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Research report

Pharmacological manipulation of glucocorticoid receptors differentially affects cocaine self-administration in environmentally enriched and isolated rats

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HIGHLIGHTS

- Rats were raised in environmental enrichment (EC) or isolation (IC).
- EC rats decreased low-dose cocaine self-administration after pretreatment with RU486.
- EC and IC rats significantly differed in responding when pretreated with CORT.
- Glucocorticoid receptor protein did not differ between EC and IC in any area tested.

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ABSTRACT

Social isolation rearing (isolated condition, IC) is used as a model of early life stress in rodents. Rats raised in this condition are often compared to rats raised in an environmentally enriched condition (EC). However, EC rats are repeatedly exposed to forced novelty, another classic stressor in rodents. These studies explored the relationship between cocaine self-administration and glucocorticoid receptor (GR) activation and measured total levels of GR protein in reward-related brain regions (medial prefrontal cortex, orbitofrontal cortex, nucleus accumbens, amygdala) in rats chronically exposed to these conditions. For Experiment 1, rats were housed in EC or IC and were then trained to self-administer cocaine. Rats raised in these housing conditions were tested for their cocaine responding after pretreatment with the GR antagonist, RU486, or the GR agonist, corticosterone (CORT). For Experiment 2, levels of GR from EC and IC rats were measured in brain regions implicated in drug abuse using Western blot analysis. Pretreatment with RU486 (20 mg/kg) decreased responding for a low unit dose of cocaine (0.03 mg/kg/infusion) in EC rats only. IC rats were unaffected by RU486 pretreatment, but earned significantly more cocaine than EC rats after pretreatment with CORT (10 mg/kg). No difference in GR expression was found between EC and IC rats in any brain area examined. These results, along with previous literature, suggest that enrichment enhances responsivity of the HPA axis related to cocaine reinforcement, but this effect is unlikely due simply to differential baseline GR expression in areas implicated in drug abuse.

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1. Introduction

Early life stress is associated with negative mental health outcomes in humans, including increased risk of developing addiction. Predictive stressors are early life events that do not have to be traumatic [1,2]. Children raised in homes where one or more parents are unemployed, where parents have low levels of education, or children from households that have lower socioeconomic status are more likely to abuse stimulants during adulthood [3–5].

Abundant preclinical evidence indicates that adult rats acutely exposed to a variety of stressors demonstrate accelerated acquisition of stimulant intake [6], enhanced stimulant reward [7], and greater cocaine consumption [8]. However, it is less clear whether there is a differential effect of acute and chronic stress on stimulant reward in adolescent rats (reviewed in [9]). Despite this, studies consistently report that rats isolated during adolescence (isolated condition, IC) self-administer low unit doses of stimulants at a greater rate compared to rats raised in social conditions [10] and compared to rats raised in enriched conditions (EC) [10–12].

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In addition to isolation, however, exposure to novel objects is often used experimentally as a stressor [13,14]. Accordingly, short-term exposure to either isolation or novelty increases circulating levels of the stress hormone corticosterone (CORT) [15,16]. However, in contrast to isolation rearing, EC rats, which experience repeated exposure to novelty, self-administer stimulants at a lower rate, perform better on a battery of behavioral tasks [17,18], and also recover more rapidly from injury than IC rats [19]. This contrasts with other work showing that all of these outcomes are usually negatively affected by other stressors [20–22]. Thus, even though both isolation and novelty exposure cause CORT release acutely, lasting or repeated exposure to these stressors results in opposite stress-related behavioral outcomes.

There are several neurobiological targets implicated in both stress and drug abuse, including corticotrophin releasing factor (CRF), the dynorphin/kappa system, norepinephrine, and the hypothalamic–pituitary–adrenal (HPA) axis (reviewed in [23–25]). Among these, the role of the HPA axis in drug abuse has been studied most extensively. CORT is a major end point of the HPA axis and it negatively regulates its own release via actions at the glucocorticoid receptor (GR) [26,27]. CORT level is correlated with cocaine self-administration, but only at low cocaine doses [28]. In fact, CORT is necessary for cocaine self-administration, as adrenalectomized rats do not acquire self-administration of cocaine [29] and do not undergo reinstatement [30]. Additionally, decreasing circulating CORT levels by inhibiting its synthesis with metyrapone [29] or ketoconazole [31] reduces maintenance of cocaine self-administration, although adrenalectomy does not affect cocaine self-administration once it has been acquired [32]. Regardless, once CORT levels have been increased to some threshold necessary for acquisition of stimulant self-administration, further increases in CORT do not amplify stimulant intake (reviewed in [33]).

The target receptor for CORT in these effects has not been defined, although GR might play some role in the maintenance of stimulant self-administration in rodents. Knockout of GR in the central nervous system attenuates cocaine self-administration in mice [34] and administration of the non-selective GR antagonist RU486 decreases stimulant self-administration in mice and rats [35,36].

Only one study has examined differences in HPA axis functioning between EC and IC rats in response to drugs of abuse. In that study, RU486 was found to decrease amphetamine self-administration to a greater extent in EC rats than IC rats [35]. Other studies have quantified aspects of the HPA axis in EC and IC rats, but the results have been mixed. Basal CORT was found to be lower in EC rats compared to IC rats in one study [35]. In contrast, other studies have found that EC rats have higher basal CORT compared to normal housed controls [37] and others have measured lower basal CORT after chronic isolation compared to rats in normal cage conditions [38,39]. Another study found no difference between IC rats and group-housed rats [40]. However, these discrepancies may be due, at least in part, to the type of cage IC rats are housed in, as rats housed in cages with wire grid floors have greater circulating CORT than rats raised in cages with sawdust bedding [41].

Studies quantifying GR mRNA from EC and IC rats found no difference in prefrontal cortex [42]. GR protein has been reported to be increased in hippocampus in EC rats compared to normal housed controls in some studies [43,44], but not in all studies [45]. Notably, few studies have directly compared GR protein expression in EC to IC rats across more than one brain area. In addition, these studies have not examined the functional consequences of altered CORT or GR levels in differentially housed animals.

Given the observed decrease in stimulant self-administration following enrichment, it has been hypothesized that repeated exposure to novelty, experienced daily by EC rats, reduces sensitivity of the HPA axis in contrast to other traditional stressors. This produces a functional anti-stress effect [46]. However, the precise mechanisms underlying the functional adaptation are largely unknown. To address this hypothesis, the current experiments examined differences between EC and IC rats in cocaine self-administration after pretreatment with the GR antagonist RU486 or the GR agonist CORT, as well as total GR expression in various stress- and drug abuse-relevant brain regions. Rats were initially trained to lever press for food and then were trained to self-administer a high unit dose of cocaine (0.75 mg/kg/infusion). The high training dose of cocaine was selected to minimize initial EC/IC differences in response rate that typically occur at low unit doses of stimulant drugs [10–12]. Since baseline differences between EC and IC rats can complicate the interpretation of drug effects [47], engendering similar baseline response rates in EC and IC rats is advantageous for interpreting the potential differential effects of RU486 and CORT.

2. Materials and methods

2.1. Subjects

Male Sprague Dawley rats were purchased from Harlan Laboratories (Indianapolis, IN) and arrived in the colony at PND 21. Rats were immediately placed on a 12 h light-dark cycle (lights on at 7:00 AM) and were allowed food and water ad libitum. All procedures were approved by the University of Kentucky's Institutional Animal Care and Use Committee and all procedures conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Housing

Upon arrival to the colony, rats were randomly assigned to EC or IC cages. EC rats were placed in large stainless steel cages (122 cm × 61 cm × 45.5 cm) with 14 hard plastic objects (commercial toys) and 5–10 age-matched cohorts. Half of the objects in the cage were switched daily. Rats in the IC condition were placed singly in small stainless steel cages (17 cm × 24 cm × 20 cm) with wire grid floors and no objects. These small cages allowed food and water changes, as well as waste disposal, without human contact. Rats were returned to their housing conditions at the end of each session and remained in their environments for the duration of the experiment.

2.3. Experiment 1: cocaine self-administration

2.3.1. Apparatus

All self-administration sessions were conducted in standard 2-lever operant conditioning chambers (28 cm × 24 cm × 21 cm; ENV-008CT; MED Associates, St. Albans, VT) equipped with syringe pumps for drug delivery (PHM-100; MED Associates).

2.3.2. Pretraining

Seven days prior to surgery (∼PND 48), all rats started training to lever press for food pellets (45 mg Dustless Precision Pellets, Bio-Serv, Frenchtown, NJ). Training continued as follows: magazine shaping for 1 day, autoshaping for 3 days, and FR1 training for 3 days. During magazine shaping, food pellets were randomly delivered to the food hopper on a random time 36-s interval. For autoshaping, both levers were extended and the cue light over the active lever was illuminated. One response on the active lever resulted in delivery of one sucrose pellet and retraction of both levers. If no response was made on the active lever, one pellet was delivered and the levers were retracted on a random time 60-s interval. After magazine shaping and autoshaping, rats were trained to lever press for food pellets on a FR1 schedule of reinforcement for 3 days. For this procedure, both levers were extended but only