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No evidence that environmental enrichment during rearing protects against cocaine behavioral effects but as an intervention reduces an already established cocaine conditioned place preference

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ABSTRACT

Objectives: Environmental enrichment (EE) produces differential effects on psychostimulant-related behaviors. Therefore, we investigated whether the timing of EE exposure - during rearing and before cocaine exposure versus in adulthood and after cocaine exposure might be a determining factor.

Methods: In Experiment 1, rats reared with EE or not (non-EE) were conditioned with cocaine (5, 10 or 20 mg/kg) in one compartment of a CPP apparatus and saline in the other, and later tested for cocaine CPP. In Experiment 2, locomotor activity in response to repeated injections of saline or cocaine was measured in rats raised with EE or non-EE. In Experiment 3 we measured the effects of EE or non-EE during rearing on food-based conditioned approach learning. In Experiment 4, rats were exposed to cocaine CPP conditioning then underwent 60 days of EE or non-EE treatment after which they were tested for cocaine CPP.

Results: Our results show that rearing in EE did not reduce cocaine CPP or cocaine-induced locomotor activity (Experiments 1 and 2) but significantly facilitated conditioned approach learning (Experiment 3). On the other hand, EE treatment introduced after cocaine conditioning significantly reduced the expression of cocaine CPP (Experiment 4).

Conclusions: These findings suggest that EE does not protect against cocaine's rewarding and stimulant effects but can reduce already established cocaine effects, suggesting that EE might be an effective treatment for cocaine addiction-related behaviors.

1. Introduction

The interaction between environmental enrichment (EE) and drug-related behaviors has received a lot of attention in recent years. Environmental enrichment refers to enriched housing conditions. Different groups of researchers use different features as part of their housing environmental enrichment condition and generally they involve a combination of sensory stimulation (i.e., novel objects) that promotes exploratory behavior, group housing that stimulates social interaction and apparatuses like running wheels that promote physical activity. When EE is implemented during rearing it can promote neuronal plasticity that involves alterations in the morphology of neurons (Greenough et al., 1973; Holloway, 1966; Kolb et al., 2003; Rosenzweig and Bennett, 1996) and glial cells (Diniz et al., 2010; Viola et al., 2009), long term potentiation and depression (Artola et al., 2006; Hosseiny et al., 2014), alterations in gene transcription (Greenwood et al., 2011) and neurogenesis (Hosseiny et al., 2014; Kempermann et al., 1997; van Praag et al., 2005). Exposure to an enriched environment during rearing also modifies the neurochemical parameters of brain-derived neurotrophic factor (BDNF) (Bakos et al., 2009) and cholinergic (Bennett et al., 1964) and glutamatergic (Melendez et al., 2004) neuronal systems, all systems that are important for learning and memory.

In addition, EE improves performance on several behavioral tests including the Morris water maze and the radial arm maze (measures of spatial memory and learning) (Bingham and Griffiths, 1952; Janus et al., 1995), object recognition and open field (a measure of exploratory behavior) (Clausing et al., 1997; Elliott and Grunberg, 2005; van Waas and Soffie, 1996). Rodents exposed to EE display less anxiogenic and depressive profiles on the elevated plus maze and forced swim tests than non-EE rodents (Brenes et al., 2009; Brenes et al., 2008; Hall et al., 1998; Wright et al., 1991).

Given these EE-induced neurochemical and behavioral effects, EE has been studied in relation to drugs of abuse. As a treatment, EE

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implemented after the establishment of a drug self-administration habit can reduce cue-, context- or stress-induced reinstatement of cocaine (Chauvet et al., 2009; Ranaldi et al., 2011; Thiel et al., 2009) and heroin seeking (Galaj et al., 2016b) and can facilitate abstinence from heroin self-administration (Peck et al., 2015). EE introduced after conditioning reduces the expression and or reinstatement of cocaine (Chauvet et al., 2011; Mustroph et al., 2016; Solinas et al., 2008), ethanol (Li et al., 2015) and heroin conditioned place preference (CPP) (Galaj et al., 2016b). Wheel-running, when used as part of an enriched environment, has been shown to reduce nicotine- (Sanchez et al., 2013), cocaine- (Lynch et al., 2010; Thanos et al., 2013) and methamphetamine-seeking in rodents (Sobieraj et al., 2016) as well as the expression (Mustroph et al., 2016) and extinction of cocaine CPP (Mustroph et al., 2011). Hence, these findings suggest that EE holds potential as an effective treatment for drug-related behaviors.

However, the effects of EE implemented during rearing (i.e., before exposure to drugs of abuse) on subsequent drug-related behaviors are still equivocal. There is some evidence suggesting that EE serves as "protection against" drug effects. Rearing with EE can attenuate opiate- (El Rawas et al., 2009; Xu et al., 2007) and cocaine-induced CPP in rodents (Nader et al., 2012; Zakharova et al., 2009). Enriched rats, especially females (Westenbroek et al., 2013), tend to show a reduction in self-administration of low doses of psychostimulants (Bardo et al., 2001; Green et al., 2010; Green et al., 2002) and a reduction in psychostimulant seeking (Green et al., 2010; Hofford et al., 2014; Lu et al., 2012; Stairs et al., 2006). EE might also protect against the escalation of cocaine intake in rats under long-access self-administration conditions (Gipson et al., 2010) and opiate- (Bardo et al., 1997; Xu et al., 2007) or stimulant-induced behavioral sensitization (Bardo et al., 1995; Green et al., 2003; Hamilton et al., 2014; Solinas et al., 2009) and response to drug challenge injections (Green et al., 2003; Solinas et al., 2009). These reports are in sharp contrast to studies that have shown either no effects or enhancing effects of rearing with EE on drug-related behaviors. It has been reported that housing conditions do not influence self-administration of high doses of amphetamine (Green et al., 2002; Schenk et al., 1988), methamphetamine- (Hofford et al., 2014; Lu et al., 2012) or cocaine- (Bozarth et al., 1989; Westenbroek et al., 2013) in male rats and, although they may attenuate the initial acquisition of heroin self-administration in rats raised in single housing, the socially-isolated rats eventually progress in heroin intake to the same level as group-housed rats (Bozarth et al., 1989). Similarly, rearing with EE (group housing; with or without toys) has no effect on psychostimulant-induced CPP (Hofford et al., 2014; Schenk et al., 1986; Thiriet et al., 2011) or behavioral sensitization to heroin (El Rawas et al., 2009) or psychostimulants (Starosciak et al., 2012). Yet others report enhancements in the behavioral effects of drugs when rearing with EE conditions. There are reports of greater locomotor activity in response to chronic injections of amphetamine (Bowling et al., 1993) and enhanced morphine (Bardo et al., 1997), amphetamine (Bardo et al., 1995; Green et al., 2010) or cocaine CPP (Dow-Edwards et al., 2014; Starosciak et al., 2012).

Of particular interest are the effects of EE during rearing on cocaine CPP. Although some studies suggest that rearing in EE has preventive abilities on the establishment of cocaine CPP (Nader et al., 2012; Solinas et al., 2009; Zakharova et al., 2009) other studies suggest that rearing with EE enhances cocaine CPP (Dow-Edwards et al., 2014; Green et al., 2010; Smith et al., 2009). Because of conflicting findings in regard to whether or not rearing in enriched environments has protective or enhancing effects on cocaine-related behaviors we investigated this problem in the current study. Our EE procedure consisted of sensory stimulation (novel objects) and physical activity (running wheel). We also studied whether rearing in EE affects behavioral sensitization to repeated injections of cocaine in rats. Finally, we investigated whether or not EE as a treatment after cocaine conditioning affects the expression of already established cocaine CPP. To our knowledge, this is the first study that presents the effects of EE treatment on cocaine CPP across different cocaine doses and demonstrates differential effects of EE during rearing versus post-cocaine exposure. In order to demonstrate that our EE procedure (i.e., sensory stimulation and physical activity) during rearing can produce behavioral effects we investigated the effects of EE during rearing on food conditioned approach.

2. Methods

The protocols used in the present experiments were in accordance with the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, 2011) and were approved by the Queens College Institutional Animal Care and Use Committee.

2.1. Subjects

Subjects were male Long Evans rats from our facility-based colony with breeders purchased from Charles River Laboratories (Kingston, NY, US). In Experiments 1–3 on postnatal day P21 rats were weaned out and placed individually in either environmental enrichment (EE) or non-environmental enrichment (non-EE) housing where they were maintained throughout the experiment. All rats were given free access to food (LabDiet chow) and water except those in Experiment 3. For these rats food was restricted to 30 g per day for the five experimental session days; on all other days food was available ad libitum. In Experiment 4, rats were weaned out on P21 and group-housed (n = 2 per cage) until P60 when they were separated to individual cages and prepared for experimentation. Animals were kept in a temperature and humidity-controlled facility and maintained on a reverse 12 h light: 12 h dark cycle (lights were turned on at 9 pm). All sessions were conducted during the animals' active period (the dark cycle).

2.2. Apparatus

2.2.1. Enrichment housing

Each enrichment cage measured 36 × 66 × 41 cm and was equipped with beta chip bedding, a running wheel, a 10-cm diameter tunnel, wooden blocks, and paper towel rolls. Three additional objects (e.g., jingly ball, mirrored bowl, glass mug, paper ball, plastic blocks, sock, string, dog chew and stuffed animals) were replaced daily with new toys of different shapes and colors. Non-enriched housing consisted of standard cages (43 × 34 × 20 cm) with beta chip bedding.

2.2.2. Conditioned place preference apparatus

Conditioned place preference studies were conducted in 2-compartment chambers (43 × 43 × 30 cm), each placed in a ventilated, sound-attenuating cubicle with an operating fan to mask outside noise. Each conditioning chamber was equipped with 32 photo emitters, 16 on each of two adjacent walls, and 32 detectors spaced along opposite walls and 6 cm above the floor. These photo-beam detectors tracked the position of the rats in one compartment or the other. The two conditioning compartments of the CPP apparatus were distinct in wall and floor features; walls were either white or had vertical white and black stripes and floors were either stainless steel mesh or rods; the combination of walls and floor was unique for each conditioning chamber. A black plastic wall with an opening separated the compartments. During place preference conditioning, a guillotine door was inserted into the opening to confine the rat to a particular compartment.

2.2.3. Locomotor activity chambers

Locomotor activity was measured in plastic-walled chambers each placed in a ventilated, sound-attenuating cubicle with an operating fan to mask outside noise. Each open field chamber measured 43 × 43 × 30 cm and was equipped with 32 photo emitters, 16 on each of two adjacent walls. Opposite to each photo emitter was a photo