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Gestational and postpartum corticosterone exposure to the dam affects behavioral and endocrine outcome of the offspring in a sexually-dimorphic manner

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ABSTRACT

Exposure to high levels of glucocorticoids *in utero* and during the postpartum period has a detrimental effect on brain development. We created an animal model of postpartum stress/depression based on administering high levels of corticosterone (CORT) to the dams during the postpartum period which caused behavioral changes and reduced hippocampal cell proliferation in the offspring. As the consequences of early exposure to glucocorticoids may depend on the dose and the developmental stage of the offspring, the present study was conducted to investigate the effects of low (10 mg/kg) or high levels of CORT (40 mg/kg) given to dams either during gestation, postpartum or across both gestation and postpartum on the outcome of the offspring. Male and female offspring were weighed throughout the experiment, tested in a series of behavioral tests (forced swim test, open field, elevated plus maze) and basal and restraint stress CORT levels were examined in adolescence or young adulthood. Results show that maternal CORT exposure, regardless of when administered, significantly attenuated body weight gain until adulthood in the offspring. Offspring exposed to low maternal CORT, but not high maternal CORT, during the postpartum had higher basal levels of CORT as young adults. Further, male and female offspring of dams exposed to high maternal CORT *in utero* showed more depressive-like behavior in the forced swim test, while males of dams exposed to high maternal CORT postpartum exhibited more anxiety-like behavior in the elevated plus maze. Taken together, maternal glucocorticoid exposure have long lasting effects on male and female offspring's behavioral and neuroendocrine measures in adolescence and adulthood depending on the time of exposure to glucocorticoids.

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1. Introduction

Stress during pre- or postnatal development can have a profound impact on the long-term outcome of the individual. The maternal hypothalamus pituitary adrenal (HPA) axis is downregulated during pregnancy, partly to protect the offspring *in utero* from harmful effects of elevated glucocorticoids (Brunton et al., 2008). However, despite the alteration of the HPA axis function of the mother, prenatal stress profoundly affects the neurodevelopment of the offspring (Talge et al., 2007). For instance, if a rat dam is exposed to psychological stress during her pregnancy, her male offspring display depressive-like behaviors in the forced swim test and altered HPA axis function compared to offspring from a non-stressed dam (Abe et al., 2007). Similarly, male and female children born to women who experienced stress during pregnancy had a higher risk for developing depressive symptoms and severe depression as young adults compared to age-matched controls from non-stressed mothers (Watson et al., 1999). Further, exposing the pregnant dam to restraint stress causes changes in anxiety, spatial learning, neuroendocrine function and receptor levels in the brain of the offspring, which are highly sex-dependent (Darnaudery and Maccari, 2008; Zuena et al., 2008). It is also well known that early postpartum stress, such as maternal separation, can have profound and sex-dependent effects on the adult phenotype of the F1 (e.g. Gross et al., in press; Renard et al., 2007; Slotten et al., 2006), and F2 offspring generations (Franklin et al., 2010). In addition early stress can affect maternal behavior in the lactating female offspring (Bosch et al., 2007) as prenatal and postnatal exposure to stress also changes maternal behavior in the dam. For instance, chronic stress during pregnancy reduces maternal licking (Smith et al., 2004), while high maternal corticosterone (CORT) treatment postpartum

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reduces time spent on the nest and nursing (Brummelte and Galea, 2010a). Thus, early stress or exposure to glucocorticoids can impact the developmental outcome of the offspring directly and indirectly by reducing maternal care (Fleming et al., 1997; Liu et al., 1997; Nomura et al., 2002).

Direct administration of glucocorticoids to the dam, rather than stress exposure, will allow us to better understand the contribution of glucocorticoids on the effects of pre- or postnatal stress. Antenatal steroids are used in threatened preterm labor to support the lung surfactant maturation (Roberts and Dalziel, 2006), but it has been suggested that multiple dosages could have a negative influence on the development of the infant (Wapner et al., 2007). From animal studies, it is well known that administration of glucocorticoids directly to the offspring during early postnatal development can cause permanent morphological, physiological, and behavioral modifications (Edwards and Burnham, 2001; Machhor et al., 2004; Theogaraj et al., 2005). These modifications include a decrease in brain weight (DeKosky et al., 1982; Ferguson and Holson, 1999), long-term and selective down-regulation of glucocorticoid receptors (Felszeghy et al., 1996), impaired adrenocortical response to stress (Erskine et al., 1979), disruptions in learning (DeKosky et al., 1982; Vicedomini et al., 1986), and delayed development (Golub, 1982; Pavlovska-Teglia et al., 1995). However, less is known on how maternal glucocorticoid levels affect the offspring, as the offspring may be partly buffered from maternal glucocorticoids during the first two weeks of life, a period known as the 'stress hypo-responsive period' (Sapolsky and Meaney, 1986).

We have shown previously that administration of high CORT to dams postpartum leads to reduced hippocampal cell proliferation in male pre-adolescent offspring and behavioral changes in adult male and female offspring (Angelucci et al., 1983; Brummelte et al., 2006). We further showed that CORT treatment to the dam during pregnancy resulted in increased serum CORT in the offspring shortly after birth (Brummelte et al., 2010). Interestingly, maternal postpartum treatment with CORT increased whole brain levels of CORT on day 7 but no significant differences were seen in CORT levels in the prefrontal cortex, hypothalamus or hippocampus in 18 day old pups from CORT-treated dams compared to controls (Brummelte et al., 2010). Further we have found that treatment with high CORT postpartum, but not during gestation, results in a depressive phenotype in the dam (Brummelte and Galea, 2010a), suggesting that the effects of elevated maternal glucocorticoids on behavior and glucocorticoid levels in the offspring may also depend on the time of exposure during gestation or postpartum.

The present study was conducted to investigate the effects of two doses of CORT (10 mg/kg; 40 mg/kg) administered to dams during gestation, postpartum or both periods on behavioral and neuroendocrine parameters in male and female offspring. For this, dams received daily injections of either oil or CORT (low or high dose) from gestational day 10–20 and/or from postnatal day 2–24. Offspring were tested on the forced swim test (depressive-like behavior), the open field test (locomotor and anxiety-like behavior), the elevated plus maze (anxiety-like behavior), and the resistance to capture test (impulsivity/aggressiveness) during late adolescence or given restraint stress during adulthood. We hypothesized that CORT administered during the postpartum period would have a different effect on the offspring than CORT administered to dams during pregnancy. Further, we expected that high maternal CORT would have a stronger effect than low maternal CORT on the offspring and that the prolonged exposure (pregnancy and postpartum) of CORT would have a more substantial effect on the offspring than during pregnancy or the postpartum alone. We also hypothesized that males and females will show different vulnerabilities for high maternal glucocorticoid levels depending on the time of exposure.

2. Materials and methods

2.1. Animals

Forty-six female and twenty male Sprague-Dawley rats, approximately 3 month old, were obtained from the University of British Columbia Animal Care Facility (Vancouver, Canada) for breeding. Rats were housed initially in same-sex pairs in opaque polyurethane bins (48 × 27 × 20 cm) with absorbent bedding and were given Purina rat chow and tap water *ad libitum*. Animals were maintained on a 12 h:12 h light/dark cycle (lights on at 7:30 a.m.). The number of animals was based on previous work in our laboratory (Brummelte et al., 2006) to give us sufficient power for the analysis. All protocols were in accordance with ethical guidelines set by the Canada Council for Animal Care and were approved by the University of British Columbia Animal Care Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used. For an overview of the experimental procedures see Fig. 1.

2.2. Hormone preparation

An emulsion of corticosterone (CORT; Sigma–Aldrich, St. Louis, MO; USA) was prepared every few days at a concentration of 10 mg/ml (low dose) or 40 mg/ml (high dose) by mixing CORT with 10% ethanol in sesame oil. The high dose was chosen because it elevates blood levels of CORT for a prolonged period of time (Johnson et al., 2006; Sapolsky, 1985), increases depressive-like behavior (Brummelte et al., 2006; Brummelte and Galea, 2010a; Gregus et al., 2005) and results in serum levels of CORT consistent with ether stress in postpartum females (Yeh, 1984). The low dose was chosen because it does not alter depressive-like behavior or baseline CORT levels in male or female rats after s.c. injections, but it

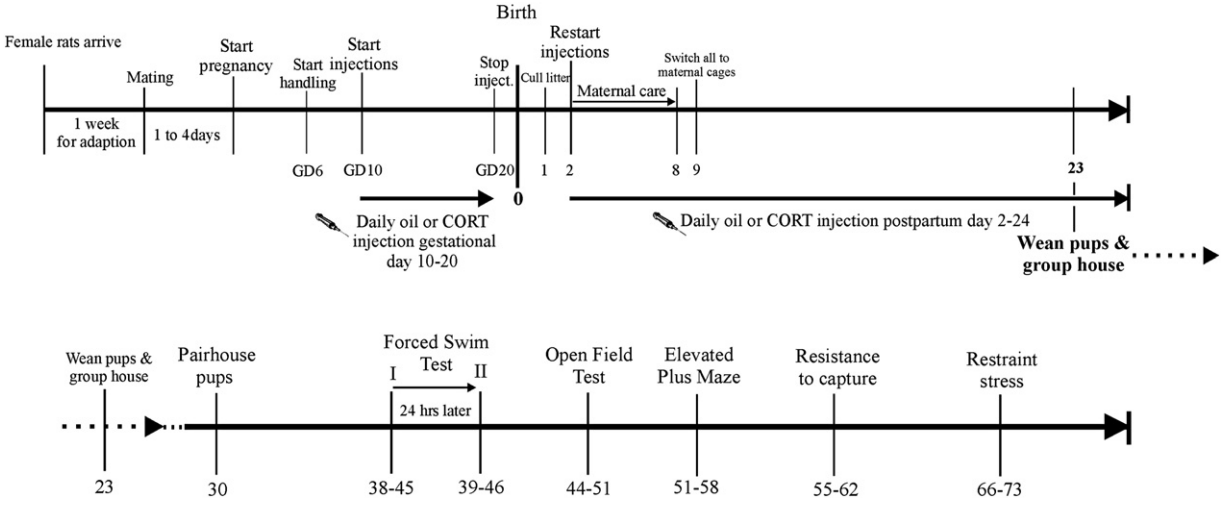

Fig. 1. Experiment overview and timeline.