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Sex differences in early-life programming of the hypothalamic–pituitary–adrenal axis in humans

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ABSTRACT

Increasing evidence supports fetal glucocorticoid exposure with associated altered offspring hypothalamic-pituitary-adrenal (HPA) axis activity as a key mechanism linking early life events with later life disease. Alterations in HPA axis activity are linked to a range of cardiometabolic and psychiatric diseases. As many of these diseases manifest sex differences in presentation we review the evidence for programmed sex-differences in the HPA axis. Available literature suggests vulnerability of the female HPA axis to prenatal stressors with female offspring demonstrating increased HPA axis reactivity. This may be due to changes in placental glucocorticoid metabolism leading to increased fetal glucocorticoid exposure. We discuss the potential consequences of increased vulnerability of the female HPA axis for later life health and consider the underlying mechanisms. Further studies are needed to determine whether sex-differences in early-life programming of the HPA axis represent a pathway underpinning the sex-differences in common cardiometabolic and psychiatric diseases.

1. Introduction

The concept that early-life development determines later life health and disease risk, known as 'early-life programming' or the 'developmental origins of health and disease', is supported by considerable evidence from epidemiological studies and data from pre-clinical models linking size at birth with cardiometabolic disease, as well as mental health and cognitive decline over the lifespan. Overexposure of the developing fetus to glucocorticoids is regarded as a key underlying mechanism (reviewed in Cottrell & Seckl [1] and Reynolds [2]). It is proposed that alterations in maternal hypothalamic-pituitary-adrenal (HPA) axis activity and/or changes in placental glucocorticoid metabolism, sensitivity and transfer mediate increased fetal glucocorticoid exposure, and that this is associated with low birthweight. The observation of a link between low birthweight and increased HPA axis activity [3,4] suggests that the HPA axis is also a 'target' of early-life programming. Alterations in the activity of the HPA axis are associated with susceptibility to a range of psychological, cardiovascular, infectious and inflammatory diseases [5]. Given the marked sex differences in presentation and prevalence of these diseases it is plausible that sex-differences in early-life programming of the HPA axis may underpin the aetiology of these conditions. In this review we discuss the evidence from human studies supporting sex-differences in activity of the HPA axis and consider the evidence that this may be programmed by early life events. We discuss the potential health consequences of sex-differences in early-life programming of the HPA axis and suggest putative underlying mechanisms.

2. The hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is a system of control and regulation that is essential to life in vertebrates, linking the central nervous system with endocrine systems via the release of glucocorticoids [5]. The key glucocorticoid effector in humans, cortisol, is released in response to external stressors and plays a critical role in metabolism, increasing energy supply in almost all cells. The HPA axis response upregulates other systems in response to stress including increasing vascular tone, and cardiac output via the sympathetic-adrenal medulla (SAM) axis, modulation of inflammatory, immune and psychological function [6]. Cortisol is released when the anterior pituitary releases adrenocorticotrophic hormone (ACTH), which is released in response to the hypothalamic peptide corticotrophin releasing hormone (CRH). Circulating cortisol is approximately 95% bound to cortisol binding globulin (CBG) in plasma, and only around 5% is biologically active. The HPA axis is tightly regulated at the level of the hypothalamus and pituitary by glucocorticoid feedback inhibition and by a range of afferent neurons from the brainstem, midbrain and limbic system [7].

Activity of the HPA axis can be quantitatively assessed by measuring concentrations of cortisol in saliva in response to stimuli such as wakening (cortisol awakening response, CAR), a predefined social stressor

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or natural diurnal changes (usually low before bed and highest in the morning). Other means include blood cortisol concentration, measuring point to point concentrations more accurately but invasively, typically in response to parenteral administration of ACTH (stimulating the adrenals) or CRH (stimulating the anterior pituitary); hair cortisol, measuring concentrations across several months, or urine, measuring total glucocorticoid metabolite concentrations over a 24 h period. During childhood, there appears to be a meaningful difference in cortisol reactivity between the sexes. A recent systematic review described all available studies in girls and boys aged ≤ 18 years. Cortisol reactivity was found to be greater in girls than boys, an effect which is reversed by adulthood [8]. The differences were greater in larger studies but also depended on the means of HPA axis testing. The higher CAR and more variable diurnal cortisol observed in girls than in boys (12 of 29 studies) is thought to represent a measurement of CRH and ACTH release, influenced by the suprachiasmatic nucleus. In contrast studies of responses to social stress tests (which had heterogeneous designs and inconsistent findings), utilised a range of stimuli, which may affect the HPA axis indirectly via the limbic system. The review identified few meaningful sex-differences in HPA responses to pharmacological stimulation of the adrenal cortex (two of seven studies reported a difference – higher cortisol responses in boys). Conversely, a further systematic review by the same authors clearly demonstrated HPA axis activity to be greater among boys than girls before eight years of age [9]. After eight years, this trend was reversed when HPA axis activity was measured by basal salivary and serum cortisol, but the findings persisted when measured by 24-hour urinary cortisol (as a marker of total cortisol secretion), remaining consistent with age. The meta-analysis demonstrated consistent (albeit modest) effects with sex differences of increased basal salivary, serum and 24 h urinary cortisol in males compared with females in children under aged eight years and the reverse effects in children aged eight to 18 years (Table 1).

It therefore appears that while a sex-specific evolution of cortisol metabolism occurs around puberty, significant differences in activity and reactivity are present beforehand, suggesting a possible effect of early life programming.

3. What is the evidence for sex-differences in early-life programming of the HPA axis in humans?

We recently systematically reviewed the available literature to determine the evidence for sex-differences in early-life programming of the HPA axis in humans [10]. We included studies with a clearly defined exposure of a prenatal 'stressor' and with outcomes of sex-differences in placental handling of glucocorticoid hormones as a surrogate for fetal glucocorticoid exposure, and/or differences in the offspring HPA axis activity and reactivity in early and later life. We identified 23 studies including data on 3739 participants. There was considerable heterogeneity in the exposures with a large range of prenatal 'stressors' including maternal inflammation (typically asthma), pharmacological interventions (glucocorticoid medication) and psychological stressors (including maternal mood, emotional complaints, subjective stress and psychopathology) as well as low birthweight and preterm birth. Likewise there was much variability in the HPA axis outcome measures. Despite this, 14 of the 23 studies reported sex differences in outcomes which overall were consistent with increased vulnerability of the female HPA axis compared to males. For example, in the studies where sex differences were noted, female offspring had higher cord blood cortisol levels than males [11,12]. In another study females born preterm had higher morning salivary cortisol levels in childhood than both females born at term, and males born pre-term or term [13]. Likewise females had increased HPA axis reactivity compared to males as evidenced by increased salivary cortisol in toddlers following a maternal-separation stress [14] and increased peak salivary cortisol responses to a modified Trier Psychosocial Stress Test in childhood and adolescence [13,15]. Consistent with the finding of Hollanders et al. [8], there were no meaningful sex differences in any of the studies using pharmacological stimulation of the HPA axis. These observations of increased 'basal' changes in HPA axis activity in girls are consistent with observations in childhood per se [9]. Intriguingly the observed increased HPA axis reactivity to social stress tests in girls contrast with the observations in childhood [8]. This suggests that the prenatal 'stressor' may impact on other pathways involved in the HPA axis responses rather than directly programming the HPA axis, for example the limbic system. Indeed, there was some evidence for sex differences in placental glucocorticoid handling including a reduction in glucocorticoid receptor messenger RNA in placentas from females compared to males [12] and a different pattern of glucocorticoid receptor isoforms [16]. The female placenta also had changes in the expression of 11β-hydroxysteroid dehydrogenase (HSD) enzymes consistent with an increased permeability to maternal glucocorticoids, thus potentially increasing fetal glucocorticoid exposure. [17–19] Further studies are needed to confirm these preliminary observations.

Table 1
Differences in sex-related HPA axis activity in children adapted from systematic review and meta-analysis by van der Voorn et al. [9].

Cortisol measurement	Mean (95% CI) difference aged < 8 years	Mean (95% CI) difference aged eight–18 years
Basal salivary cortisol nmol/L	0.21 (0.05 to 0.37) nmol/L favouring males	0.42 (0.38 to 0.47) nmol/L favouring females
Basal serum cortisol nmol/L	0.17 (0.05 to 0.29) nmol/L favouring males	0.39 (0.32 to 0.46) nmol/L favouring females
24 h urinary cortisol µg/24 h	0.34 (0.05 to 0.64) µg/24 h favouring males	0.32 (0.17 to 0.47) µg/24 h favouring males

CI, confidence interval.

4. What are the consequences of sex differences in early-life programming of the HPA axis?

No studies have directly tested whether the suggested increased vulnerability of the female HPA axis to early-life programming [10] is associated with health consequences in later life. However a handful of studies examining the link between maternal cortisol in pregnancy [20,21] and/or fetal glucocorticoid exposure [22] with offspring outcomes provide strongly supportive evidence.

A prospective, longitudinal study in 65 normal, healthy mother-child dyads found that higher maternal cortisol levels in early gestation were associated with a larger right amygdala volume in girls at aged 7 years (a 1 SD increase in cortisol was associated with a 6.4% increase in right amygdala volume), but not in boys. Moreover, higher maternal cortisol levels in early gestation were associated with more affective problems in girls, and this association was mediated, in part, by amygdala volume [20]. Prenatal exposure to elevated maternal cortisol levels has also been linked with increased cardiovascular risk factors in female, but not male, offspring at age 42 years [21]. The adult daughters of mothers with the highest free cortisol tertile during the third trimester of pregnancy versus daughters of mothers with the lowest cortisol tertile had a 36.7% (95% CI 8.4% to 72.5%) greater mean 10-year coronary heart disease risk score, calculated using the Framingham risk algorithm incorporating diabetes, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, smoking, age and sex. There was no association in men (− 2.8%, 95% CI − 23.8% to 24.0%).

The confectionary liquorice contains glycyrrhizin, an 11β-HSD type 2 enzyme (11βHSD2) inhibitor. Maternal consumption of liquorice during pregnancy leads to reduction in activity of placental 11βHSD2, the key 'barrier' enzyme which metabolises cortisol into inactive cortisone. Observational studies of children whose mothers ate liquorice during pregnancy have thus been used as a model of fetal glucocorticoid overexposure [23]. A follow-up study of children aged 12.5 years