Programming of the Hypothalamus-Pituitary-Adrenal Axis by Very Preterm Birth

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Keywords

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Abstract

Background: Many very preterm (i.e., <32 weeks of gestation) newborns fail to mount an adequate adrenocortical response to stress or illness, termed relative adrenal insufficiency. Conversely, later in life these infants show features of increased glucocorticoid bioactivity, such as abdominal adiposity, insulin resistance, raised blood pressure, shorter stature and internalizing problem behavior. **Summary:** Studies suggested that very preterm newborns have impairments along multiple levels of the hypothalamus-pituitary-adrenal (HPA) axis. Among the impairment were defects in: (1) the pituitary responsiveness to exogenous corticotropin-releasing hormone, (2) 11 β -hydroxylase activity, and (3) the interconversion between cortisol and inert cortisone. There is some evidence suggesting that later in life these infants have an increased basal secretion rate of cortisol and adrenal hyperandrogenism. However, the response to acute (psychosocial) stress was blunted rather than enhanced in them. The mechanisms explaining this switch in HPA axis activity are complex and not yet fully understood. **Key Mes-**

sages: Very preterm newborns have several impairments along the HPA axis that could impede an adequate adrenocortical response to stress or illness. Later in life, these infants are predisposed to increased HPA axis activity, which could partially explain their phenotype.

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Introduction

There is emerging evidence linking preterm birth to cardiometabolic risk factors such as abdominal adiposity, insulin resistance and raised blood pressure [1–4], as well as to shorter stature [5] and internalizing problem behavior [6]. The clustering of these features resembles effects of increased glucocorticoid bioactivity, such as in Cushing's syndrome.

A lower activity of the placental barrier enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 2 – induced by maternal stress, disease or licorice consumption – allows a larger proportion of maternal cortisol to reach the fetus, which has been associated with intrauterine growth restriction (IUGR) and shorter gestation [7]. In addition, there is some evidence suggesting that resetting of the hypothalamus-pituitary-adrenal (HPA) axis

by a greater transfer of cortisol through the placenta could result in long-lasting consequences for the offspring, such as neurodevelopmental problems and cardiometabolic diseases [7].

For several reasons, these mechanisms cannot wholly explain the triad of preterm birth, permanent alteration in HPA axis activity, and adverse outcomes. First, several studies in children and adults born very preterm (i.e., <32 weeks of gestation) or with very-low-birth-weight (VLBW; i.e., <1,500 g) showed that insulin sensitivity was equally reduced in IUGR and non-IUGR subjects [2, 3]. Second, in the early-postnatal phase a considerable proportion of very preterm infants manifested clinical signs of adrenocortical insufficiency [8]. Such observations pose the question as to whether the HPA axis in preterms could be programmed postnatally by adversities related to preterm birth.

Relative Adrenal Insufficiency

Very preterm newborns encounter serious problems, including hypotension and hypoglycemia. Among the causes of hypotension are abnormalities in the regulation of the vascular tone, left-to-right shunting through a persistent ductus arteriosus, volume depletion and myocardial dysfunction [9]. Hypoglycemia is often attributed to a combination of factors, including small energy depots, poor availability of gluconeogenic substrates and impairments in activities of glucose-6-phosphatase (which is the final step of both glycogenolysis and gluconeogenesis), lipolysis and ketogenesis [10]. Hypotension and hypoglycemia typically emerge during acute illness in the first weeks of life, and relative adrenal insufficiency (RAI) has been postulated to play a role [11]. Cortisol raises the blood pressure, mainly by its permissive effect on the vascular tone [9]. It increases the serum glucose level by its (direct and indirect) effect on energy depots, hepatic glucose production and peripheral insulin resistance.

RAI is the term given to inadequate production of glucocorticoids for the degree of stress or illness, and its causes are multifactorial (Fig. 1). During pregnancy, the placental barrier enzyme 11 β -HSD type 2 protects the fetus from overexposure to maternal cortisol [7]. Decreased activity of placental 11 β -HSD type 2 has been implicated to play a role in preterm delivery [7]. Furthermore, late in gestation the placenta secretes increasing amounts of corticotropin-releasing hormone (CRH), which stimulates the fetal adrenal to secrete cortisol in a self-perpetuating

Fig. 1. The HPA axis in very preterm newborns and how it develops with age.

positive feedback loop [11]. Both these mechanisms can lead to a suppression of fetal hypothalamic CRH that may continue after birth. Indeed, studies showed that the pituitary response to exogenous CRH was impaired in preterm newborns [12], suggestive of enhanced central feedback suppression by glucocorticoids. Another mechanism contributing to RAI is the immaturity of adrenal cortex enzymes, notably decreased 11 β -hydroxylase activity, which is necessary for the conversion of 11-deoxycortisol to cortisol [13, 14]. Furthermore, there is some evidence suggesting that the interconversion between cortisol and cortisone, by 11 β -HSD isozymes in peripheral tissues, favors cortisone with decreasing gestational age [15].

Synthetic glucocorticoids have proven to be effective for the prevention and treatment of hypotension after preterm birth [16–18]. Furthermore, antenatal glucocorticoid treatment for fetal lung maturation has been associated with a lower risk of hypotension in the first days after very preterm birth [19], and with markers of insulin resistance in cord blood [20]. The latter might protect the brain against glucose deprivation.

Adrenocortical Function in Childhood and Its Clinical Correlates

The onset of puberty was probably age-appropriate in cross-sectional studies of 11- to 15-year-old boys and girls with VLBW [25, 26]. There is some evidence suggesting that puberty progresses more rapidly in them, with data linking VLBW to a younger age at take-off of pubertal height velocity [26] and a more advanced bone age at adolescence [25, 26]. However, girls with VLBW were no different from girls born at term in age at menarche [25–27], which argues against a major contribution of the hypothalamus-pituitary-gonadal axis to these associations. Two studies showed that adrenal androgens were higher in young adults born preterm [28, 29].

Several studies have addressed the long-term impact of prematurity on HPA axis activity [12]. Evidence encompassed a higher corticosteroid production rate [30], and increases in the serum or salivary cortisol concentration during early morning, at nadir, or throughout the day in subjects born preterm were observed (Fig. 1) [28, 31, 32]. However, 2 out of 3 studies that performed social stress tests found blunted rather than enhanced cortisol responses at lower gestational ages (Fig. 1) [33–35]. These observations suggest that HPA axis activity in subjects with a history of preterm birth is characterized by an increased basal secretion rate and a poorer response to acute (psychosocial) stress.

In summary, increased HPA axis activity might explain, at least in part, the clustering of cardiometabolic risk factors in preterm survivors (Fig. 2). Furthermore, after an age-appropriate adrenarche, the production of adrenal androgens is suggested to increase rapidly, which may contribute to an earlier pubertal growth spurt and advancement of bone maturation at adolescence, resulting in premature epiphyseal closure and shorter adult stature (Fig. 2).

Exploring Associations between Prematurity and Long-Term Outcomes with Focus on HPA Axis Activity

Exogenous Glucocorticoids

Antenatal glucocorticoids have proven to be effective in the prevention of respiratory distress syndrome and associated complications [36], but animal studies have raised concerns about their long-term cardiometabolic and neurodevelopmental effects [37]. However, findings from randomized trials and observational studies that had followed subjects exposed to a single course of antenatal

Fig. 2. Schematic representation of putative mechanisms of the associations between very preterm birth, child HPA axis activity and long-term cardiometabolic outcomes. IGFs, insulin-like growth factors.

glucocorticoids until adolescence or young adulthood were inconsistent, especially for cardiometabolic outcomes [38–42]. In the project on preterm and small-for-gestational-age cohort, we found that carriers of a glucocorticoid receptor (GR) polymorphism, which has been associated with an increased sensitivity to glucocorticoids, had a greater waist circumference and poorer cognitive test scores at age 19 years after exposure to synthetic glucocorticoids antenatally [43, 44]. Thus, whether a single course of antenatal glucocorticoids could produce long-lasting deleterious effects might be dependent on the sensitivity of tissues to these hormones. There is a need for long-term follow-up data of children born to mothers who remained at risk of preterm delivery and were, therefore, treated with additional courses of glucocorticoids [45].

Parental Care and Stress

Pups exposed to maternal separation, or non-handling, were found to have increased HPA axis activity and anxiety-like behavior as adults [46]. Other animal experiments showed that poor maternal care had similar effects on offspring through persistent alterations in the epigenome at the level of the hippocampal GR promotor [47]. In humans, poor quality of parental care, such as neglect

or emotional or physical maltreatment, early in childhood was associated with greater HPA axis activity, mental illnesses and cardiometabolic disease [48]. In an autopsy study, childhood abuse was associated with increased DNA methylation at the GR promotor and decreased expression of GR mRNA in the hippocampus [49]. Whether such findings could be extrapolated to very preterm babies, who receive less parental care and are exposed to stressors like invasive procedures, pain, interruption of sleep states and noise during their admission to the neonatal intensive care unit, remains to be explored.

Nutrition

In rodents, perinatal undernutrition has been associated with increased HPA axis activity later in life [50]. Whether this also applies to very preterm babies, who accumulate a significant nutrient deficit in the first postnatal weeks [21], is unknown.

We have recently shown that cortisol and cortisone are secreted into human milk in concentrations comparable to those in saliva [51]. We have also demonstrated that their concentrations in milk are lower after preterm delivery, and follow the diurnal rhythm of maternal HPA axis activity [51]. These findings could have important implications for donor milk banks, which often provide preterm infants with

milk from mothers who delivered at term and do not take the time of collection into account. Although human milk is considered superior for infant outcomes, it is unknown whether it also protects against RAI. Moreover, to our knowledge there are no studies that have investigated the intestinal absorption of glucocorticoids in preterm infants.

Conclusions

Early in life, the HPA axis of very preterm infants is characterized by an inability to secrete sufficient glucocorticoids for the degree of stress or illness. Emerging evidence suggests that the axis becomes overactive with age, which might offer an explanation for the clustering of features such as increased abdominal fat contents, insulin resistance, raised blood pressure, shorter adult stature and internalizing problem behavior. Research into the mechanisms that may drive this switch in HPA axis activity is ongoing.

Disclosure Statement

The authors declare no conflicts of interest.

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