Prenatal Alcohol Exposure and Prenatal Stress Differentially Alter Glucocorticoid Signaling in the Placenta and Fetal Brain

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Abstract—Adverse intrauterine environments increase vulnerability to chronic diseases across the lifespan. The hypothalamic–pituitary–adrenal (HPA) axis, which integrates multiple neuronal signals and ultimately controls the response to stressors, may provide a final common pathway linking early adversity and adult diseases. Both prenatal alcohol exposure (PAE) and prenatal stress (PS) induce a hyperresponsive HPA phenotype in adulthood. As glucocorticoids are pivotal for the normal development of many fetal tissues including the brain, we used animal models of PAE and PS to investigate possible mechanisms underlying fetal programing of glucocorticoid signaling in the placenta and fetal brain at gestation day (GD) 21. We found that both PAE and PS dams had higher corticosterone (CORT) levels than control dams. However, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme levels were increased in PAE and unchanged in PS placentae, although there were no differences in 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) levels. Moreover, only PAE fetuses showed decreased body weight and increased placental weight, and hence a lower fetal/placental weight ratio, a marker of placenta efficiency, compared to all other prenatal groups. Importantly, PAE and PS differentially altered corticosteroid receptor levels in placentae and brains. In the PS condition, maternal CORT was negatively correlated with both 11β-HSD1 and mineralocorticoid receptor (MR) protein levels in placentae and brains. In the PAE condition, there were trends for a positive correlation between maternal CORT and 11β-HSD1, regardless of sex, and a negative correlation between maternal alcohol intake and MR in male placentae. In fetal brains, sexually dimorphic changes in MR and glucocorticoid receptor (GR) levels, and the MR/GR ratio seen in C fetuses were absent in PAE and PS fetuses. In addition, PS but not PAE female fetuses had higher MR and lower GR expression levels in certain limbic areas compared to C female fetuses. Thus the similar adult HPA hyperresponsive phenotype in PAE and PS animals likely occurs through differential effects on glucocorticoid signaling in the placenta and fetal brain.

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Key words: prenatal alcohol exposure, hypothalamic–pituitary–adrenal axis, glucocorticoid receptor, mineralocorticoid receptor, placenta, 11β-hydroxysteroid dehydrogenase.

INTRODUCTION

In the last two decades, a Developmental Origins of Health and Disease (DOHaD) approach has begun to elucidate the links between adverse changes in the intrauterine or early postnatal environment (e.g., alcohol, undernutrition, stress) and the development of chronic diseases or disorders (e.g., cardiovascular disease, type II diabetes, mental health disorders) across the life span (Barker, 1995, 1998). For example, although the etiology of depression/anxiety disorders is not fully understood, it is generally accepted that the incidence of these mental health problems occurs in greater proportion among vulnerable populations that are exposed to adverse early life experiences, such as prenatal alcohol exposure (PAE) and prenatal stress (PS) (Maccari et al., 2003; Riley and McGee, 2005). This suggests the possibility that different early adverse insults may share some common mechanisms.

Fetal programing of the hypothalamic–pituitary–adrenal (HPA) axis, which integrates multiple neuronal signals and ultimately controls the hormonal response to stressors, may provide a final common pathway linking early adversity and adult diseases. The inability to respond appropriately to stress is a crucial determinant in later vulnerability to neuropsychiatric disorders (Nestler et al., 2002). Indeed, epidemiological, clinical,
and basic animal studies have shown that both PAE and PS increase the risk of adverse neurodevelopmental outcomes including HPA hyper-responsiveness and vulnerability to mental health disorders (Maccari and Morley-Fletcher, 2007; Hellemans et al., 2010; Weinstock, 2015). These adverse outcomes may be due, at least partly, to increased fetoplacental glucocorticoid (cortisol in human; corticosterone [CORT] in rats) exposure, as studies in animal models have shown that PAE and PS both increase maternal plasma CORT levels (Weinberg and Bezio, 1987; Maccari et al., 2003), which could, in turn, impact the fetus.

As the interface between mother and fetus, the placenta is the key conduit of nutrient, hormone, and oxygen supply to the fetus. The placenta plays an essential role in modulating and filtering signals from the maternal milieu, and thus is critical to fetal development. Although glucocorticoids could potentially cross the fetoplacental barrier freely, levels of fetal glucocorticoid exposure are predominantly regulated by placental 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes. 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyzes the conversion of active CORT into inert 11-dehydrocortisosterone (cortisol into cortisone in humans). This enzyme functions as a physiological fetoplacental glucocorticoid barrier by protecting the fetus from overexposure to maternal glucocorticoids. On the other hand, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes conversion in the opposite direction, thus regenerating and amplifying glucocorticoid action. In rodents, the expression of 11β-HSD1 increases starting at gestation day (GD) 16.5, which is thought to assist in organ maturation (Thompson et al., 2002). Both 11β-HSD enzymes contribute to the intracellular “gating” of glucocorticoid action (Chapman et al., 2013), and thus play a critical role in glucocorticoid signaling in the placenta and determining the amount and timing of intrauterine glucocorticoid exposure.

Adverse intrauterine environments such as alcohol or stress exposure, and the concomitant increase of maternal glucocorticoids, are important signals for fetuses from the maternal milieu. While gating by the 11β-HSD2 enzymes provides a partial barrier at the fetoplacental interface, as noted, some glucocorticoids will in fact reach the fetus, critically impacting fetal brain development, including the development and activity of the HPA axis, with possible long-term behavioral and physiological effects (Seckl and Holmes, 2007). In the case of maternal alcohol consumption however, effects on the fetus are more complex than those of maternal stress. In addition to the effects of alcohol in activating the maternal HPA axis, and thus, indirectly affecting the fetal HPA axis, alcohol itself can cross the fetoplacental barrier and directly activate the fetal HPA axis, which is functional before birth. Thus, increased plasma and adrenal CORT levels observed in PAE neonates (Taylor et al., 1982; Weinberg, 1989) result from a combination of both direct and indirect effects of alcohol, and indeed, synergistic effects of alcohol and glucocorticoids on the fetus may exist. Of relevance, no studies, to our knowledge, have examined PAE or PS effects on placental 11β-HSD1, and reports on the effects of both PAE and PS on placental 11β-HSD2 mRNA levels have been somewhat inconsistent. Decreased 11β-HSD2 expression levels have been reported in PAE and PS placenta in some studies (Mairesse et al., 2007; Rosenberg et al., 2010; Liang et al., 2011; Pena et al., 2012). However, increased placental 11β-HSD2 expression levels were reported in mouse models of glucocorticoid exposure starting at mid-gestation, rat models of periconceptional alcohol exposure, and in pregnant women at term following inhaled glucocorticoid treatment (Clifton et al., 2006; Cuffe et al., 2012; Gardet et al., 2014). Furthermore, in one study that tested effects of PAE on both male and female placentae, 11β-HSD2 mRNA levels were decreased in female, but increased in male placentae (Wilcoxon et al., 2003). Thus it is not clear whether the effects of PAE and PS on the developing HPA axis occur through similar or different mechanisms, at least in terms of effects on 11β-HSD2 expression and subsequent, possibly sexually dimorphic effects, on the fetal brain.

The developing brain is particularly vulnerable to intrauterine adversity. Indeed, neurodevelopmental deficits induced by PAE and PS have been shown in human and animal studies (West et al., 1994; Maccari et al., 2003; Schneider et al., 2004; Riley and McGee, 2005; Seckl, 2008). Importantly, the effects of PAE and PS on neurodevelopmental outcome may be sexually dimorphic. For example, sex differences in HPA responsiveness have been observed in animal models of both PAE and PS (Weinstock, 2007; Weinberg et al., 2008; Brunton and Russell, 2010; Hellemans et al., 2010).

The effects of glucocorticoids in the brain are largely dependent on the site of action and the relative expression levels of mineralocorticoid (MR) and glucocorticoid (GR) receptors, and the balance in functions mediated by MR and GR appears critical for neuronal excitability, stress responsiveness, and behavioral adaptation (De Kloet et al., 1998). The limbic brain areas (medial prefrontal cortex [mPFC], hippocampus and amygdala), which are part of the stress-responsive neurocircuitry, are rich in MR and GR. To date, most of the studies investigating glucocorticoid signaling in the brain have been done in adult PAE and PS offspring. How PAE and PS affect the expression of corticosteroid receptors in key limbic brain areas during the fetal period, and whether these effects are sexually dimorphic, is largely unknown. Understanding the mechanisms underlying fetal programming of the HPA axis and how it is affected by early life adversity such as PAE and PS, may provide insights for both the development of clinical biomarkers during early development and for early intervention.

The present study utilizes animal models of PAE and PS to investigate possible mechanisms underlying fetal programming of glucocorticoid signaling in the placenta and fetal brain at GD 21 and determine whether these mechanisms are similar or different following PAE and PS. In light of the more complex effects of maternal alcohol consumption compared to those of maternal stress on fetal HPA activity, we tested the hypotheses...
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