Pharmacology, Biochemistry and Behavior 154 (2017) 20–30

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Differential housing and novelty response: Protection and risk from locomotor sensitization

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ARTICLE INFO

Article history:
Received 2 July 2016
Received in revised form 17 December 2016
Accepted 16 January 2017
Available online 17 January 2017

Keywords:
Differential rearing/housing
Enrichment
Novelty and sensation seeking
Amphetamine
Sensitization
Mediation and prediction

ABSTRACT

High novelty seeking increases the risk for drug experimentation and locomotor sensitization. Locomotor sensitization to psychostimulants is thought to reflect neurological adaptations that promote the transition to compulsive drug taking. Rats reared in enrichment (EC) show less locomotor sensitization when compared to rats reared in isolation (IC) or standard conditions (SC). The current research study was designed to test if novelty response contributed locomotor sensitization and more importantly, if the different housing environments could change the novelty response to protect against the development of locomotor sensitization in both adolescence and adulthood.

Experiment 1: rats were tested for their response to novelty using the inescapable novelty test (IEN) and pseudorandomly assigned to enriched (EC), isolated (IC), or standard (SC) housing conditions for 30 days. After housing, they were tested with IEN. Rats were then administered amphetamine (0.5 mg/kg) or saline and locomotor activity was measured followed by a sensitization test 14 days later. Experiment 2: rats were tested in the IEN test early adulthood and given five administrations of amphetamine (0.3 mg/kg) or saline and then either stayed in or switched housing environments for 30 days. Rats were then re-tested in the IEN test in late adulthood and administered five more injections of their respective treatments and tested for locomotor sensitization.

Results indicate that IC and SC increased the response to novelty. EC housing decreased locomotor response to amphetamine and saline, and SC housing increased the locomotor response to amphetamine. Mediation results indicated that the late adult novelty response fully mediates the locomotor response to amphetamine and saline, while the early adulthood novelty response did not.

Conclusions: Differential housing changes novelty and amphetamine locomotor response. Novelty response is altered into adulthood and provides evidence that enrichment can be used to reduce drug vulnerability.

1. Introduction

The transition to drug dependence has been characterized as a process that involves several phases (Koob & Le Moal, 1997, 2001; Koob & Volkow, 2010; Kreek & Koob, 1998). Numerous reports have observed that high novelty and sensation seeking individuals are more vulnerable to the initiation of drug use (Blanchard et al., 2009; Donohew et al., 1999; Martin et al., 2002; Zuckerman, 1994). Novelty and sensation seeking reaches maximal expression during adolescence (Arnett, 1992); a time when drug experimentation is also elevated (Arnett, 1992). Therefore, animal models of novelty response are widely used preclinical models for understanding the relationship between individual differences in novelty response and drug-use vulnerability.

One widely used animal model to examine the relationship between novelty and drug use examines the response to inescapable novelty. Piazza et al. (1989) categorized rats as either high (HR) or low (LR) novelty responders based on their amounts of locomotor activity in an inescapable novel environment. HR rats are more sensitive than LR rats to amphetamine-induced locomotor activity (Exner and Clark, 1993; Hooks et al., 1991; Hooks et al., 1992) and to amphetamine self-administration (Marinelli, 2005; Piazza et al., 1989; Pierre and Vezina, 1997). The difference between HR and LR rats is most robust at low unit doses (Cain et al., 2008; Kabbaj, 2006; Piazza et al., 1989). Numerous studies have demonstrated that the response to inescapable novelty predicts vulnerability to the early phases of drug use (Kabbaj, 2006; Marinelli, 2005; Piazza et al., 1989), prior to the development of compulsive drug taking (Belin et al., 2011; Blanchard et al., 2009).

While this model predicts the binge-intoxication stage of drug use, it is not clear what, if any, factors can alter this predisposition to novelty-

Abbreviations: EC, enriched condition; IC, isolated condition; SC, standard condition; IEN, inescapable novelty test; PND, post-natal day.

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http://dx.doi.org/10.1016/j.pbb.2017.01.004
0091-3057/

seeking or the response to drugs of abuse. Therefore, the current experiments were designed to test if the differential housing manipulation will alter the novelty response and the response to amphetamine. Understanding if the environment can alter the response to novelty and, subsequently the response to amphetamine will enable development of interventions to reduce sensitivity to the reinforcing effect of psychostimulants during the development of hyperactivity.

While a variety of methods examining human sensation seeking and drug use have been employed, these studies frequently use novelty seeking or sensation seeking as continuous variables in multiple regression analyses (Donohew et al., 1991; Roberti, 2004; Zuckerman, 1994). The animal models for novelty seeking are also measured on a continuous scale. However, the scores traditionally are dichotomized into high and low groups by a median split (Marinelli, 2005). The median split is problematic because it assumes the members of each group are similar and the members of different groups are categorically different, neither of which may be true. Further, the median split discards the precision of the original continuous measure, and may underestimate the relationship and decrease statistical power (Cohen, 1983; Humphreys and Fleishman, 1974; Irwin and McClelland, 2003; Maxwell and Delaney, 1993). The current experiments used mediation regression analyses to analyze how novelty was changed and predicts amphetamine-induced locomotor activity. These analyses allow for the detection of more subtle differences changed by housing condition, because we can determine a change from a known baseline. Detecting a change in novelty response when novelty response is categorized requires a shift from one category to another category, which may not occur, despite a change in novelty response. The precision in measurement ensures more accurate analyses and relationships and precise descriptions of said relationships (Bissonnette et al., 1990a; Bissonnette et al., 1990b; Cohen, 1968).

In the differential housing paradigm, rats are raised in different environments from the post-weaning period through mid to late adolescence. In the enriched environment, rats receive daily handling and are raised in a large cage with several other rats and novel objects. Each of these factors is critical elements that create the enriched environment (Renner and Rosenzweig, 1987). Rats in the isolated environment are reared individually without novel objects or contact with other rats or the experimenters. The differential housing environments result in numerous neurobiological differences including (Green and Greenough, 1986; Renner and Rosenzweig, 1987) changes within brain regions in the mesolimbic dopamine system that contribute to the response to novelty and drugs of abuse (Bardo et al., 2013; Green and Greenough, 1986; Melendez et al., 2004; Rahman and Bardo, 2008; Renner and Rosenzweig, 1987; Zhu et al., 2005).

The mesolimbic alterations that result from differential housing contribute to robust differences in novelty response. Post-weaning enrichment decreases locomotor activity in an inescapable novel environment (Fuller, 1967; Lore and Levowitz, 1966; Simpson and Kelly, 2011). In addition, enriched rats approach novel stimuli more quickly, and decrease responding to novel stimuli faster than do isolated rats (Zimmermann et al., 2001). Enrichment also reduces the locomotor response to low doses of psychostimulants (Bardo et al., 1995; Green et al., 2002). Enrichment decreases acute amphetamine-induced hyperactivity when compared to isolation (Bardo et al., 1995; Cain et al., 2012; Gill et al., 2012). Enrichment also decreases psychostimulant-induced sensitization across a range of psychostimulants when compared to isolation (Bardo et al., 1995; Cain et al., 2012; Coolon and Cain, 2009; Smith et al., 1997; Wooters et al., 2011).

Given the well established effect of housing in an enriched environment on the response to psychostimulants, the ability of enrichment to function as an intervention following exposure to psychostimulants has been examined. Adult mice placed in enrichment following group housing had a decrease in cocaine-induced sensitization, but only after 30 days of enrichment (Solinas et al., 2008). This suggests that enrichment during adulthood may be able to decrease the locomotor response to psychostimulants, when enrichment is used as an intervention. However, research has not attempted to manipulate the novelty response to change the development of amphetamine-induced locomotor sensitization.

Therefore, the current experiments examined if differential housing, during the post-weaning period or in adulthood following psychostimulant exposure, can alter the response to novelty and the response to amphetamine. Generally, we hypothesized that enrichment would reduce the response to inescapable novelty and would therefore decrease the response to amphetamine. Conversely, we predicted that isolation housing would increase the inescapable novelty response and the response to amphetamine. We also predicted the adult novelty response is stable and will not be significantly changed by housing condition. Interestingly, the response to inescapable novelty does not predict the transition from controlled drug use to compulsive drug use (Belin et al., 2008; Belin et al., 2011), but enrichment reliably decreases psychostimulant sensitization. Therefore, the current experiments also examined amphetamine-induced sensitization to determine if differential housing or novelty seeking is the better predictor of amphetamine-induced sensitization.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, Portage, MI, USA) arrived in the laboratory at 21 days of age and were housed in one of three differential housing conditions: enriched (EC), isolated (IC), or standard (SC). The colony room operated on a 12-h light-dark cycle and was maintained at approximately 22 °C, with humidity ranging from approximately 30–45%. All behavioral tests were conducted during the light portion of the cycle. All procedures conducted and research reported was in accordance with the Institutional Animal Care and Use Committee at Kansas State University, and complied with NIH guidelines (National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011).

2.2. Differential housing conditions

Both Experiments utilized differential housing conditions, enriched (EC), isolated (IC), and standard (SC). Our EC, IC, and SC environmental conditions have been explained previously (Arndt et al., 2014; Arndt et al., 2015; Cain et al., 2012; Gill et al., 2012). Briefly, rats in the EC were housed in a large metal cage (60 × 120 × 45 cm) that was lined with paper pulp bedding. The EC cage contained 8–12 other rats and contained 14 objects (toys, PVC pipe). To maintain novelty, seven of the 14 objects were changed daily and all objects were changed two times weekly. The EC rats were also handled during the 30 day housing periods for ~1 min per day. The IC rats were housed in hanging metal cages (17 × 24 × 20 cm), were not handled throughout the 30 day housing periods, and did not have access to novel objects or other rats. The SC rats were housed in pairs in standard shoebox cages (20 × 43 × 20 cm) with the same bedding as the EC rats. The SC rats did not have access to objects and were not handled during the 30 day housing periods. In Experiment 1, rats were placed in the EC, IC, or SC condition on postnatal day (PND) 22 and remained in this housing for the duration of the experiment. In Experiment 2, rats were placed in the EC or IC condition on Day 21 and housed for 30 days. After five administrations of amphetamine or saline, they stayed in their original housing condition or were switched to the EC or IC condition. Rats remained in the new housing assignment for an additional 30 days. After the additional 30 days, another round of behavioral testing commenced and the rats remained in their respective conditions for the duration of the experiment.