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Review Article

The Hypothalamus-Pituitary-Adrenal Axis Induced Adrenal Insufficiency and Onset of Chronic Lung Disease in Preterm Neonates

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Abstract

The hypothalamus-pituitary-adrenal (HPA) axis, is a negative feedback system which functions to maintain homeostasis when the body is exposed to a stressful situation [1-3]. Some stressors and therefore activators of the HPA axis include trauma, surgery and critical illness [1,4]. These are situations in which the physical demands placed on the body, exceed the body's ability to cope with them [5]. In this state, the body responds with the endocrine mediated secretion of cortisol [1-15]. Cortisol is a glucocorticoid hormone which is secreted in increased amounts when the adrenal glands are neurologically stimulated during times of stress [1-3,5]. Cortisol acts by binding to various receptors throughout the body, mediating cardiovascular, immunological and neurological functions [3,5]. In neonatal pathology, maturation of the fetal adrenal gland does not take place until approximately 30 weeks gestation, and therefore the fetal hypothalamus and placenta work in conjunction to regulate and secrete cortisol precursors during that time [3,5-7,8]. This system plays a pivotal role in both intrauterine growth as well as maturation of vital organs. The HPA axis and cortisol act as intermediate regulators in the pathway responsible for surfactant synthesis [9] and are also vital in ensuring intrauterine viability in neonates, therefore essential for extrauterine survival [3,8]. However, in the event that the fetus is exposed to an intrauterine stressor, the increase in fetal and placental endocrine activity can jeopardize timely parturition and lead to immature neurological development contributing to adrenal insufficiency [8].

Keywords: *Hypothalamus-Pituitary-Adrenal Axis; Chronic Lung Disease; Preterm Neonates*

Abbreviations

HPA axis: Hypothalamus-Pituitary-Adrenal axis; ADH: Antidiuretic Hormone; CRH: Corticotropin Releasing Hormone; DHEA-S: Dehydroepiandrosterone Sulphate; 3B-HSD: 3B-Hydroxysteroid Dehydrogenase; 11B-HSD2: 11-Beta-Hydroxysteroid Dehydrogenase; T3: Triiodothyronine; T4: Thyroxine; hCRH: Human Corticotropin Releasing Hormone; RDS: Respiratory Distress Hormone; BPD: Bronchopulmonary Dysplasia

Relative adrenal insufficiency ensues when the HPA axis' release of cortisol is inadequate to compensate for the stress faced by the neonate, leading to the onset of hemodynamic and cardiac instability, as well as respiratory distress and chronic lung diseases secondary to inadequate surfactant production [1-4,7-9]. This paper is going to address the importance of a mature HPA axis in neonatal pathology, by reviewing studies carried out on premature infants with an immature HPA axis characterized by adrenal insufficiency, leading to immature lung development and progressive chronic lung disease [9]. Intrauterine HPA axis function is also mentioned to better help the reader understand the onset of relative adrenal insufficiency. In addition to patient presentation, appropriate sources of therapy and their subsequent limitations are also discussed.

The hypothalamus-pituitary-adrenal (HPA) axis

The hypothalamus is an endocrine organ and the control center in the brain [10]. One of its primary functions involves the maintenance of a homeostatic state when there is a disruption to normal body processes, often via a negative feedback system [10]. For example, in a state of dehydration, the hypothalamus will stimulate the secretion of antidiuretic hormone (ADH) from the anterior pituitary, having the kidneys retain more water and increases level of thirst [10]. In doing so, patients blood levels are slowly restored, and ADH secretion is no longer needed. Similarly, when the body faces a stress stimulus, the hypothalamus works in conjunction with the pituitary and adrenal gland to secrete cortisol [3,10]. Following complete neurological development, acute physiological and psychological stressors [3] influence the hypothalamus to secrete corticotropin-releasing hormone (CRH) [3,5,11] which travels via the infundibulum to stimulate the pituitary gland to secrete adrenocorticotropin hormone (ACTH) into the bloodstream [3]. Cortisol release is stimulated when ACTH binds to receptors on the adrenal gland [2,3,11]. Cortisol secretion is regulated to be released in appropriate doses proportional to and in lieu of the degree of the stressor [3]. Cortisol then acts on various receptors throughout the body, enough to maintain homeostatic function, decrease the physiological effects of stress, and thereby inhibit further release of cortisol downstream [1-3]. This negative feedback release of cortisol in response to illness or stress is important and vital for survival [3].

The transition between intrauterine and extrauterine HPA axis function

In terms of neonatal pathology, HPA axis maturity is dependent on the stages of gestational development [3]. In utero, hormone secretion by the HPA axis commonly begins at approximately eight to twelve weeks gestation, however the HPA axis is not completely developmentally functional yet [8]. The HPA axis in utero utilizes positive and negative feedback loops to facilitate cortisol release. The fetal hypothalamus secretes fetal CRH in a timely fashion or in response to stress [8]. Fetal CRH stimulates the downstream fetal pituitary gland to secrete ACTH which then acts on both the fetal adrenal gland and on the placenta [8]. Once the fetal adrenal gland is stimulated, this negative feedback mechanism inhibits further CRH release. In addition to the fetal hypothalamus, placental regulation of cortisol also occurs with the help of two specific enzymes which work in conjunction with one another: dehydroepiandrosterone sulphate (DHEA-S) and 3B-hydroxysteroid dehydrogenase (3B-HSD). 3B-HSD is an enzyme responsible for the conversion of placental pregnenolone to progesterone. Progesterone is then converted to placental cortisol by DHEA-S [8,12,13]. DHEA-S functions in a positive feedback manner, and its expression is very important in maintaining the placental transfer of cortisol. In addition, DHEA-S is also a prostaglandin stimulant, a potent vasodilator of fetoplacental circulation, and can cause an increase in myometrial contractions [8,12]. For this reason, if exposed to an intrauterine stressor severe enough, this positive feedback system may actually contribute to premature labor and delivery [8,12]. Stress in utero, will increase placental CRH which stimulates an increase in DHEA-S synthesis [8]. This is further supported by studies which found that premature infants < 34 weeks presented with a higher maternal CRH concentration than term infants [8]. In general though, it is expected for adrenal function to normalize in preterm infants by the second week of extrauterine life [12,14].

Term infants do not readily present with HPA axis dysfunction secondary to immature development, as the last trimester of pregnancy is a time during which the adrenal gland undergoes structural and functional changes [12] At this time, the placental enzyme 11B-HSD2 also increases to enzymatically convert maternal cortisol to inactive cortisone [3,8,12,13]. This way, cortisol concentrations in the term infant decrease to a level which results in an increase in HPA axis function [3].

The role of Cortisol

Cortisol is a steroid hormone which is synthesized in the adrenal cortex [3,9,14]. Although cortisol is the primary hormone released in response to stress, endogenous levels of cortisol are released as well in a circadian rhythm fashion. Normally, cortisol levels are highest in the morning before waking, decreasing throughout the day [1,2,5,15]. Cortisol is vital in the maintenance of physiological homeostasis [3]. Once released into the bloodstream, cortisol mediates its effects by binding on to cortisol-binding globulin, albumin or specific glucocorticoid receptors located throughout the body, regulating cardiovascular, metabolic and immune responses [3,5,8]. Furthermore, cortisol maintains "blood glucose levels, electrolyte imbalance, endothelial integrity, vascular permeability" ([3], p 44), and hemodynamic stability [3]. Cortisol especially becomes important in septic shock patients experiencing a high level of systemic inflammatory mediators, by acting on the immune system to decrease systemic inflammation [1,2]. In fact, septic shock actually increases adrenal insufficiency in patient population by 20 - 40% [6]. The regulation of inflammation in this situation is furthermore important in preventing progression of chronic lung diseases [9].

In utero, cortisol plays a vital role in fetal maturity and intrauterine homeostasis [8]. Its role in antepartum maturation of organ systems, and structural and functional development, ensures extrauterine survival of the neonate. In particular, the third trimester of gestation involves a progressive increase in endogenous cortisol levels [13]. Around 30 weeks gestation, levels are as low as 5 - 10 ug/mL, increasing to 20 ug/mL by 36 weeks gestation to 45 ug/mL by term, > 34 weeks [13]. This pattern is followed by a characteristic surge in cortisol, reaching 200 ug/mL at term labor [13]. This increase in cortisol occurs as a result of the negative feedback system following increased fetal adrenal gland activity and decreased cortisone production downstream [13]. Hence, infants who do not reach term or are born prematurely have adrenal insufficiency and lack the cortisol surge [13]. The cortisol surge is important in fetal development as it facilitates "surfactant synthesis in lung tissue, increases reabsorption of [fetal lung fluid], increases methylation of norepinephrine to epinephrine, increases conversion of [thyroid hormones] T4 to T3, facilitates ductus closure," and facilitates liver and intestinal enzymatic maturation ([12], p427-428) [3,9,12,13].

Diagnosis of adrenal insufficiency

Relative adrenal insufficiency can be brought upon by a multitude of factors and causes, and therefore a presumptive diagnosis of adrenal insufficiency is usually clinically made based on patient presentation and history [13]. There are no clear diagnostic criteria, however some of the factors that are taken into consideration when making a diagnosis include: gestational age, in-utero stressors, immature neural development secondary to premature birth, insufficient release of cortisol. As a result, a lot of clinical judgment and experience is important here. Health care workers such as physicians, nurses, and respiratory therapists, who may be involved in and managing patient care, need to be cognizant of any deterioration or abnormal course of development in their patients [16]. If there is suspicion that the infant is not doing well on current therapy, this will usually prompt further testing [16]. Quantification of cortisol levels is done in order to gain a relevance of cortisol levels in patients' blood, to patient presentation and relative adrenal insufficiency [13]. Generally, patients will have an average basal cortisol level in their blood, with increases in cortisol seen during times of stress. Adrenal insufficiency is diagnosed when random blood cortisol concentrations are <15 mcg per 100 mL [1,3,13]. To diagnose adrenal insufficiency in preterm infants, an initial low basal cortisol level, followed by a direct correlated increase between glucocorticoid administration and blood serum levels indicates a positive response [3,14]. One study conducted a human CRH (hCRH) stimulation test on preterm infants [14]. The test group consisted of 23 neonates with a median gestational age and birth weight of 26 weeks and 854 grams respectively, all admitted to the NICU at Kyoto University Hospital in Japan [14]. This test consisted of blood serum cortisol measurements and salivary cortisol analysis. An assay consisting of a set hCRH dose diluted with 0.9% NaCl, was then administered to these infants via peripheral IV. Based on previously set studies, cortisol peaks should occur within 30 minutes of administration, and therefore both blood sample collection time, and saliva samples were collected accordingly [14]. Prior to the administration of hCRH, basal serum total cortisol and saliva samples were collected as a means of comparison [14]. Total serum cortisol levels prior to testing were within 5.5 - 1655 nmol/liter, and salivary cortisol assay were within 0.033 - 82.77 nmol/L. After the 30 minute collection period, total serum cortisol levels were found to have increased to 448.5 nmol/L +/- 150.1 nmol/L, with salivary cortisol increases of 21.876 nmol/L +/- 12.02 nmol/L [3].

Overall, this groups serum and salivary cortisol levels and response to hCRH, were of statistical significance and a good indicator of possible HPA axis dysfunction [14].

To further understand how HPA axis dysfunction and adrenal insufficiency can affect pulmonary development, Srivastava., *et al*. [9] conducted a study comparing cord blood cortisol levels to the onset of respiratory distress syndrome (RDS) [9]. From 121 vaginal deliveries, the newborns were divided into three test groups. Group A consisted of 42 preterm infants < 34 weeks gestational whose mothers received no antenatal dexamethasone. Group B consisted of 32 preterm infants < 34 weeks gestation whose mothers received "2 doses of 12 mg IM dexamethasone at 12 hourly intervals, the second dose being given at least 12 hours prior to delivery of the neonate" ([9], pg 924). Group C consisted of 47 newborns > 38 weeks gestation with birthweights > 2500g. To facilitate this study, cord blood gases were collected almost immediately following birth and centrifuged to separate the blood serum. An antisera specific for cortisol was added to assess for sensitivity [9]. Results showed that preterm infants in both groups A and B, had a significant lower amount of cord blood cortisol levels in comparison to group C [9]. In addition, the onset of RDS was found to be greater in preterm infants whose cord blood

cortisol levels were lower than those who did not develop RDS. Preterm infants who did not develop RDS, were found to have comparable yet still lower cord blood cortisol levels to group C term infants [9]. When comparing groups A and C, in which no exogenous steroids were involved, it was noted that group A preterms had significantly lower cord blood cortisol levels with a direct correlation between low cord blood cortisol and onset of RDS. RDS was lower in group B, indicating the effectiveness of antenatal dexamethasone prior to delivery [9]. Mortality rate for group A was 19%, with zero mortality in groups B or C [9]. Further results and discussion of this study concluded cortisol to be important in the maturation of fetal lungs [7] and significance of early administration of exogenous corticosteroids in threatened preterm labor [9]. To ensure viability of the study results, mothers with known endocrine problems were not involved in this study [9].

Due to the adrenal insufficiency, the administration of exogenous corticosteroids can aid in preventing the onset of chronic lung disease. In terms of neonates whose pathological course may involve the progression to bronchopulmonary dysplasia (BPD), early courses of glucocorticoid therapy may aid in the prevention of BPD by decreasing the inflammatory markers responsible for the progression [7]. Mutlu., *et al.* conducted this study on a group of 87 neonates, < 32 weeks or < 1500g, who were all given a BPD diagnosis and were either intubated and mechanically ventilated or supplemental oxygen dependent [7]. To facilitate this study, these neonates were administered an initial 1 mg/kg dose of hydrocortisone therapy twice daily for one week. The initial dose was then decreased 10 - 20% depending on the patients clinical response, defined to be either weaning from mechanical ventilation or decreased supplement oxygen requirements [7]. The outcome of this study proved hydrocortisone therapy to be beneficial in reducing the progression of BPD. Respiratory support was significantly reduced as 82% of neonates were taken off supplemental oxygen, and 80% of the neonates were successfully weaned off the ventilator and extubated [7] following hydrocortisone therapy.

Patient presentation of relative adrenal insufficiency and appropriate treatment

The postnatal adrenal gland is important in maintaining metabolism, vascular responsiveness to circulating vasoconstrictors, suppression of the inflammatory mediators, and regulating the central nervous system [3,13]. Most often, adrenal insufficient preterm infants are associated with conditions such as cardiovascular insufficiency, refractory hypotension, oliguria, BPD and an increased inflammatory response [3,6,14]. Additional signs indicating possible adrenal insufficiency include "hyponatremia, lung edema, increased [oxygen requirements], hypovolemia, anemia [and/or a] patent ductus arteriosus," to name a few ([13], p428). These conditions are again commonly associated with prematurity, and although some may not directly influence the adrenal gland per se, they can cause other co-morbidities increasing stress on the patient, thereby contributing to adrenal insufficiency [6].

When treatment options are discussed, glucocorticoid replacement therapy is the primary route taken [3,17]. With that said, this treatment is prescribed and used hesitantly, as there is insufficient evidence to support routine use of glucocorticoid therapy [3,11]. The most commonly used glucocorticoid is hydrocortisone, analogous to cortisol [17,18]. Administration of hydrocortisone therapy is a continued form of treatment in most infants, commonly used in situations involving hypotension refractory to vasopressor and fluid therapy [1,3,6,12-15]. In this situation, when administering hydrocortisone therapy, treatment steps include an initial basal blood cortisol sample and continuous monitoring of blood cortisol levels, following incremental increases in doses given which indicate the patient's hypotension is resolving. The use of hydrocortisone therapy in this state not only resolves patient hypotension, but also increase overall cardiac functioning by "increasing calcium availability to muscle cells, reversing the down-regulation of adrenergic receptors, inhibiting nitric oxide synthase expression and/or prostacyclin production, decreasing the reuptake of norepinephrine, [and] improving capillary integrity" [6] ([3], p423) Furthermore, hydrocortisone reduces expression of inflammatory markers which contribute to progressive chronic lung disease [9]. Treatment is to be terminated if a patient's cortisol levels surpass the accepted baseline, or if there is no improvement to patient normals [3].

Conclusion

Neonatal HPA axis regulation is a complex neural system which relies on timely parturition, the help of enzymatic and hormonal processes, as well as both positive and negative feedback circuits. This system is a vital component in intrauterine development and is essential for extrauterine survival. Relative adrenal insufficiency in preterm neonates is generally brought upon by the immature neural development secondary to premature labor. As a result, these infants are commonly faced with hemodynamic instability and failure to thrive with traditional medicinal therapy. Although entire bodily systems are affected, problems pertaining to the respiratory system are prominent due to inadequate surfactant production, and therefore increased susceptibility to chronic lung diseases such as BPD. With that said, this is further supported by the studies mentioned in this paper, which prove that premature infants, when compared to term infants are born with low cord blood cortisol concentrations, and that they are more prone to surfactant deficiency and therefore have an increased susceptibility for the development of RDS and progression to BPD. Furthermore, medical practice and studies have shown positive outcomes when the regulation of the HPA axis occurs with the administration of glucocorticoids, further validating the importance of a mature HPA axis. Glucocorticoid therapy, commonly hydrocortisone in particular, helps mediate similar effects of endogenous cortisol and has been shown to have improved outcomes in patients suffering from adrenal insufficiency. Its use, however, is limited as there is a lack of extensive studies despite it proving to be beneficial with certain neonatal pathologies; the use of the drug is to be routinely monitored and used in minimal doses. Overall, as more studies are being conducted on premature infants, there has been an increase in the administration of prenatal steroids in the instance of premature labor, and initiating corticosteroid therapy earlier rather than later in infants born prematurely in an attempt to reduce the likelihood and onset of respiratory distress secondary to adrenal insufficiency.

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