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Research Report

Effects of perinatal cocaine exposure on open field behavior and the response to corticotropin releasing hormone (CRH) in rat offspring

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ABSTRACT

Previous reports indicate that prenatal cocaine exposure alters specific behaviors and hypothalamic–pituitary–adrenal axis (HPA) function in the offspring. In most previous studies, cocaine was given via subcutaneous injections. However intravenous administration more closely mimics human cocaine abuse during pregnancy. Therefore, we investigated the effects of prenatal cocaine exposure via intravenous injection to the mothers on open field behavior and HPA axis function of the offspring. We hypothesized that prenatal cocaine exposure decreases immobility in a novel environment, and enhances the HPA response to stress. Dams received cocaine (COC) or vehicle (control, CON) intravenously from gestation day 8 to postnatal day (PD) 5. Behaviors were recorded in the open field on PD 28 (weanlings). As expected, perinatally cocaine-exposed offspring spent less time immobile and had a longer latency to entering the center zone. No other behavioral activities were different between the groups. On PD 43–50, adolescent male and female offspring received either corticotropin releasing hormone (CRH) or saline intravenously. Plasma adrenocorticotropic hormone (ACTH) and corticosterone (CORT) levels were determined before, and up to 60 min after injection. COC-exposed offspring of both sexes had higher basal CORT levels. Prenatal cocaine enhanced the CORT response to CRH/saline injections up to 60 min in males but not in females. These novel results show that perinatal administration of cocaine in a manner that most closely mimics human cocaine use has long-term effects on the offspring's behavioral response to stress and on HPA axis functions.

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Abbreviations: COC, cocaine; CON, control; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone; CORT, corticosterone

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1. Introduction

Cocaine abuse during pregnancy remains a significant public health problem in spite of a recent decrease in overall prevalence of cocaine use. During pregnancy, cocaine abuse elevates maternal plasma adrenocorticotropin hormone (ACTH) and cortisol levels (Owiny et al., 1991), which together with elevated catecholamines can lead to maternal hypertension (Woods et al., 1987), decreased uterine blood flow (Sherman and Gautieri, 1972), uterine contraction (Moore et al., 1986) and fetal hypoxemia (Woods et al., 1987, 1989). Cocaine also activates the HPA axis by potentiating ACTH secretion through central serotonin (5-HT) 1A receptor-mediated functions (Battaglia and Cabrera, 1994). Cocaine use is associated with the altered HPA axis responses to stress (Mantsch et al., 2007; Sarnyai et al., 1998). Alterations of the HPA axis response to stressors have been associated with neuropsychiatric disorders, including depression, and posttraumatic stress disorder (Chrousos, 2009). The question arises as to whether a long-lasting effect of prenatal cocaine exposure on the offspring's HPA axis could serve as an underlying mechanism for aberrant neurobehavioral outcomes, such as impulsivity or risk taking behavior, in children prenatally exposed to cocaine (Bennett et al., 2007). This possibility is supported by the observations of higher arousal or reactivity in infants (Eiden et al., 2009a) and decreased immobility in an open field test in adult rats that had been exposed to cocaine prenatally (Molina et al., 1994). Under basal conditions, neurobehavior may appear normal, but deficits may emerge under stress, including environmental, pharmacological or cognitive challenges (Spear et al., 2002). Therefore in the following study, we first tested the hypothesis that in young weanling offspring, prenatal cocaine exposure is associated with decreased immobility in response to a novel environment such as the open field test. Second, we determined whether prenatal cocaine exposure increases the HPA axis response to stress in adolescent offspring.

Extensive studies have shown that acute administration of cocaine increases levels of ACTH and corticosterone (CORT) in rats (Mello and Mendelson, 1997). The increase in plasma ACTH or CORT levels after acute cocaine administration was completely abolished by pretreatment with CRF antiserum (Rivier and Vale, 1987), CRF antibody or antagonist for CRF receptor (Sarnyai et al., 1992), indicating that corticotropin releasing factor (CRF) mediates the acute increases in ACTH (and CORT) in response to cocaine administration. However whether prenatal cocaine has life-long effects on pituitary response to CRH has not been investigated. In addition for some neuropsychiatric and endocrine disorders, CRH stimulation tests are utilized as a diagnostic tool to reveal changes in pituitary responsiveness. Therefore, we administered CRH to test the hypothesis that pituitary responsiveness is increased by prenatal cocaine exposure.

Gender-specific effects of prenatal cocaine exposure on behaviors (Bendersky et al., 2006; Heyser et al., 1995; Spear et al., 2002; Wood and Spear, 1998) and on HPA axis function (Choi et al., 1998) have been observed previously in animals and humans. Furthermore, it has been suggested that gender differences may predispose individuals to stress-related disorders, such as affective disorders (Gorman, 2006; Grigoriadis and Robinson, 2007), drug addiction (Becker and Hu, 2008; Le Moal, 2009; Schulte et al., 2009) and to the effects of prenatal stress on HPA axis function and behaviors of the offspring (Mueller and Bale, 2008; Thomas et al., 2009; Weinstock, 2008).

Therefore we also examined whether there are gender differences in the effects of prenatal cocaine exposure on postnatal behavior and the stress response of the HPA axis.

The long-term effects of prenatal cocaine exposure on the HPA axis have been previously studied using a variety of approaches. Use of animal models allows better control of experimental parameters. However, the animal models used did not always mimic human cocaine abuse. For instance, the commonly used subcutaneous or oral routes of drug administration in rats fail to mimic the pharmacokinetic profiles or cardiovascular effects of cocaine abuse in humans (Mactutus et al., 1994, 2000), in whom cocaine is most often administered via intravenous injection or inhalation. Moreover, animal studies that have used subcutaneous injections have found conflicting results; the HPA stress response was either unchanged (Planeta et al., 2001) or enhanced (Choi et al., 1998) in contrast to the attenuated basal activity or stress response of the HPA axis reported in some human studies (Jacobson et al., 1999; Magnano et al., 1992). The best route of cocaine administration in rats is chronic intravenous injection because it produces peak arterial plasma levels that are close to those reported following human recreational use with no evidence of acute toxicity to the dams (Booze et al., 1997; Evans et al., 1996; Morgan et al., 2002). Therefore in the following study, we administered cocaine by intravenous injection to determine the effect of prenatal cocaine exposure on the postnatal open field behavior and the response of the HPA axis to a CRH stimulation test in the offspring and whether there are sex differences in these outcomes.

2. Results

There was no difference between groups in mean body weights at birth or through adulthood as shown in Fig. 1. The litter sizes of cocaine-exposed dams (COC) ($n=11$) and control (CON) ($n=10$) were not different (COC: 12.7±0.5 vs. CON: 12.7±0.9 pups per litter, mean ± SE, $p=0.98$).

2.1. *Open field test*

There were no gender differences in locomotion, pivoting, rearing, grooming, sniffing or immobility behaviors in 25 COC

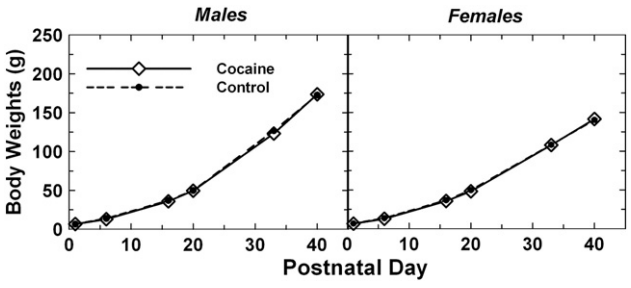

Fig. 1 – Mean body weights (g) of the male and female offspring from cocaine and control groups.