Is perinatal neuroendocrine programming involved in the developmental origins of metabolic disorders?

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Abstract

The discovery that small size at birth and during infancy is associated with a higher risk of diabetes and related metabolic disease in later life has pointed to the importance of developmental factors in these conditions. The birth size associations are thought to reflect exposure to adverse hormonal factors during early development but the mechanisms involved are still not fully understood. Animal and human work has pointed to the importance of changes in the set-point of a number of key hormonal systems controlling growth and development. These include the IGF-1/GH axis, gonadal hormones and, in particular, the systems mediating the classical stress response. Several studies show that small size at birth is linked with increased activity of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system in adult life. More recent human studies have shown associations between specific adverse experiences during pregnancy, such as famine or the consumption of adverse diets, and enhanced stress responses many decades later. The mediators of these neuroendocrine responses are biologically potent and are likely to have a direct influence on the risk of metabolic disease. These neuroendocrine changes may also have an evolutionary basis being part of a broader process, termed phenotypic plasticity, by which adverse environmental cues experienced during development modify the structure and physiology of the adult towards a phenotype adapted for adversity. The changes are clearly advantageous if they lead to a phenotype which is well-adapted for the adult environment, but may lead to disease if there is subsequent overnutrition or other unexpected environmental conditions.

Key words: Neuroendocrine fetal programming; Metabolic disease; Diabetes; Hypothalamic-pituitary-adrenal axis; Stress responses; Birth weight

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INTRODUCTION

Evidence that adult type 2 diabetes and related metabolic conditions might have a developmental origin came originally from a series of studies showing that they were associated with small size at birth[1,2]. Size at birth is the product of a fetus’ trajectory of growth, which is set up at an early stage in development, and the maternoplacental capacity to supply sufficient nutrients and oxygen to...
maintain that trajectory. Although many factors contribute towards fetal growth, reductions in fetal size at term in otherwise normal population are thought to reflect fetal environmental adversity. However, it is clearly a surrogate marker that itself is probably not causally linked with long-term risks of diabetes and metabolic disease. It is generally recognised that measurements such as birth and infant weights are crude measurements that only represent a summary measure of the success of fetal and infant development. However, recent studies demonstrate associations between specific maternal adversities, such as undernutrition during pregnancy, and features of the metabolic syndrome.

One important feature of the epidemiological findings is that the associations with metabolic disease are graded across the birth weight range. Not all small babies develop diabetes and the proportion affected generally declines with increasing birth weight. In addition, birth weight or other measures of fetal growth are not linear measurements of developmental potential. Fetal overgrowth or macrosomia is often linked with maternal diabetes and is known to precede to obesity, metabolic and vascular disease in later life. Consequently, many studies report inverse J-shaped or U-shaped relationships between measures of early growth and subsequent disease risk. So, for example, diabetes is associated with both low and high birth weights. However, despite the shortcomings of these measurements, a body of evidence has emerged linking patterns of fetal growth with metabolic outcomes in later life.

Despite the substantial evidence that an adverse early environment as indicated by small size at birth is linked with a higher prevalence of metabolic disease in adult life, it is still unclear as to how events in utero can affect disease predisposition some five to six decades later. Recently there has been much interest in the possibility that the early environment may have long-term effects through resetting a diverse array of hormonal systems that control growth and development. It has been known for a long time that the set point of these systems is plastic and can be programmed or permanently altered by events in utero or early infancy. Several neuroendocrine systems appear to be involved but of particular importance is evidence that the major hormonal systems which mediate the stress response including the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system are involved. Because the hormonal mediators of the stress response, including glucocorticoids and catecholamines, have biologically potent effects on metabolism and the vasculature, it has proved to be an attractive idea that these may have an important role in mediating the effects of the early environment.

PERINATAL PROGRAMMING OF THE NEUROENDOCRINE STRESS RESPONSE

Animal studies
A very large number of animal studies have clearly demonstrated that manipulation of the fetal or early post-natal environment can profoundly influence stress responsiveness and behaviors in later life in juvenile and adult offspring. A general consensus, maternal stress during pregnancy leads to increased HPA activity in rat, guinea pig and primate offspring. However, the outcomes of these animal studies have been quite variable. Within a species, outcomes in the offspring have been shown to be highly dependent on the nature of the maternal manipulation (i.e., maternal stress, glucocorticoid exposure, undernutrition or overnutrition) as well as the timing, intensity and duration of the manipulation in pregnancy. For example, while maternal stress in the guinea pig in late gestation leads to elevated HPA activity in male offspring, exposure to synthetic glucocorticoid, at very similar times in gestation, results in adult offspring that exhibit reduced HPA activity. Timing of exposure is also critical. A brief exposure to maternal stress at 70% of the duration of gestation in the guinea pig resulted in adult male offspring that exhibited elevated baseline plasma cortisol levels but normal adrenocortical responses to stress. In contrast, an identical stress given at 90% of the duration of gestation resulted in adult male offspring that exhibited normal basal cortisol concentrations but increased cortisol responses to challenge. Outcomes in offspring following maternal manipulation are also dependent on sex, age at which the outcome analysis is undertaken and, in females, the stage of the reproductive cycle when outcome is assessed. As an example, adult female guinea pigs, born to mothers exposed to stress in late gestation, showed a reduced cortisol response to stress compared to control offspring, but only in the estrous phase of the reproductive cycle. Overall, females are underrepresented in studies undertaken in animal models, likely due to the considerations above. There also appears to be strong interaction between the prenatal and post-natal environments, such that manipulation of the post-natal environment (such as cross-fostering) can reduce or reverse the effects of the prenatal manipulation.

Modification of the early post-natal environment can also have profound influences on HPA function and behaviors. A large number of these studies have been undertaken in mice and rats. Manipulations have included altered levels of maternal care, neonatal handling of pups and maternal stress during lactation. Timing of exposure is also critical. A brief exposure to maternal stress at 70% of the duration of gestation in the guinea pig resulted in adult male offspring that exhibited elevated baseline plasma cortisol levels but normal adrenocortical responses to stress. In contrast, an identical stress given at 90% of the duration of gestation resulted in adult male offspring that exhibited normal basal cortisol concentrations but increased cortisol responses to challenge. Outcomes in offspring following maternal manipulation are also dependent on sex, age at which the outcome analysis is undertaken and, in females, the stage of the reproductive cycle when outcome is assessed. As an example, adult female guinea pigs, born to mothers exposed to stress in late gestation, showed a reduced cortisol response to stress compared to control offspring, but only in the estrous phase of the reproductive cycle. Overall, females are underrepresented in studies undertaken in animal models, likely due to the considerations above. There also appears to be strong interaction between the prenatal and post-natal environments, such that manipulation of the post-natal environment (such as cross-fostering) can reduce or reverse the effects of the prenatal manipulation.
vulnerable during phases of rapid brain growth. Rapid brain growth occurs during fetal life in sheep, guinea pigs, and many primates. In humans, the rapid phase of brain development is initiated in the last trimester and extends into the neonatal period. However, in many rodent species, including rats and mice, maximal brain growth is not initiated until approximately 7 days after birth. As such, a period of maternal stress in the guinea pig at mid-gestation would correspond to a very different phase of fetal brain and neuroendocrine development in the mouse or rat at the same stage of gestation.

Most recently it has been shown that prenatal stress, maternal glucocorticoid treatment, maternal nutrient restriction and maternal stress during lactation can have transgenerational influences on HPA function, metabolic and cardiovascular function, and behaviors. Considerable work is now being undertaken to determine the mechanisms involved in this process. Emerging evidence suggests that these include epigenetic modifications that can be transmitted through the germline.

**Human studies**

There have now been a number of studies which have reported associations between birth size and fasting plasma cortisol concentrations. In the Hertfordshire Cohort Study, a birth to death study of a large number of men and women born in the country of Hertfordshire, England, between 1920 and 1936, fasting cortisol concentrations decreased linearly from 408 nmol/L in those who weighed 5.5 lb or less to 309 nmol/L amongst those who weighed 9.5 lb or more, a trend which was paralleled by the concentration of the biologically active, free hormone concentrations. Similar findings have been reported in other populations and a meta-analysis of 11 studies of the relationship between birth weight and cortisol concentrations reported that cortisol concentrations fell on average by 25.3 nmol/L/kg (95% CI: 5.9-44.8) increase in birth weight. In more detailed studies in the Hertfordshire Cohort Study, lower birth weight was found to be associated with enhanced plasma cortisol responses to Synacthen (ACTH) in both men and women. The cortisol response following an ACTH (adrenocorticotrophic hormone) stimulation test reflects both adrenal size and the trophic effect of ACTH stimulation but does not elucidate the reason for the increased HPA activity in men or women of low birth weight. A number of groups have reported that the secretion of cortisol in the unstressed state did not appear to be related to birth weight. Hence, the previously observed relationship between birth weight and morning cortisol concentrations was not caused by alteration in the underlying rhythm of cortisol secretion but rather might represent a stress response involving higher centers in the brain and probably occurring as a result of the combination of fasting and the novel clinic setting in which the blood samples were obtained. A number of studies now suggest that people with low birth weight do have an enhanced biological response to stress. Studies of a large cohort of Swedish army recruits have shown a continuous relationship between size at birth and stress susceptibility at a psychological assessment which was carried out to assess their suitability for military combat duties. These results are supported by a study of 106 young healthy males who were exposed to the Trier Social Stress Test: a psychological stress test involving a public speaking task. These findings were also supported by a study of young children born in Southampton, who formed part of a prospective study of mothers and babies born at Princess Anne Hospital, Southampton. Again using the Trier test, a cross-sectional study of 68 boys and 72 girls (aged 7-9 years) was realized. In boys, markers of fetall growth restriction, such as low birth weight, were associated with raised arterial pressure and systemic vascular resistance, particularly following the stress test. In contrast, girls who were small at birth showed no such associations, but did show greater cardiac sympathetic nervous system activation as indicated by measures of pre-ejection period and corrected QT interval, both at rest and during stress. The findings of these studies suggested that there were marked gender differences in the nature of the relationship between size at birth and the stress response which reflect many of the findings of animal studies.

Other adverse maternal factors during pregnancy, such as famine or the consumption of unusual diets, are also associated with alterations in the biological response to stress, again supporting the idea that these neuroendocrine changes are not merely a consequence of low birth weight per se but rather a response to adversity.

Relatively little is known about the relationship between infant growth and the development of the stress response. However, work in two groups of Jamaican children who experienced growth retardation during infancy has shown that in comparison with controls, stunted children have higher heart rates, raised salivary cortisol concentrations and increased urinary catecholamine secretion following a psychological stressor.

**Neuroendocrine stress response and the metabolic syndrome**

A number of studies utilizing animal models have shown that the same prenatal and postnatal manipulations that lead to programming of HPA function and behaviors also lead to altered cardiovascular function and glucose homeostasis, and predisposition to metabolic disease. It is well established that the HPA axis plays a major role in the regulation of metabolic function; indeed, modification of metabolic function is a key component of the stress response. As such, increases in HPA function which are known to result from these early life manipulations may lead directly to predisposition to metabolic disease. Alternatively, early life manipulation, such as maternal glucocorticoid treatment may lead to permanent changes in the development and subsequent function systems that regulate blood pressure, glucose insulin homeostasis and adipose function. For example, prenatal glucocorticoid treatment leads to permanent changes in

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the expression of hepatic genes that are involved in glucose homeostasis (i.e., phosphoenolpyruvate carboxykinase and tissue specific changes in glucocorticoid receptors in the liver, brain and adipose as well as structural changes in the kidney (including reduced nephron number). Bjortorp was among the first to suggest that a neuroendocrine disturbance involving the HPA axis may play an important part in the causation of the metabolic syndrome in humans. As patients with Cushing’s syndrome develop a severe form of the metabolic syndrome with hypertension, insulin resistance, glucose intolerance, dyslipidemia and central obesity, it is an attractive idea that less profound disturbances of the HPA might underlie the metabolic syndrome. Case-control and cross-sectional studies of people without pituitary or adrenal disease show that elevated plasma cortisol concentrations in morning samples are associated with high blood pressure, glucose intolerance, insulin resistance and hyperlipidemia. However, an increasing body of evidence also suggests that physiological alterations in autonomic responses are also likely to be involved in the syndrome. For example, stress responsiveness to stressors that predominantly! involve sympathetic activation are associated with carotid atherosclerosis, increased left ventricular mass and, in follow-up studies, with subsequent blood pressure and the prevalence of hypertension.

EVOLUTIONARY IMPLICATIONS

It is likely that these neuroendocrine mechanisms have an important evolutionary basis in that they allow adaptation of organisms to their expected postnatal environments within a single generation while genetic adaptation in response to environmental pressures would take much longer to influence survival characteristics. These short-term adaptations are part of a process known as developmental plasticity which is widely recognized in animal species, including vertebrates and invertebrates. Exposure of the mother to various forms of adversity during gestation triggers changes in the offspring phenotype affecting both morphology and physiology. These adversities include the level of resources, population density, temperature, the prevalence of parasites and the presence of predators. The phenotypic changes produced in the offspring tend to be adaptive as they are linked to an increase in offspring survival and reproductive success. It is thought that the HPA axis, which is highly conserved in vertebrate taxa, plays a central role in producing these phenotypic adaptations to adversity in vertebrates. Glucocorticoids are known to influence the expression of approximately 10% of the genome, including genes controlling metabolism, growth, repair and reproduction. Glucocorticoid exposure during growth and development leads to a variety of physiological and anatomical changes appropriate to adversity. These include insulin resistance, which reduces energy invested into growth and metabolism, the development of visceral fat to provide a fuel reserve and buffer in unpredictable conditions, and reduced skeletal muscle mass to decrease energetic demands. A heightened stress response enables greater chance of survival in a nutrient-deprived and, therefore, predator-rich environment.

It is likely that these endocrine effects are particularly important in species where the period of development and lifespan is relatively brief and the organism can respond appropriately to short-term changes in the environment. The situation is more complicated in long-lived species, including humans, where development occurs over more than one season and environmental cues operating during pregnancy may not be appropriate for the environment up to several decades later. Many of these species are “capital breeders” as the energy for reproduction is stored by the mother prior to conception. This buffers the offspring against short-term ecological fluctuations or annual cycles but there is still need to be able to respond to longer-term changes in the environment. One suggestion as to how this could occur is for HPA axis responses in the fetomaternal unit to reflect the experiences of the prior generation or generations. Thus, the signal received by the fetus is an integrated signal conditioned not only by the mother’s current environment but also by her neuroendocrine experience back to her own uterine environment, and by prior generations of the matriline. There is increasing evidence that HPA axis responses show intergenerational transmission, perhaps through epigenetic modifications; this may allow the fetus to “see” an average environment sampled over several decades or even generations and make appropriate phenotypic adaptations.

CONCLUSION

Despite the wealth of animal data, neuroendocrine programming in humans is largely neglected. The mechanisms involved are clearly complex and hard to disentangle. For example, the effects of stressful influences on the mother are complex and are likely to be conditioned by other factors, such as the maternal social environment, the fetal and maternal genetic backgrounds, the maternal early environment and transgenerational effects. However, neuroendocrine programming may be a common pathway by which a wide variety of adverse external influences have long-term effects on the fetus. These influences include psychosocial stress, ergonomic challenges (for example, prolonged standing or carrying heavy loads), maternal diet (macro- and micronutrient intakes, dietary balance), the physical environment (heat or cold), exposure to environmental toxins or drugs and maternal illness. It is likely that maternal stressors affect the fetus by the transplacental passage of maternal hormones, such as cortisol. The human fetal HPA axis is well developed and functional in late gestation and able to respond to external factors, especially hypoxia and nutrient restriction. Therefore, external factors that reduce uterine blood flow would restrict fetal nutrient or oxygen supply and
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