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Review

# Glucocorticoids, prenatal stress and the programming of disease

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ABSTRACT

An adverse foetal environment is associated with increased risk of cardiovascular, metabolic, neuroendocrine and psychological disorders in adulthood. Exposure to stress and its glucocorticoid hormone mediators may underpin this association. In humans and in animal models, prenatal stress, excess exogenous glucocorticoids or inhibition of 11β-hydroxysteroid dehydrogenase type 2 (HSD2; the placental barrier to maternal glucocorticoids) reduces birth weight and causes hyperglycemia, hypertension, increased HPA axis reactivity, and increased anxiety-related behaviour. Molecular mechanisms that underlie the 'developmental programming' effects of excess glucocorticoids/prenatal stress include epigenetic changes in target gene promoters. In the case of the intracellular glucocorticoid receptor (GR), this alters tissue-specific GR expression levels, which has persistent and profound effects on glucocorticoid signalling in certain tissues (e.g. brain, liver, and adipose). Crucially, changes in gene expression persist long after the initial challenge, predisposing the individual to disease in later life. Intriguingly, the effects of a challenged pregnancy appear to be transmitted possibly to one or two subsequent generations, suggesting that these epigenetic effects persist.



**Contents**



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## Introduction

Early life events have long lasting impacts on tissue structure and function. These effects appear to underlie the developmental origins of vulnerability to chronic degenerative diseases that have been revealed by human epidemiological studies. In addition to the well-recognised effects of both genes and adult environment, it is clear that undernutrition, stress and exposure to excess glucocorticoids (the main hormonal mediator of stress) during foetal development cause permanent cardiometabolic, neuroendocrine and cognitive effects (Meaney et al., 2007; Seckl and Meaney, 2006). The concept of 'developmental programming' was put forward in an attempt to explain this association between environmental challenge during pregnancy, altered foetal growth and development and later pathophysiology (Barker et al., 1993a; Seckl, 1998). During programming, environmental adversity is transmitted to the foetus and acts on specific tissues during sensitive periods in their development to change developmental trajectories and thus their organisation and function. Since different cells and tissues are sensitive to various factors at different times, the effects of adversity on an animal's biology will be tissue, time and challenge specific.

It is currently unclear what the biological 'purpose' of early life programming is. However, since the phenomenon of programming seems highly conserved through evolution (humans, non-human primates and many animal models show evidence of developmental programming) it may be assumed that programming confers adaptive Darwinian advantages. For example, a mother may transmit a signal to the foetus 'it is tough out here' be it because of reduced food availability and/or increased stress (e.g. predation, war, etc.) and the resulting changes in the foetus affect the offspring to promote survival until reproduction is secured. However, in the post-reproductive period these changes may prove to be disadvantageous. This has been suggested to be particularly pertinent if the adult environment does not match that for which the developmental plasticity is aimed, e.g. if early life undernutrition programmes a 'thrifty phenotype' and then food is plentiful, the adult may be at risk of developing metabolic diseases such as diabetes and obesity (Gluckman and Hanson, 2004).

## Birth weight and the programming of disease

In humans there is a clear association between low birth weight and the development of hypertension, type 2 diabetes and cardiovascular disease in adulthood (Barker et al., 1993b; Fall et al., 1995; Moore et al., 1996; RichEdwards et al., 1997). This relationship is independent of other life style-associated risk factors (e.g. smoking, excess alcohol consumption, obesity, and social class) and holds true over a continuum of birth weights within the normal range (Leon et al., 1996; Levine et al., 1994; Osmond et al., 1993). While it is possible that shared genetics explains the above findings, data from twin studies show that the twin with the lowest birth weight has higher blood pressure in adulthood (Gluckman and Hanson, 2004) though not always (Baird et al., 2001). Additionally, findings from apparently isogenic rodent models provide further evidence of a link between early life environmental manipulations, reduced birth weight and adult pathophysiology.

Low birth weight is also associated with affective and cognitive disorders in adulthood (Thompson et al., 2001; Wiles et al., 2005). For example, low birth weight has been linked to schizophrenia, attention deficit/hyperactivity disorder (ADHD), antisocial behaviour, increased vulnerability to post-traumatic stress disorder (PTSD), anxiety disorders, learning difficulties and depression (Cannon et al., 2002; Famularo and Fenton, 1994; Jones et al., 1998; Khashan et al., 2008a; Lahti et al., 2009; Raikkonen et al., 2008; Wust et al., 2005). And crucially, rodent models show that early environmental challenges (such as restraint stress in third week of pregnancy) increase anxiety and depressive-like behaviour and impair cognitive ability in adults, further substantiating the human correlative data (Meaney and Szyf, 2005). Consequently, low birth weight has been proposed as an indicator of environmental adversity during foetal development. Though low birth weight *per se* may not be the cause of disease, it does seem to suggest foetal programming processes are at work. Birth weight is, however, an unsophisticated measure and presumably there are many factors or lesser degrees of challenge that may alter offspring biology without affecting birth weight. Furthermore, humans and rodents with reduced birth weight may experience rapid postnatal catch-up growth, altered fat content and distribution and low adiponectin levels, which may predispose to cardiovascular disease, obesity and type 2 diabetes in adulthood (Owen and Matthews, 2007). However, postnatal dexamethasone treatment of newborn rat pups, whilst causing immediate and marked growth retardation with subsequent catch-up growth does not appears to induce cardiometabolic sequellae (Nyirenda et al., 1998) suggesting that the window of sensitivity in prenatal life is key in this species at least.

## Mechanisms of programming

Two mechanistic hypotheses have been proposed to explain how foetal programming may arise: foetal malnutrition and foetal overexposure to glucocorticoids, which may have effects either directly or indirectly upon the developing foetus (Barker et al., 1993a; Berney et al., 1997; Edwards et al., 1993; Matthews, 2000; Meaney et al., 2007). However, these hypotheses are not mutually exclusive since stress may reduce maternal food intake and reduced food intake may invoke stress responses in the mother and foetus (Gardner et al., 1997). Moreover, maternal glucocorticoids may mediate the effects of diet on foetus biology. For example, the feeding of low-protein diets to rats during pregnancy results in higher blood pressure in the offspring from the age of weaning. However, blocking maternal glucocorticoid synthesis eliminates the impact of protein restriction on the offspring (Gardner et al., 1997; Langley and Jackson, 1994; Langley-Evans, 1997; Langley-Evans et al., 1996a). And it would seem that the relevant physiological systems are glucocorticoid-sensitive from an early age, since infusion of glucocorticoids directly to the foetus *in utero* or at birth elevates blood pressure, at least in sheep (Berry et al., 1997; Tangalakis et al., 1992). Furthermore, the 'low birth weight syndrome' rather resembles the endocrinological disorder Cushing's syndrome (glucocorticoid excess) which also causes type 2 diabetes, hypertension, dyslipidemia, atherosclerosis and osteoporosis (Anagnostis et al., 2009; Andrew et al., 2002; Seckl et al., 2004; Walker, 2006; Wei et al., 2004). Here we focus predominantly on antenatal glucocorticoid and stress-mediated effects.

### *Glucocorticoids during pregnancy*

Glucocorticoids influence the developing foetus by binding to glucocorticoid and mineralocorticoid receptors (GR and MR, respectively), which subsequently act as transcription factors to alter gene expression. In addition, MR and GR can also mediate fast non-genomic actions via membrane-located receptors, at least, in the hippocampus (de Kloet et al., 2008; Karst et al., 2005). Although, any role of this biology in developmental programming is unexplored. GR is expressed in most foetal tissues, including the placenta, from early embryonic stages and is essential for survival, as indicated by the lethal postnatal phenotype of GR null mice (Cole et al., 1995). Indeed, glucocorticoids play a vital role during normal foetal development. Most notable is their role in promoting maturation of the lung and production of the surfactant necessary for extra-uterine lung function (Ward, 1994). Glucocorticoids also promote correct brain development by initiating terminal maturation, remodelling of axons and dendrites, and affecting cell survival (Meyer, 1983; Yehuda et al., 1989). Expression of the higher affinity MR is more limited and present only during the later stages of development in rodents (Brown et al., 1996; Diaz et al.,