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Early-life adversity facilitates acquisition of cocaine self-administration and induces persistent anhedonia

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ABSTRACT

Early-life adversity increases the risk for emotional disorders such as depression and schizophrenia. Anhedonia, thought to be a core feature of these disorders, is provoked by our naturalistic rodent model of childhood adversity (i.e., rearing pups for one week in cages with limited bedding and nesting, LBN). Drug use and addiction are highly comorbid with psychiatric disorders featuring anhedonia, yet effects of LBN on drug-seeking behavior and the reward and stress-related circuits that underlie it remain unknown. Here we examined the effects of LBN on cocaine intake and seeking, using a battery of behavioral tests measuring distinct aspects of cocaine reward, and for comparison, chocolate intake. We also examined activation of neurons within the pleasure/reward and stress circuits following cocaine in LBN and control rats. Early-life adversity reduced spontaneous intake of palatable chocolate, extending prior reports of sucrose and social-play anhedonia. In a within-session cocaine behavioral economic test, LBN rats self-administered lower dosages of cocaine under low-effort conditions, consistent with a reduced hedonic set-point for cocaine, and potentially anhedonia. In contrast, cocaine demand elasticity was not consistently affected, indicating no major changes in motivation to maintain preferred cocaine blood levels. These changes were selective, as LBN did not cause an overt anxiety-like phenotype, nor did it affect sensitivity to self-administered cocaine dose, responding for cocaine under extinction conditions, cocaine- or cue-induced reinstatement of cocaine seeking, or locomotor response to acute cocaine. However, high Fos expression was seen after cocaine in both reward- and stress-related brain regions of LBN rats, including nucleus accumbens core, central amygdala, and lateral habenula. In contrast, hypothalamic orexin neuron activation after cocaine was significantly attenuated in LBN rats. Together, these findings demonstrate enduring effects of early-life adversity on both reward- and fear/anxiety-related neural circuits, as well as anhedonia-like reductions in consumption of natural and drug rewards.

1. Introduction

Early-life adversity in humans is associated with increased risk for emotional disorders such as depression and schizophrenia (Heim et al., 2008; Klengel and Binder, 2015; Pratchett and Yehuda, 2011; Sharma et al., 2016). An early or predictive sign for these disorders is anhedonia, defined as a lack of pleasure derived from otherwise enjoyable activities. Indeed, anhedonia has recently been recognized as an important Research Domain Criterion (RDoC) by the National Institute of Mental Health (Insel, 2014). In agreement with these findings in humans, we have identified anhedonia for natural rewards as a long-term consequence of early-life adversity in our naturalistic model, in which an impoverished early-life environment (limited bedding and nesting: LBN) induces aberrant maternal care (Molet et al., 2016a). LBN-induced anhedonia, evidenced by decreased preference for sucrose and reduced social play, was reversed by knockdown of corticotropin releasing hormone (CRH) in the central nucleus of the amygdala (CeA) (Bolton et al., 2018). In addition, social play induced aberrant Fos activation of CeA CRH neurons in LBN rats, and neuroimaging suggested increased connectivity between amygdala and medial prefrontal cortex (mPFC). These findings suggest that early-life adversity disrupts the normal maturation of interconnected anxiety/fear-and reward circuits. However, the extent to which early-life adversity influences reward circuitry remains poorly understood.

A potential consequence of LBN-induced changes in reward circuits is altered sensitivity to drug rewards, and risk for addiction (Enoch,

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Nonstandard abbreviations

ABC	avidin-biotin complex
A	motivation, reflecting slope of the decay in responding at higher effort requirements
BLA	basolateral amygdala
CeA	central amygdala
CRH	corticotropin releasing hormone
Ctrl	Control
DAB	diaminobenzidine
DMH	dorsomedial region of hypothalamus
FR1	fixed ratio 1 schedule
ILC	infralimbic medial prefrontal cortex
LBN	limited bedding and nesting
LH	lateral region of hypothalamus
LHb	lateral subregion of habenula
MHb	medial subregion of habenula
mPFC	medial prefrontal cortex
NAcC	nucleus accumbens core
NAcSh	nucleus accumbens shell
PD	postnatal day
PFA	perifornical region of hypothalamus
PLC	prelimbic medial prefrontal cortex
Q_0	hedonic set point, reflecting extrapolated value of cocaine at price 0
RDoC	Research Domain Criterion
SA	self-administration

2011). The neural circuits underlying pleasure and motivation for natural and drug rewards heavily overlap (Kelley and Berridge, 2002), but animal studies using intermittent early-life stress caused by repeated maternal separation have shown complex and sometimes conflicting effects on addiction-related behaviors (Lehmann and Feldon, 2000; Moffett et al., 2007). For example, Meaney et al. (2002) showed that repeated maternal separation increases cocaine-induced locomotion, whereas O'Connor et al. (2015) showed that maternal separation decreases cocaine self-administration (SA). One possible explanation for these conflicting findings is the variability inherent to intermittent stress caused by maternal separation. Unlike human early-life adversity, maternal separation stress in rodents is intermittent and predictable and may not fully recapitulate the experiences of children receiving poor or distracted parental care (Davis et al., 2017). In contrast, the LBN paradigm provides both the chronicity and the fragmented and chaotic maternal care elements found in humans, which seem to contribute to long-lasting anhedonia-like behaviors in adult rodents, as well as humans reared under these conditions (Baram et al., 2012; Bolton et al., 2017; Davis et al., 2017; Molet et al., 2016a). However, how the early-life adversity provoked by LBN influences drug and natural reward-seeking in rodents is unknown.

Therefore, we examined effects of early-life adversity on cocaine intake and seeking, using a suite of specific behavioral tests of preferred low-effort cocaine intake, economic demand elasticity, dose-responsivity, relapse-like behavior, and locomotor activation. With this approach, we determine the specific behavioral processes affecting cocaine reward that are influenced by early-life adversity. To identify the LBN-induced neural circuit alterations underlying changes in cocaine hedonics or motivation, we examined Fos expression in reward- and anxiety/fear-related brain regions after acute cocaine. Among these were hypothalamic orexin/hypocretin neurons, which play important roles in motivational activation associated with drug- and natural-reward seeking, as well as stress and arousal (Berridge et al., 2010; Mahler et al., 2014a). These studies, focusing on addiction- and anhedonia-related changes in neural circuits caused by LBN in early life, suggest potential targets for therapeutic interventions in those who experienced a chaotic and/or traumatic early childhood.

2. Materials and methods

2.1. Animals

Four primiparous, timed-pregnant rats were obtained from Envigo (Livermore, CA) on E15, and maintained in an uncrowded, quiet animal facility room on a 12 h light/dark cycle. Parturition was checked daily, and the day of birth was considered postnatal day (PD)0. Male offspring were used in these experiments (n = 16), and equal numbers from each dam were assigned to LBN and control groups. Rats were weaned at PD21, housed in pairs until PD49 +, and single-housed in a reverse light cycle thereafter. Food and water were available *ad libitum* throughout experiments. All procedures were approved by the University of California Irvine Institutional Animal Care and Use Committee and conducted in accordance with the National Institutes of Health guide for the care and use of laboratory animals. Experimental timeline is shown in Fig. 1.

2.2. Limited bedding and nesting (LBN) procedures

On PD2, pups from four litters were gathered, and 12 pups (8 males) were assigned at random to each dam, to prevent the potential confounding effects of genetic variables or litter size. Dams and pups assigned to the LBN group were transferred to cages fitted with a plastic-coated aluminum mesh platform sitting ~2.5 cm above the cage floor. Bedding only sparsely covered the cage floor under the platform, and one-half of a 24.2 cm × 23.5 cm paper towel was provided for nesting material. Control group (Ctrl) dams and pups were placed in cages containing a standard amount of bedding (~0.33 cubic feet of corn cob) without a platform, and one full paper towel. Ctrl and LBN cages remained undisturbed during PD2-9, during which maternal behaviors were monitored as previously described (Ivy et al., 2008). The LBN paradigm provokes significant chronic stress in the pups, as measured by increased corticosterone levels and adrenal hyperplasia, which return to normal by adulthood (Brunson et al., 2005). The stress likely arises because of an abnormal, fragmented pattern of maternal behaviors provoked by the limited nesting material (Molet et al., 2014, 2016a).

2.3. Intravenous catheter surgery

At PD48, rats were anesthetized prior to surgery using ketamine and

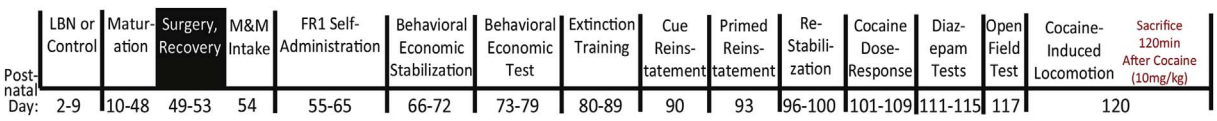

Fig. 1. Experimental Timeline: Timeline of experimental procedures is shown. Manipulation or test is shown at top, postnatal test day or range shown at bottom. Rats were sacrificed 120 min after 10 mg/kg cocaine on postnatal day 120.