., 2008; Scholl et al., 2010), microdialysis experiments were conducted under urethane anesthesia to allow implantation and recording from multiple microdialysis probes within the same rat for simultaneous recordings from the NAc and mPFC. Urethane is a long-lasting anesthetic that has minimal effects on neuronal firing rates and neurotransmitter release (Maggi and Meli, 1986), and we have previously shown that elicited monoamine responses are similar between urethane-anesthetized and awake rats (Forster et al., 2006, 2008; Mo et al., 2008; Scholl et al., 2010). Rats were anesthetized with urethane (1.8 g/kg ip.; Sigma) and placed in a stereotaxic frame (David Kopf Institute, Tujunga, CA, USA) with the incisor bar set at + 3.3 mm. Body temperature was maintained at 37 °C with a temperature regulated heating pad (Harvard Apparatus, Holliston, Massachusetts, USA). A laboratory-made concentric microdialysis probe (MW cutoff 5000) with a membrane length of 2 mm (Lukkes et al., 2009) was inserted into the right NAc core (AP: +1.8 mm from bregma; ML: −1.4 mm from midline; DV: −8.1 mm from dura; Paxinos and Watson, 2007), and a second probe 4 mm in membrane length (Forster et al., 2008) was inserted into the ispilateral mPFC (AP: +3.4 mm from bregma; ML: −0.5 mm from midline; DV: −5.4 mm from dura; Paxinos and Watson, 2007) to allow simultaneous sampling from both regions. The probes were attached to a 1.0 ml syringe by PE-20 tubing, and artificial cerebrospinal fluid was continuously perfused through the probes using a microinfusion pump (Harvard Apparatus) at a rate of 0.4 μl/min. Microdialysis sampling began 4 h after the implantation of the probes (Forster et al., 2008; Lukkes et al., 2008, 2009), with dialysates (8 μl) collected at 20 min intervals and analyzed for DA. Following at least three stable baseline DA samples, saline or amphetamine (1.0 mg/kg, ip.) was injected systemically and dialysates were collected for 200 min thereafter and analyzed for DA.

2.5. Dopamine analysis

Analysis of DA in dialysates was accomplished using high-performance liquid chromatography (HPLC) with electrochemical detection. The mobile phase used for DA separation (0.34 g EDTA, 0.25 g 1-decanesulfonic acid, 4.70 g sodium phosphate monobasic, 85 ml methanol, 0.25 ml triethylamine in 500 ml nanopure water, pH 5.8; chemicals obtained from Sigma) was pumped through an UniJet 5 μm C18 silica column (Bioanalytical Systems, West Lafayette, IN, USA) under nitrogen gas pressure (2000 psi). Dialysate (8 μl) was injected using a rheodyne injector into a 5 μl loop to overfill the loop, and DA was detected by a glassy carbon electrode (Bioanalytical Systems) maintained at +0.60 V with respect to the $Ag/AgCl_2$ reference electrode using an LC-4C potentiostat (Bioanalytical Systems). The voltage output was recorded by Clarity v2.4. Chromatography Station for Windows (DataApex, Prague, Czech Republic). Dopamine peaks were identified by comparison to a DA standard (11.05 pg/5 μl DA). The 2:1 signal to noise detection limit for DA using this system for the mPFC was 0.09 ± 0.00 pg, and for the NAc core was 0.06 ± 0.00 pg. For the acute amphetamine experiment, the levels of DA prior to amphetamine injection (baseline; uncorrected for probe recovery) were 0.84 ± 0.13 pg/5 μl for social defeat rats and 0.90 ± 0.17 pg/5 μl for controls in the mPFC, and 3.51 ± 0.87 pg/5 μl for social defeat rats and 2.38 ± 0.53 pg/5 μl for controls in the NAc core. For the repeated amphetamine experiment, the levels of DA prior to amphetamine injection were 0.83 ± 0.13 pg/5 μl for social defeat rats and 0.68 ± 0.08 pg/5 μl for controls in the mPFC, and 1.98 ± 0.21 pg/5 μl for social defeat rats and 2.22 ± 0.39 pg/5 μl for controls in the NAc core. Baseline DA levels were not statistically different between the defeated and control groups within each brain region and within each experiment ($P > 0.05$).

2.6. Histology

Following each microdialysis experiment, rats were euthanized by a lethal dose of Fatal-plus (0.5 ml, ip., Vortech, Dearborn, MI, USA), and the brains were removed

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