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Susceptibility to traumatic stress sensitizes the dopaminergic response to cocaine and increases motivation for cocaine

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ABSTRACT

Patients with post-traumatic stress disorder have a heightened vulnerability to developing substance use disorders; however, the biological underpinnings of this vulnerability remain unresolved. We used the predator odor stress model of post-traumatic stress disorder with segregation of subjects as susceptible or resilient based on elevated plus maze behavior and context avoidance. We then determined behavioral and neurochemical differences across susceptible, resilient, and control populations using a panel of behavioral and neurochemical assays. Susceptible subjects showed a significant increase in the motoric and dopaminergic effects of cocaine, and this corresponded with heightened motivation to self-administer cocaine. Resilient subjects did not show differences in the motoric effects of cocaine, in dopamine signaling in vivo, or in any measure of cocaine self-administration. Nonetheless, we found that these animals displayed elevations in both the dopamine release-promoting effects of cocaine and dopamine autoreceptor sensitivity ex vivo. Our results suggest that the experience of traumatic stress may produce alterations in dopamine systems that drive elevations in cocaine self-administration behavior in susceptible subjects, but may also produce both active and passive forms of resilience that function to prevent gross changes in cocaine's reinforcing efficacy in resilient subjects.

1. Introduction

Post-traumatic stress disorder (PTSD) and substance use disorder are highly co-morbid psychiatric conditions (Jacobsen et al., 2001; Kessler et al., 1995; Pietrzak et al., 2011), with PTSD onset generally occurring prior to the development of substance use disorders (Jacobsen et al., 2001). These observations suggest that the experience of traumatic stress may confer a vulnerability to developing substance use disorders. Interestingly, only 20–30% of individuals who experience traumatic stress develop PTSD symptoms (Cohen et al., 2012), and individuals that undergo traumatic stress without developing PTSD do not show an increased vulnerability to developing substance use disorders (Chilcoat and Breslau, 1998). This evidence indicates that the development of PTSD, rather than the experience of traumatic stress *per se*, is tied to the development of substance use disorder vulnerability in humans.

Animal models of PTSD and addiction may be useful for discerning some of the behavioral and biological disruptions that predispose an individual to developing substance use disorders following traumatic stress. Indeed, increases in motoric sensitization to cocaine (Garcia-Keller et al., 2013; Prasad et al., 1998) as well as increases in various aspects of cocaine self-administration have been observed following multiple stress protocols (Boyson et al., 2014; Garcia-Keller et al., 2016; Goeders, 2002; Miczek et al., 2011; Piazza and Le Moal, 1998; Tidey and Miczek, 1997). While these studies have generally examined stressed subjects as a homogenous population, it has recently become evident that, like in humans, stress exposure often produces a heterogeneous population in rodents (Cao et al., 2010; Cohen et al., 2012; Edwards et al., 2013; Friedman et al., 2014; Koresh et al., 2016; Krishnan et al., 2007; Levkovitz et al., 2015). This heterogeneity in response to stress may mask some of the behavioral and physiological factors that predispose individuals to developing cocaine self-administration behaviors when stressed populations are viewed as a homogenous group (Holly and Miczek, 2015). To date, the relationship between the variable expression of behavioral

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aberrations following traumatic stress and cocaine self-administration has not been directly tested (Holly and Miczek, 2015).

Emerging evidence suggests that susceptibility to stress may be tied to neuroadaptations that underlie the propensity for cocaine addiction. Specifically, physiological changes to mesolimbic dopamine (DA) neurons determine susceptibility vs resilience to stress (Friedman et al., 2014; Krishnan et al., 2007), and extensive evidence indicates that the mesolimbic DA system is critically involved in the acute reinforcing effects of cocaine (Koob and Volkow, 2010; Roberts et al., 2013). Consistent with these observations, susceptible and resilient rodents express differential conditioned place preference for cocaine (Krishnan et al., 2007), and thus it is feasible that susceptible and resilient subjects may also express differences in the dopaminergic response to cocaine.

We sought to determine if the neurochemical and behavioral effects of cocaine varied with the appearance of maladaptive behaviors following traumatic stress. To this end, we used the predator odor stress model of PTSD, which has repeatedly been shown to produce prolonged behavioral changes representative of PTSD symptoms (Cohen et al., 2012; Cohen and Zohar, 2004; Edwards et al., 2013). We first characterized the heterogeneous response to predator scent stress in our laboratory by measuring a panel of PTSD-like phenotypic indicants. We then used these data to define behavioral cutoffs which were used to segregate subjects based on anxiety behavior in the elevated plus maze (Cohen et al., 2012) and context avoidance (Edwards et al., 2013). Following behavioral segregation we used in vivo microdialysis or ex vivo fast scan cyclic voltammetry (FSCV) to query differences in the mesolimbic DA system of cocaine-naïve rats following traumatic stress. Finally, we tested how the variable response to stress corresponds to changes in the behavioral economics of cocaine self-administration. Our results provide the first evidence that susceptible, but not resilient, rats express increases in the motivation to self-administer cocaine, and provide a putative mechanism by which enhanced dopaminergic sensitivity to cocaine drives elevations in the reinforcing effects of cocaine.

2. Methods

2.1. Animals

Male Sprague–Dawley rats (300–350 g, Harlan, Frederick, MD) were given ad libitum access to food and water and kept on a reverse 12:12 h light:dark cycle (lights on at 15:00 h). All protocols and animal care procedures were maintained in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals: Eighth Edition (The National Academies Press, Washington, DC, 2011) and approved by the Institutional Animal Care and Use Committee at Drexel University College of Medicine.

2.2. Chemicals

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. 2,4,5-trimethyl-3-thiazoline (TMT), butyric acid, sucrose, and all reagents used to make Dulbecco's phosphate buffered saline and artificial cerebrospinal fluid were obtained from Sigma–Aldrich (St. Louis, MO).

2.3. Predator odor stress, context avoidance, and elevated plus maze testing

Treatment of control and stressed rats differed only in the odor of exposure, otherwise all rats underwent the same series of procedures. Stressed rats were exposed to TMT, a compound isolated from fox feces that produces a reliable fear response (Endres and Fendt, 2009) and increases PTSD-like behaviors (Endres and Fendt, 2009; Hacquemand et al., 2013). Control rats were exposed to butyric acid, an unpleasant but not fear-inducing odor (Endres and Fendt, 2009).

Odor exposure and context avoidance testing were performed in a three-chamber place conditioning box (Med Associates, St. Albans, VT) held within a custom cabinet fitted with a ventilation system, bright lighting, and an overhead camera. Rats were exposed within one of two context chambers (11″ x 8.5″ x 8.5″) that differed in both visual (white with vertical black stripes vs. black with horizontal white stripes) and tactile (grid vs. bar floor) features. On the first day of testing, rats were placed in the gray center chamber (6″ x 8.5″ x 8.5”) and were allowed to freely explore all chambers of the apparatus in a recorded 5-min preference test. Time spent in each context chamber was recorded as baseline preference. All rats were single-housed following initial testing. On the following day, rats were confined to one of the two context chambers and 10 μl of either TMT or butyric acid was pipetted onto tissue paper placed below the chamber floor. Odor exposures were performed at the beginning of the light phase (ZT 0:00), and lasted for 15 min.

Elevated plus maze and context avoidance tests were performed 7 days after odor exposure since it has been repeatedly shown that maladaptive behaviors apparent at 7 days after predator odor stress generally persist over extended periods (Cohen et al., 2004, 2012). Rats were first tested in a recorded 5-min, free exploration of an elevated plus maze (File et al., 2004). Elevated plus maze tests were performed under dim red light, and were recorded with an overhead camera. To quantify behavior in the elevated plus maze, we measured time spent in the open arms of the maze. Animals were scored as being in an open or closed arm only when both forepaws passed over the open/closed dividing line. All subjects that fell off of the maze were excluded from further testing.

To test for context avoidance, rats were placed in the center chamber of the place conditioning box and were allowed to freely explore all three chambers of the apparatus in a recorded 5-min avoidance test. Time spent in the predator odor-paired and the unpaired chambers was scored. To quantify context avoidance behavior we calculated the change in time spent in the odor-paired chamber (Δ Paired), which was defined as the difference in time spent in the odor-paired chamber during the avoidance and preference tests. Likewise, we calculated nonspecific avoidance (Δ Unpaired) as the difference in time spent in the unpaired chamber during the avoidance and preference tests. All animals included in these studies underwent this series of procedures and tests, and we refer to this process as “stress and segregation testing” (Fig. 1A).

2.4. Acoustic startle response and circulating corticosterone testing

A cohort of rats was tested for acoustic startle response and late-dark phase corticosterone levels on the day after elevated plus maze and context avoidance testing. Acoustic startle response was measured in sound-attenuated startle chambers (SR-LAB system, San Diego Instruments, San Diego, CA) consisting of a Plexiglas cylinder resting on a movement-sensitive platform. Sound levels inside the chambers were calibrated with a sound level meter (Radio Shack, Fort Worth, Texas), and platform sensitivity was calibrated daily. Rats were tested in pairs and underwent a 5-min acclimation period with background noise of 68 dB before the onset of acoustic startle trials. The experiment consisted of 6 blocks of 5 trials, for a total of 30 trials, each containing a 120 dB burst of noise that lasted for 40 ms. Inter-trial intervals varied from 12 to 30 s with an average interval of 15 s. Acoustic startle response was calculated as the average startle amplitude across 30 trials. Percent