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Social isolation rearing increases dopamine uptake and psychostimulant potency in the striatum

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ABSTRACT

Social isolation rearing (SI) is a model of early life stress that results in neurobiological alterations leading to increased anxiety-like behaviors. These animals also exhibit an increased propensity to administer psychostimulants, such as cocaine; however, the mechanisms governing this increased addiction vulnerability remain to be elucidated. Long-term stressors have been shown to produce important alterations in nucleus accumbens core (NAc) function. The NAc regulates motivated and goal-directed behaviors, and individual differences in NAc function have been shown to be predictive of addiction vulnerability. Rats were reared in group (GH; 4/cage) or SI (1/cage) conditions from weaning (PD 28) into early adulthood (PD 77) and dopamine release was assessed using voltammetry in brain slices containing the NAc and dorsomedial striatum. SI rats exhibited enhanced dopamine release and uptake in both regions compared to GH rats. In regard to psychostimulant effects directly at the dopamine transporter (DAT), methylphenidate and amphetamine, but not cocaine, inhibited uptake more in SI than GH rats. The increased potencies were positively correlated with uptake rates, suggesting that increased potencies of amphetamine-like compounds are due to changes in DAT function. Cocaine's effects on uptake were similar between rearing conditions, however, cocaine enhanced evoked dopamine release greater in SI than GH rats, suggesting that the enhanced cocaine reinforcement in SI animals involves a DAT independent mechanism. Together, the results provide the first evidence that greater psychostimulant effects in SI compared to GH rats are due to effects on dopamine terminals related to uptake dependent and independent mechanisms.

1. Introduction

Early life stress in humans is associated with increased risk for developing severe psychological disorders including schizophrenia, depression, and anxiety disorders, as well as risk for abusing and becoming addicted to drugs such as psychostimulants (Scheller-Gilkey et al., 2004; Nugent et al., 2011; Enoch, 2012). Adolescent social isolation rearing (SI) in rats is a translational model that produces early life stress and results in behavioral changes that model many of the deficits observed in humans exposed to early life stress. Accordingly, our laboratory, as well as others, has reported increased anxiety-like behaviors under SI conditions as compared to group housed (GH) counterparts (Da Silva et al., 1996; McCool and Chappell, 2009; Chappell et al., 2013; Yorgason et al., 2013). SI also increases voluntary consumption and preference for abused drugs, and reduces the latency to acquire cocaine self-administration (Schenk et al., 1987; Bozarth et al., 1989; Yajie et al., 2005; McCool and Chappell, 2009; Chappell et al., 2013; Whitaker et al., 2013), demonstrating that SI increases the reinforcing properties of these drugs. However, while increased reinforcement is well documented, the mechanism by which early life stress increases psychostimulant abuse vulnerability is unclear.

Abbreviations: DAT, Dopamine transporter; DMS, Dorsal medial striatum; GH, Group housed rearing; App K_m, Apparent affinity of dopamine for the dopamine transporter; NAc, Nucleus accumbens; PD, Postnatal day; SERT, Serotonin transporter; SI, Social isolation rearing; V_{max}, Maximal rate of dopamine uptake.

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Dopaminergic activity in the striatum is involved in reward learning, drug self-administration and reinforcement behaviors (Pierce and Kumaresan, 2006; Sora et al., 2009). The striatum is divided into multiple subregions, which have been shown to have different functions. The ventral region of the striatum, including the nucleus accumbens core (NAc), is integral in reward-prediction error encoding, and is involved in the acute reinforcing effects of abused compounds as well as motivational and incentive processes (Graybiel, 1995; Di Chiara, 2002; Porrino et al., 2004; Graybiel, 2008; Saddoris et al., 2013). The dorsal regions of the striatum are thought to regulate goal-directed and habitual drug seeking behaviors. For instance, dopamine activity in the dorsomedial striatum (DMS) is required for initial drug seeking behavior, whereas dopamine activity in the dorsolateral striatum is more important for maintaining habitual drug seeking (Murray et al., 2012). Microdialysis studies have established that SI rats have greater dopamine elevations in the NAc after systemic cocaine and amphetamine injections than GH counterparts (Jones et al., 1992; Hall et al., 1998; Howes et al., 2000; Lapiz et al., 2001, 2003), which may help explain increased preference in SI rats. Currently, the direct mechanisms underlying the enhanced ability of stimulants to increase dopamine after SI is unknown. Furthermore, it is unclear if psychostimulant effects on dopamine are similarly enhanced in the DMS of SI rats.

The aim of the present study was to investigate the mechanisms involved in increased psychostimulant effects in SI rats. *Ex vivo* voltammetric methods were used to assess dopamine release and dopamine transporter (DAT) function in the NAc and DMS of SI and GH rats. These measures were examined to determine if changes in dopamine release/uptake kinetics could contribute to the divergent responses to psychostimulants in SI and GH rats. Next, amphetamine, methylphenidate and cocaine's effects on dopamine release and uptake were examined across multiple concentrations in the NAc and DMS of SI and GH rats. Lastly, pre-drug uptake rates and drug effects at maximally tested psychostimulant concentrations were examined for relationships that might help explain increased psychostimulant sensitivity in SI rats. Understanding the early life stress induced adaptations that underlie alterations in psychostimulant potency are particularly important as they may allow for the identification of individuals that are “at risk” or allow for treatments that reverse these adaptations and minimize risk.

2. Materials and methods

2.1. Animal housing

SI procedures were performed as previously described (Yorgason et al., 2013). Briefly, male Long-Evans rats (Harlan Laboratories, Indianapolis, IN) were procured on post-natal day (PD) 21 and housed for one week under standard conditions (4 rats/cage, food/water *ad libitum*, 12/12 h light/dark). On PD 28, rats were randomly assigned to two groups, SI (1 rat/cage; 20 × 27 cm cages; Allentown Inc, Allentown, NJ) and GH (4 rats/cage; 33 × 60 cm cages; Ancare, Bellmore, NY) for six weeks. We have previously reported increases in anxiety-like behavior in SI rats (Chappell et al., 2013; Yorgason et al., 2013; McCool and Chappell, 2009). As in these previous studies, preceding the end of the initial housing period (PD 93), SI and GH rats were tested for anxiety-like behavior on the elevated plus maze (PD 74). *Ex vivo* voltammetry experiments were performed from PD 93–116. Multiple brain slices were obtained from the same rat to reduce the amount of animals used in the present study. Brain slices were from 14 GH to 16 SI rats that were spread across two cohorts, and randomly selected on experimental days, with experimenters blinded to rearing conditions. Experimental protocols adhered to the National Institutes of Health guide for the care and use of laboratory animals and were approved by the Wake Forest University Institutional Animal Care and Use Committee.

2.2. Ex vivo slice preparation

Rats were euthanized and their brains rapidly removed and prepared as described previously (Yorgason et al., 2013). Coronal slices (400 μM) of the striatum were maintained at 32 °C in oxygen perfused (95% O_2–5% CO_2) artificial cerebrospinal fluid which consisted of (in mM): NaCl (126), $NaHCO_3$ (25), D-glucose (11), KCl (2.5), $CaCl_2$ (2.4), $MgCl_2$ (1.2), NaH_2PO_4 (1.2), L-ascorbic acid (0.4), pH adjusted to 7.4. A capillary glass-based carbon-fiber electrode was positioned ~175 μm below the surface of the slice in the NAc or DMS as outlined in Fig. 1. Dopamine release was evoked every 5 min by a 4 ms, single-pulse stimulation (monophasic, 350 μA) from a bipolar stimulating electrode (Plastics One, Roanoke, VA) placed 100–200 μm from the carbon-fiber electrode.

2.3. Fast scan cyclic voltammetry

Fast scan cyclic voltammetry recordings were performed and analyzed using Demon Voltammetry and Analysis software (Yorgason et al., 2011). Carbon fiber electrodes used in voltammetry experiments were made in-house. Briefly, a carbon fiber (~7 μm diameter, Thornel T-650, Cytec, Woodland Park, NJ) was aspirated into a borosilicate glass capillary tube (A-M Systems, Sequim, WA). Subsequently, electrodes were pulled on a PE-22 vertical pipette puller (Narshige International USA, Long Island, NY) and cut so that ~100–200 μm of carbon fiber protruded from the tip of the glass. The electrode potential was linearly scanned as a triangular waveform from −0.4–1.2 V and back to −0.4 V (Ag vs AgCl) using a scan rate of 400 V/s. Cyclic voltammograms were recorded at the carbon fiber electrode every 100 ms by means of a potentiostat (Dagan Corporation, Minneapolis, MN). Once the stimulated dopamine response was stable for three successive collections, baseline measurements were taken and evaluated using a Michaelis–Menten based kinetic model (Wightman, 1988; Yorgason et al., 2011). Michaelis–Menten based changes in

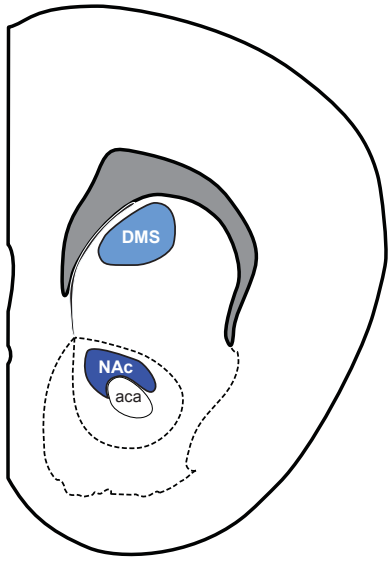

Fig. 1. Dopamine release and uptake were measured in the core of the nucleus accumbens (NAc) and dorsal medial striatum (DMS) of socially isolated (SI) and group housed (GH) rats.