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Environmental enrichment facilitates cocaine abstinence in an animal conflict model☆

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ABSTRACT

In this study, we sought to discover if housing in an enriched environment (EE) is an efficacious intervention for encouraging abstinence from cocaine seeking in an animal "conflict" model of abstinence. Sixteen Long-Evans rats were trained in 3-h daily sessions to self-administer a cocaine solution (1 mg/kg/infusion) until each demonstrated a stable pattern of drug-seeking. Afterward, half were placed in EE cages equipped with toys, obstacles, and a running wheel, while the other half were given clean, standard laboratory housing. All rats then completed daily 30-min sessions during which the 2/3 of flooring closest to the self-administration levers was electrified, causing discomfort should they approach the levers; current strength (mA) was increased after every day of drug seeking until the rat ceased activity on the active lever for 3 consecutive sessions (abstinence). Rats housed in EE abstained after fewer days and at lower current strengths than rats in standard housing. These results support the idea that EE administered after the development of a cocaine-taking habit may be an effective strategy to facilitate abstinence.

1. Introduction

Despite advances in the prevention and treatment of drug addiction, cocaine use remains stable and problematic in the US; recent data estimate that 1.87 million Americans have used cocaine in the last month, and 867,000 met DSM-IV-TR criteria for a cocaine-specific stimulant use disorder in 2016 (APA, 2000; Center for Behavioral Health Statistics and Quality, 2017). Many struggle to abstain from cocaine and relapse is common, as cravings often overshadow the immediate, legal, and social costs, medical risks (e.g., Fonseca and Ferro, 2013; Maraj et al., 2010; Riezzo et al., 2012), and the possibility of neuropsychological injury (Buttner, 2012; Spronk et al., 2013). Psychological and pharmacotherapeutic interventions provide relief from craving in some users, but a deeper understanding of the contribution of environmental factors to cocaine dependence could open doors to more effective treatments.

While it is widely known from studies of human addicts that exposure to negative or stressful stimuli can intensify addictive behaviors and trigger drug relapse, decades of research with rodents have demonstrated myriad benefits induced by access to positive, enriched environments (EE). EE studies have varied greatly in methodology, including types of enrichment, duration of exposure, and the age, breed, and gender of rodent subjects, but most involve a larger habitat when compared to standard housing and interaction with novel objects and/or social cohorts (for a review, see Simpson and Kelly, 2011). Housing in EE cages has been shown to reduce anxiety (Leal-Galicia et al., 2007; Pena et al., 2009; Qian et al., 2008), responsivity to stress (Fox et al., 2006; Segovia et al., 2009), depressive phenotypes and endogenous markers of depression (Brenes et al., 2009, 2008; Fox et al., 2006; Koh et al., 2007; Segovia et al., 2009), and improve cognitive functioning, such as learning and memory (for a review, see Simpson and Kelly, 2011).

In studies specific to the effects of EE on cocaine exposure, housing in EE (when compared to standard housing) has often been shown to significantly reduce behavioral responses to cocaine and the incidence of addiction-related behaviors. These phenomena are observed using a variety of behavioral paradigms, including quantification of cocaine-induced locomotor activity (Bezard et al., 2003; Galaj et al., 2017; Solinas et al., 2008, 2009), conditioned place preference (CPP; Galaj et al., 2017; Green et al., 2010; Solinas et al., 2008; Solinas et al., 2009), and intravenous self-administration (IVSA) studies, which may provide more direct insight into motivations behind cocaine-seeking (Chauvet et al., 2009; Gipson et al., 2011; Green et al., 2010; Peck et al., 2015; Puhl et al., 2012; Ranaldi et al., 2011; Thiel et al., 2011, 2009). The use

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of EE as a protective tool (i.e., pre-cocaine exposure) for prevention of cocaine-related behaviors has yielded inconsistent results (for a brief review, see Galaj et al., 2017); rearing in EE or short-term, pre-cocaine EE exposure has been shown to likewise inhibit (e.g., Gipson et al., 2011; Solinas et al., 2009), enhance (e.g., Schenk et al., 1986; Smith et al., 2009) or have no effect on behavioral responses to cocaine (e.g., Bozarth et al., 1989; Galaj et al., 2017). However, when EE is employed as an intervention (i.e., post-cocaine exposure), it appears to be more consistently effective in moderating cocaine addiction-related behaviors. Housing in EE after cocaine exposure can eliminate the expression of pre-established CPP (Galaj et al., 2017; Solinas et al., 2008), prevent cocaine-induced reinstatement of preference (Solinas et al., 2008), and reduce cocaine-induced locomotor activity to cocaine-naïve levels after behavioral sensitization (Solinas et al., 2008). Also, in animals well-trained in cocaine self-administration, subsequent housing in EE reduces responding during extinction training (Chauvet et al., 2009; Ranaldi et al., 2011) and can reduce or eliminate reinstatement of cocaine-seeking triggered by the presentation of previously cocaine-paired conditioned stimuli (Chauvet et al., 2009; Ranaldi et al., 2011; Thiel et al., 2011, 2009). These results suggest that some feature of EE may decrease incentive motivation for cocaine and limit the experience of craving that often precedes relapse.

However, while these studies may effectively demonstrate a reduction of cocaine reward and the provocative power of conditioned stimuli, most animal addiction models may not adequately speak to the human problems of cocaine abstinence and relapse. The extinction/reinstatement paradigm is frequently used to model relapse (e.g., Chauvet et al., 2009; de Wit and Stewart, 1981; Galaj et al., 2016; Thiel et al., 2009): drug self-administration behaviors are extinguished by removing drug reinforcement, and subsequent exposure to the drug or to conditioned stimuli causes the animal to resume these behaviors. As noted by Cooper et al. (2007), the human experience of abstinence and relapse is quite different. Drug-addicted individuals nearly always have access to their drug of choice, but must endure negative repercussions (e.g., legal, financial, social) in order to acquire it; the conflicts that arise from such stressful experiences during drug pursuit can maintain abstinence (Cooper et al., 2007). In the “conflict model” introduced by Cooper et al. (2007) animals still have access to the drug, but obtaining it requires crossing a floor that is electrified by a current that increases in strength after each day of continued drug-seeking. “Abstinence” is attained when the animal ceases drug-seeking activity for a predefined number of IVSA sessions, and “relapse” occurs when drug-seeking resumes upon presentation of an inducing stimulus, such as a drug-paired cue. Such a design may come closer to emulating the choice a human addict may face: abstain or endure the consequences of continued use. Recent studies have demonstrated that this animal conflict model can be successfully employed in drug addiction research (Barnea-Ygael et al., 2012; Cooper et al., 2007; Peck et al., 2015, 2013). Previously, we have shown that EE could accelerate abstinence from heroin seeking (Peck et al., 2015), but the utility of EE as a therapeutic intervention to foster cocaine abstinence has not yet been explored.

The present study sought to determine if housing in an enriched environment may assist in achieving cocaine abstinence within the animal conflict paradigm when compared to standard housing (non-EE). Rats well-trained in cocaine self-administration were subsequently placed in EE or non-EE, and both groups underwent sessions identical to IVSA training sessions, with the addition of electrified flooring in front of the self-administration levers. We hypothesized that rats housed in EE would reach abstinence criteria faster and at a lower electric barrier strength than non-EE rats. Current strength and latency to achieve abstinence were compared between groups.

2. Methods

2.1. Subjects

The subjects were male Long-Evans rats (Charles River, Kingston, New York, USA; $n = 16$) weighing 350–380 g at study onset. All rats were housed individually in standard laboratory cages with free access to water and food (LabDiet chow). Cages were placed in windowless rooms with an automated 12-h light/12-h dark cycle, and rats were only engaged in study procedures during the dark (active) phase of the cycle. This experiment was conducted in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978) and was approved by the Queens College Institutional Animal Care and Use Committee.

2.2. Surgery

Each rat was given an intraperitoneal injection of atropine (0.54 mg in 0.1 mL of distilled water) to reduce salivary and bronchial secretions, and then anaesthetized with an intraperitoneal injection of sodium pentobarbital (65 mg/kg). The rat was then placed in a stereotaxic apparatus, an incision was made on the top of the head, and six screws were partially implanted into the skull in an oval pattern to mount a head cap assembly. Next, another incision was made in the neck, the jugular vein was isolated and opened, and one end of a silastic catheter (Dow Corning, Midland, Michigan, USA) was inserted into the vein so that its tip fell just short of the heart. The other end of the catheter was routed subcutaneously around the neck, emerging from the scalp incision. Lastly, a head cap assembly was built using a cannula, acrylic screw, and dental acrylic; the resulting head cap allowed for attachment to a tether through which cocaine was infused. Both incisions were stitched, and a topical antibiotic was applied to the neck incision and around the head cap to prevent infections. To maintain catheter patency, catheters were flushed with a heparin-saline solution (0.05 mL, 200 U.S.P.) immediately after surgery and after each daily IVSA session. All animals were housed individually and given 3 days to recover from surgery before beginning self-administration training.

2.3. Drugs

The cocaine for this experiment was a gift from the National Institute on Drug Abuse (NIDA), and was delivered in saline solution (0.125 mL/infusion) at an estimated dose of 1 mg/kg/infusion.

2.4. Equipment

All study sessions were conducted in operant conditioning chambers run by Med Associates interfacing and software (Georgia, VT). Chambers measured 26 × 26 × 30 cm and were constructed with 3 aluminum sides, a transparent plastic front, a hinged plastic top, and a floor of stainless steel rods. Each chamber was housed in a larger, sound- and light-attenuating wooden box and was illuminated by a central house light on the inner surface of this box. The back of each chamber held two levers located 10 cm above the floor; one served as the active lever and the other as an inactive lever (right and left levers were designated as active or inactive in a balanced fashion across chambers). A small white cue light was located 3 cm above each lever. For IVSA, each rat was attached via head cap assembly to a tethered line, which was connected to a fluid swivel directly above the chamber. Polyethylene tubing within the tether provided fluid connection to a cocaine-filled syringe in a Razel pump (3.33 rpm). The electric barrier (discussed below) was generated by constant-current aversive stimulators connected to the stainless-steel flooring (Model ENV-414; Med Associates).