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Research report

Cocaine exposure prior to pregnancy alters the psychomotor response to cocaine and transcriptional regulation of the dopamine D1 receptor in adult male offspring

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HIGHLIGHTS

- Cocaine prior to pregnancy enhanced psychomotor sensitivity to cocaine in adult male offspring.
- This enhanced sensitivity to cocaine in the offspring was associated with increased gene expression of DRD1 in mPFC.
- Cocaine prior to pregnancy had no effect on maternal behavior during lactation.
- Cocaine prior to pregnancy had no effect on CORT, GR or CRF gene expression in offspring.

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ABSTRACT

There is evidence that maternal experience prior to pregnancy can play an important role in behavioral, physiological, and genetic programming of offspring. Likewise, exposure to cocaine in utero can result in marked changes in central nervous system function of offspring. In this study, we examined whether exposure of rat dams to cocaine *prior to* pregnancy subsequently alters indices of behavior, physiology, and gene expression in offspring. Multiple outcome measures were examined in adult male offspring: (1) behavioral expression of cocaine-induced psychomotor activation; (2) levels of corticosterone in response to immobilization stress; and (3) expression of multiple genes, including dopamine receptor D1 (DRD1) and D2 (DRD2), glucocorticoid receptor (GR), and corticotropin-releasing factor (CRF), in functionally relevant brain regions. Adult Sprague-Dawley females were exposed to cocaine (15–30 mg/kg, i.p.) or saline for 10 days, and were then mated to drug naïve males of the same strain. Separate groups of adult male offspring were tested for their acute psychomotor response to cocaine (0, 15, 30 mg/kg, i.p.), corticosterone responsivity to 20 min of immobilization stress, and expression of multiple genes using quantitative PCR. Offspring of dams exposed to cocaine prior to conception exhibited increased psychomotor sensitivity to cocaine, and upregulated gene expression of DRD1 in the medial prefrontal cortex (mPFC). Neither stress-induced corticosterone levels nor gene expression of GR or CRF genes were altered. These data suggest that cocaine exposure before pregnancy can serve to enhance psychomotor sensitivity to cocaine in offspring, possibly via alterations in dopamine function that include upregulation of the DRD1.

Abbreviations: AMG, amygdala; CORT, corticosterone; CRF, corticotrophin releasing factor; DRD1, dopamine receptor D1; DRD2, dopamine receptor D2; GR, glucocorticoid receptor; HC, hippocampus; HPA, hypothalamic-pituitary-adrenal axis; HYP, hypothalamus; LG ABN, licking and grooming, arched-back nursing; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PND, postnatal day; VTA, ventral tegmental area.

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1. Introduction

Prenatal exposure to cocaine can lead to detrimental effects in the physiology and central nervous system function of offspring. In humans, the most common outcomes of cocaine use during pregnancy include premature birth, lower than average birth weight, respiratory distress, and increased risk of seizures in offspring [1]. Prenatal exposure to cocaine has also been shown to affect the developing nervous system, by delaying structural brain maturation of dopamine-rich cortical and subcortical brain structures, such as the prefrontal cortex (PFC) and basal ganglia, respectively [2]. For example, in a recent study carried out in adolescents exposed to cocaine during pregnancy, significant impairments in structural brain maturation of the PFC were observed, possibly owing to cocaine-induced elevations in synaptic levels of serotonin and dopamine as a result of interference in monoamine reuptake [3].

Rodents exposed to cocaine prenatally display deficits analogous to those found in humans. For example, cocaine exposure during gestation leads to dose-dependent increases in maternal blood pressure and decreases in uterine blood flow, impairing oxygen transfer to the fetus; such impairment may in turn contribute to observed increases in fetal levels of cocaine and catecholamines [4]. Likewise, prenatal cocaine exposure leads to abnormalities in fetal brain development, particularly within the dopamine-rich neurons of the primary reward pathway projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and PFC. In addition, prenatal cocaine exposure has been shown to delay the migration of GABA neurons during the embryonic period, leading to altered laminar positioning of neurons in the medial PFC [5] and marked reduction of GABAergic function in the medial PFC [6]. Prenatal cocaine exposure has also been linked to altered cocaine-primed dopamine release in the NAc in adulthood [7]. Taken together, these data indicate that prenatal exposure to cocaine in both humans and animals leads to physiological dysregulation and neural alteration in reward-related circuitry of offspring.

Importantly, cocaine crosses the placenta and is metabolized slowly in the fetus, which can lead to direct and prolonged exposure to significant levels of cocaine in the developing fetus [1]. Notably, in an in vitro model, fetal neuronal cells exposed to cocaine showed alterations in the expression of many genes involved in brain development [8]. Because gestational exposure to cocaine potentially involves direct effects of cocaine on both the mother and offspring, the maternally mediated effects of cocaine exposure are unclear.

The purpose of the present study was to determine whether exposure of adult rat dams to cocaine prior to conception changes the behavioral and transcriptional phenotypes of adult offspring. By studying the effects of cocaine exposure before pregnancy, we were able to disentangle the potential intergenerational effects of cocaine exposure in dams from the direct effects of cocaine to the developing fetus. To this end, we assessed three major outcome measures in the adult male offspring of dams given cocaine prior to conception, all of which can be influenced by a history of prior cocaine experience [9–20]: (1) cocaine-induced psychomotor activation; (2) stress-induced activation of the hypothalamic pituitary adrenal (HPA) axis, as reflected in plasma levels of corticosterone; and (3) expression of DRD1 and DRD2 genes within discrete regions of the brain reward circuitry (i.e., VTA, NAc, and mPFC), as well as expression of the stress-related glucocorticoid receptor (GR) and corticotropin releasing factor (CRF) genes in limbic regions (i.e., hypothalamus [HYP], hippocampus, [HC], and amygdala [AMG]).

2. Materials and methods

2.1. Animals

Twenty female Sprague-Dawley rats were purchased from Charles River Canada (St.-Constant, QC). Rats were pair-housed in cages in a humidity-controlled vivarium on a 12 h light–dark cycle. Standard rat chow and water were freely available. All rats were allowed at least 1 week of acclimatization to the vivarium before the start of the cocaine pre-exposure regimen, which consisted of once daily injections of cocaine for 10 days (see below). After the cocaine pre-exposure regimen, rats were left undisturbed for 5 days, after which time they were housed with sexually experienced male Sprague-Dawley rats. One male was housed with each pair of females for 7 days. After this mating period, males were returned to their home cages and females were singly housed.

Of the original 20 female subjects, 18 became pregnant: 9 cocaine pre-exposed and 9 saline pre-exposed. The offspring of six dams from each pre-exposure condition were randomly selected for the experiments. On Postnatal Day 1 (PND1), all litters were weighed and culled to six males and six females. After weaning on PND21, offspring were pair-housed with a littermate of the same sex.

All procedures were performed in accordance with the guidelines of the Canadian Council on Animal Care and were approved by the University of Toronto Animal Care Committee.

2.2. Procedures

2.2.1. Procedural manipulations of dams

2.2.1.1. Cocaine pre-exposure. The cocaine pre-exposure regimen was started when the rat dams were approximately 65 days of age. One day prior to the start of cocaine (or saline) injections, all rats were given a habituation session, to acclimatize them to the experimental apparatus and treatment procedures. During this session, rats were placed in locomotor activity chambers (26 cm × 48 cm × 21 cm) for a period of 30 min. Then they were given a saline (1 kg/ml i.p.) injection, after which they were replaced in the activity chambers for an additional 60 min. Locomotor activity both before and after the injection was monitored and recorded by a video tracking system that measured distance traveled during each min of the session (Ethovision, Noldus Information Technology, Inc., Leesburg, VA). In order to equate baseline levels of activity in the cocaine and saline pre-exposure conditions, animals were assigned to the conditions based on activity during the habituation session.

Over a subsequent and consecutive 10-day period, rats were given once daily injections of cocaine or saline. On Days 1 and 10, cocaine (15 mg/kg, i.p.) or saline injections were given in the locomotor activity chambers, under the same conditions described for the habituation session. Thus, rats were placed in the chambers for 30 min, injected with cocaine or saline, and placed back in the chambers for an additional 60-min recording period. On Days 2–9, cocaine (30 mg/kg, i.p.) or saline injections were given in the home cages. This is a cocaine dosing regimen that we and others have found previously to produce robust behavioral sensitization to cocaine [20,21].

2.2.1.2. Test for cocaine sensitization. Approximately 8 weeks after the termination of the cocaine exposure phase, and within 1 week of weaning (which occurred on PND21), all dams were tested for their locomotor response to a challenge injection of 15 mg/kg of cocaine (i.p.). For this test, rats were placed in the locomotor chambers for