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5

Nutritional programming by glucocorticoids in breast milk: Targets, mechanisms and possible implications

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Vertical transmission of glucocorticoids via breast milk might pose a mechanism through which lactating women could prepare their infants for the postnatal environment. The primary source of breast-milk glucocorticoids is probably the systemic circulation. Research from our group showed that milk cortisol and cortisone concentrations follow the diurnal rhythm of maternal hypothalamus–pituitary–adrenal axis activity, with a higher abundance of cortisone compared to cortisol. Measurement of breast-milk glucocorticoid concentrations is challenging due to possible cross-reactivity with progestagens and sex steroids, which are severely elevated during pregnancy and after parturition. This requires precise methods that are not hindered by cross reactivity, such as LC–MS/MS. There are some data suggesting that breast-milk glucocorticoids could promote intestinal maturation, either locally or after absorption into the systemic circulation. Breast-milk glucocorticoids might also have an

Abbreviations: HPA axis, hypothalamus–pituitary–adrenal axis; 11β-HSD, 11β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropin hormone; CRH, corticotropin releasing hormone; LC–MS/MS, liquid chromatography tandem mass spectrometry; CBG, corticosteroid binding globulin; BDI, Beck Depression Inventory; POMS, Profile of Mood States; STAI, State Trait Anxiety Inventory; IBQ, Infant Behavior Questionnaire; BMI, body mass index.

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effect on the intestinal microbiome, although this has not been studied thus far. Findings from studies investigating the systemic effects of breast-milk glucocorticoids are difficult to interpret, since none took the diurnal rhythm of glucocorticoids in breast milk into consideration, and various analytical methods were used. Nevertheless, glucocorticoids in breast milk might offer a novel potential pathway for signal transmission from mothers to their infants.

Introduction

Numerous studies suggest that adversities occurring in early life could predispose to later diseases such as cardiovascular diseases, type 2 diabetes mellitus and neuropsychiatric diseases. The mechanisms that could explain these associations relate to the concept of early-life programming, stating that insults early in life could persistently alter the body's structure and/or function. These alterations, although adaptive in nature, might become deleterious with age [1].

Glucocorticoids are known for their programming effects on metabolism and the brain [2]. The fetal cortisol hypothesis postulates that a lower activity of the placental barrier enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 allows a larger proportion of maternal cortisol to reach the fetus, leading to permanent alterations in hypothalamus–pituitary–adrenal (HPA) axis settings, and, hence, predisposition to cardiometabolic and neuropsychiatric diseases in offspring [3].

Emerging data suggest that postnatal nutrition could play a role in early-life programming [4]. Breast feeding has been associated with improved health outcomes, including reduced risks of infections and obesity [4,5]. Although glucocorticoids were recovered in breast milk already in the early 1970s [6], only few studies have addressed their effects in offspring. The recent discovery of a diurnal rhythm in the secretion of glucocorticoids into breast milk has opened new avenues for the study of the postnatal programming effects of maternal glucocorticoids.

Glucocorticoids, pregnancy and the mammary gland

Cortisol is produced by the zona fasciculata of the adrenal cortex. Its synthesis is regulated by adrenocorticotropin hormone (ACTH) from the anterior pituitary gland. The release of ACTH, in turn, is under the control of corticotropin releasing hormone (CRH) from the hypothalamus. When cortisol is present in adequate amounts, a negative feedback system operates on the pituitary gland and hypothalamus. The hypothalamus also receives input from multiple brain areas involved in the stress response. In healthy individuals, the secretion of cortisol follows a diurnal rhythm, with a peak in the early morning, followed by gradual decline over the day, and a nadir at midnight.

Pregnancy-induced changes in HPA axis activity

Maternal cortisol increases sharply in the last part of gestation due to an exponential rise in the secretion of CRH from placental origin, which stimulates the release of ACTH from the pituitary [7]. In contrast to the inhibitory effect of glucocorticoids on the secretion of CRH by the hypothalamus, glucocorticoids stimulated the expression of the CRH gene in cultures of human placenta [8]. In the fetal compartment a similar rise in cortisol occurs, which is necessary for the maturation of several organs, such as the lungs and the liver [9]. The cortisol rise has also been implicated to play a pivotal role in the onset of parturition [9].

Glucocorticoids as hormonal regulators of lactation

Glucocorticoids seem to be involved in the lobulo-alveolar development of the mammary gland during the last stage of pregnancy [10]. Although glucocorticoid receptors were detectable in the

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