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Alterations in stress responses of the hypothalamic-pituitary-adrenal axis in small for gestational age infants

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Summary Mounting epidemiologic evidence and animal models suggest that stressful conditions during the intrauterine period may increase susceptibility to several adult conditions, including metabolic syndrome, cardiovascular disease, and psychiatric disorders. Increased cortisol levels due to alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis are believed to be one mediating mechanism. Infants born after significant exposure to stressful conditions are often small for gestational age (SGA) based on standardized growth norms. Lifelong programming of the HPA axis has been proposed as a mechanism to explain the association between SGA infants and adult disease. However, few studies have measured HPA axis function proximal to birth as done in this study of SGA infants during the first week of life. Participants included 37 infants in two groups based on birth size (gestational age range: 34—41 weeks). SGA infants were <10th percentile for age (n = 21) and appropriate for gestational age (AGA) infants (n = 16) were from 20 to 90th percentile for age. Cortisol response to a heel lance for blood collection was measured for all infants. Hierarchical Linear Modeling was used to test the effect of AGA/SGA group status on cortisol trajectories in response to the stressor. Group was a significant predictor of quadratic slopes (t = 2.84, χ^2 = 8.19, p = .004) after controlling for the effect of group on intercepts and linear slopes. Predicted growth curves for ln-cortisol were plotted for each group based on regression coefficients. The predicted curves capture the significant group difference in trajectories, as well as the blunted response for the SGA group and the robust peak in cortisol production in response to the stressor for the AGA group. This evidence suggests SGA neonates have blunted HPA axis responses to stressors in comparison to AGA infants. These findings are consistent with animal models showing that adverse intrauterine conditions can result in blunted cortisol responses to acute stressors and may provide a mechanism for adult susceptibility to disease for individuals that are SGA at birth.

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1. Introduction

Mounting epidemiologic evidence and animal models have demonstrated that stressful conditions during intrauterine life may have a substantial impact on susceptibility to several adult conditions including metabolic syndrome, cardiovascular disease, and psychiatric disorders such as depression (Barker et al., 1989a,b; Kajantie et al., 2002; Matthews, 2002; Newsome et al., 2003; Ward et al., 2004). These associations have been found to be independent of adult size or lifestyle. One mediating mechanism is believed to be intrauterine exposure to stress leading to alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased cortisol levels in both mothers and infants. Over time, increased cortisol levels have been shown to negatively affect the functioning of biologic systems (Barker et al., 1989a,b; McEwen, 2008). Infants who are born after significant exposure to adverse conditions are often small for gestational age (SGA) based on standardized growth norms. Lifelong programming of the HPA axis has been proposed as a mechanism to explain the association between low birth weight infants and later development of the metabolic syndrome and hypertension as adults (Barker et al., 1989a,b; Phillips et al., 1998; Reynolds and Phillips, 1998). Although most of the previous epidemiologic research uses low birth weight as a measure of reduction in intrauterine growth, it is important to distinguish between those infants that are smaller than expected size for their gestational age norms. SGA infants are defined unequivocally as those $<$10th percentile for gestational age which more accurately identifies a population of fetuses experiencing adverse intrauterine conditions. By including all low birth weight infants, one fails to distinguish premature infants from those who are potentially full term, but smaller than expected for age. With the inclusion of only SGA infants, one may expect to more clearly identify infants who had reduction in intrauterine growth as compared to others of the same gestational age.

Programming implies that an insult at a critical period of development results in permanent adaption of the organism's physiology or structure, in this case, altering the regulation of the HPA axis. While these theoretical proposals are biologically plausible, studies of adults who were low birth weight as infants provide only partial evidence for the lifelong programming hypothesis. These studies have not measured HPA axis function proximal to birth in SGA infants. The present study measured HPA axis function in SGA infants during the first week of life to address this gap in the literature.

Overactivity of the HPA axis has been associated with increased central adiposity, a known risk factor for cardiovascular disease (Larsson et al., 1992). Abnormally increased concentrations of glucocorticoids from pharmacologic administration of steroids or from conditions such as Cushing's syndrome are associated with increased abdominal fat deposition, hypertension, and glucose intolerance. The fetus is usually protected from normal levels of active glucocorticoids during pregnancy by the placental enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) which converts glucocorticoids to an inactive form (Clark et al., 1996). In a rat model, reduction in enzyme activity is associated with reductions in birth weight of offspring, supporting the hypothesis that increased exposure to active maternal steroid hormones due to either very high maternal levels that cannot be handled by the enzyme barrier or less efficient production of 11β-HSD may be one mechanism leading to small size at birth and the potential for long lasting effects on the HPA axis (Lindsay et al., 1994).

Despite the well-supported argument that chronic stress increases vulnerability to disease by increasing the activity of the HPA axis, there is a growing body of evidence demonstrating contradictory findings with stress-induced declines in cortisol. The possibility that chronic stress may both increase and decrease HPA activity exists, but likely at different time points over the course of the stressful period. Early in the course of a stressful situation, the HPA axis will be activated, elevating cortisol output. After a period of time if stress persists, the body will mount a counter-regulatory response, resulting in blunted cortisol output. Thus, after chronic stress, rather than an acute event, a period of hypoactivity is expected (Miller et al., 2007). Once the chronic stress is alleviated, measures may reveal that the axis has been reset at a higher level of activity (Gunnar and Vazquez, 2001).

This study evaluated stress reactivity in SGA neonates after birth to more fully understand the development of patterns of fetal neuroendocrine regulation that have been proposed as a predisposing factor in the pathogenesis of disease for former low birth weight infants. There are few studies to date that have examined HPA reactivity in SGA human newborns. Previous work by Schaffer et al. demonstrated a blunted cortisol response to a heel lance stressor in small for gestational age infants (Schaffer et al., 2009). Current evidence suggests that SGA infants have higher cortisol levels as adults, however, there is no data on when the actual shift from hyporesponsive to hyperresponsive cortisol reactivity occurs. In previous work by Grunau et al. (2004, 2007), salivary cortisol levels in preterm infants at 3 months corrected gestational age were lower than term infants, however, by 8 and 18 months corrected gestational age, there was a shift to significantly higher levels of salivary cortisol in the preterm groups. These results suggest a long term resetting of endocrine stress systems in these preterm infants possibly due to physiologic immaturity at birth with the cumulative stress of hospitalization, as well as the normal developmental changes in the fetal adrenal gland. This study hypothesized that late preterm and term SGA infants would also demonstrate resetting of endocrine stress systems similar to preterm infants.

2. Methods

2.1. Participants

The Institutional Review Board for the protection of human subjects approved all aspects of this study protocol. Informed consent was obtained from one or both parents prior to enrollment in this study.

The study sample comprised 37 participants who were born at a university-based children's hospital in the Midwest. Subjects were recruited serially into two groups based on size at birth. Group one (n = 21) included small for gestational age (SGA) infants with birth weight $<$10th percentile for gestational age based on the Fenton Growth Curve for Preterm and Term Infants. Group two (n = 16) included appropriate for