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Review

Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes☆

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ABSTRACT

Epidemiological studies have shown that low birthweight is associated with increased risk of development of diabetes and obesity in later life. Over-exposure of the developing fetus to glucocorticoids is one of the major hypotheses that has been proposed to explain this association. In animal models, a range of manipulations that increase fetal glucocorticoid load, 'programme' permanent changes in glucose and insulin metabolism and adiposity. This may be mediated by alterations in regulation of the hypothalamic–pituitary–adrenal (HPA) axis. In humans, low birthweight is associated with increased circulating glucocorticoid levels, and an increased cortisol response to physiological and psychosocial stressors, in child- and adulthood. This activation of the HPA axis is also associated with increased risk of development of diabetes and obesity in later life.

Contents

1. Introduction

Epidemiological studies have shown that adverse influences during early development, and particularly during intrauterine life, can result in permanent changes in physiology and metabolism, which have long-term consequences on health and disease in adulthood. These processes act during specific, sensitive 'windows' of development in fetal life, affecting the development and subsequent organization of specific tissues. This concept is termed 'early life programming' or the 'developmental origins of health and disease' [1,2]. A large number of studies have reported associations between an adverse prenatal environment and a range of diseases in adult life including glucose intolerance, hypertension and cardiovascular disease, as well as depression and osteoporosis.

The idea that alterations in regulation of the hypothalamic–pituitary–adrenal (HPA) axis may explain part of the epidemiological association between birthweight and later cardiometabolic

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disease was proposed in the 1990s [3]. This is an attractive proposal as patients with Cushing's syndrome develop glucose intolerance, hypertension, dyslipidaemia, and central obesity, i.e., many of the clinical features of the metabolic syndrome in which the 'low birthweight baby' is at increased risk of developing in adult life. The hypothesis is supported by a series of animal studies dissecting the potential mechanisms whereby glucocorticoids might mediate programming and by translational studies in humans in whom birthweight records are available. This review will focus on the role of glucocorticoids in mediating programming and their potential role in underlying the link between low birthweight and the later development of diabetes and obesity. The review will explore some of the potential mechanisms underlying glucocorticoid programming, for example the molecular mechanisms underlying the long-term biochemical changes in glucose metabolism. Risk of development of diabetes and obesity as a consequence of overnutrition as explored in the 'fetal overnutrition hypothesis' is beyond the scope of this review but has been discussed elsewhere [4].

2. Birthweight and early life programming of diabetes and obesity

There is now much evidence that size at birth, in particular low birthweight, predicts the subsequent development of metabolic disorders in adult life including insulin resistance, type 2 diabetes and obesity, as well as hypertension and death from cardiovascular disease [1]. The first report describing the relationship between birthweight and glucose intolerance was in a study of 64-year-old men in Hertfordshire, UK. This showed that those who were smaller at birth had a 6-fold increased risk of type 2 diabetes compared to those who were heaviest at birth and an 18-fold increased risk of developing the cluster of cardiovascular risk factors comprising the metabolic syndrome including glucose intolerance, dyslipidaemia and hypertension [5]. These relationships were independent of other lifestyle factors, although those who were obese at the time of the study had worse glucose tolerance. Importantly, the relationship between birth size and adult disease is continuous and represents birthweights within the normal range, rather than severely undersized or premature babies. Poor fetal growth is thought to be a crude marker of an adverse intrauterine environment, but as not all fetuses respond to such insults by reducing growth, and as birthweight is an imprecise measure, the size of the relationship between birthweight and adult diseases varies in different studies. For glucose intolerance, the relationship with low birthweight is widely accepted and reproduced in numerous cohorts and populations worldwide [6].

A large number of epidemiological studies have also linked low birthweight to the later development of central adiposity [7] following the key cohort study of 300,000 men exposed *in utero* to the Dutch famine of 1944–1945. Exposure to this insult during the first half of pregnancy resulted in offspring with low birthweight and was associated with significantly higher obesity rates at age 19 years [8]. Intriguingly, recent data has now shown that the adverse effects of exposure to the famine are not limited to the first generation, but persist into the second generation. The offspring of those who were *in utero* at the time of the famine were also at increased risk of obesity [9]. This suggests that insults *in utero* have long-term consequences on health of not only the immediate next generation, but also of future generations [10].

Two major hypotheses have been proposed to underlie early life programming: fetal undernutrition [1] and over-exposure of the fetus to glucocorticoids [2,3]. These hypotheses are probably not mutually exclusive, as, for example, in animal models, glucocorticoids can alter maternal food intake, and conversely, maternal malnutrition increases maternal glucocorticoid secretion, reduces placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity (as discussed below) and thus alters fetal glucocorticoid exposure. It remains unknown whether the observed alteration in 11β-HSD2 activity in association with malnutrition is due to a direct effect of diet on enzyme activity, or a secondary effect in response to altered maternal cortisol levels. Nevertheless, altered nutrition and glucocorticoid exposure may overlap as programming influences and act via common pathways to produce long-term changes in adult disease risk.

3. Role of glucocorticoids in programming

Glucocorticoids are essential for life, playing a key role in the regulation of fluid and electrolyte homeostasis, blood pressure, the immune system, metabolism and physiological responses to stress.

Circulating levels of glucocorticoids (cortisol in humans and other mammals, corticosterone in rodents) synthesized in the zona fasciculata/reticularis of the adrenal cortex, are regulated by activity of the hypothalamic–pituitary–adrenal (HPA) axis in a classical negative feedback loop. Cortisol is released in a pulsatile and circadian fashion, with plasma levels peaking prior to activity (i.e., in the morning in humans) and declining through the day. Circadian secretion of ACTH (adrenocorticotrophic hormone) from the pituitary is stimulated by the action of CRH (corticotropin releasing hormone) and AVP (vasopressin) from the parvicellular neurons of the hypothalamus under control of the suprachiasmatic nucleus of the hypothalamus. This diurnal cycle of cortisol release is tied to the sleep-wake cycle and to the light–dark cycle but can be interrupted by stressors, which cause a premature secretory burst of glucocorticoids.

Glucocorticoids exert their effects by binding to intracellular glucocorticoid receptor (GR), members of the nuclear hormone superfamily of ligand-activated transcription factors [11]. Additionally, in some tissues, glucocorticoids bind with high affinity to mineralocorticoid receptors (MR). GR and MR are activated upon ligand binding and the receptor–ligand complex translocates to the nucleus, binding to glucocorticoid response elements in the promoter regions of target genes to influence gene transcription. In addition, emerging evidence suggests that rapid non-genomic effects of glucocorticoids by direct actions on membrane lipids, membrane and cytoplasmic proteins may be mediated via novel cell-membrane receptors. These effects remain poorly understood [12].

GR is expressed in most fetal tissues from mid-gestation onwards as well as in the placenta and fetal membranes [13]. Expression of MR is more limited and is present only at later gestational stages, at least in rodents [14]. During development, glucocorticoids are important in regulating fetal growth and organ maturation to prepare the fetus for extra-uterine life. For example, antenatally they are used to improve neonatal viability in threatened preterm delivery, by accelerating lung maturation. In humans and many animal species, there is a rise in cortisol concentrations during late pregnancy that parallels the increased maturity of fetal organs [15].

3.1. The placental glucocorticoid barrier

Although glucocorticoids are lipophilic, and so readily cross the placenta, fetal glucocorticoid levels are normally much lower than maternal levels. This is due to placental expression and activity of the enzyme 11β-HSD2, which catalyses the conversion of active glucocorticoids (cortisol in humans and corticosterone in rodents) to physiologically inert 11-keto forms (cortisone and 11-dehydrocorticosterone, respectively). Placental 11β-HSD2 activity increases through gestation in humans, forming a functional 'bar-

rier' to maternal glucocorticoids to prevent inappropriate action at glucocorticoid-responsive tissues during fetal development. The barrier is not complete as a minor proportion (~10–20%) of maternal glucocorticoid crosses intact to the fetus. In addition, studies in rodents and humans indicate that the efficiency of placental 11β-HSD2 varies considerably [2].

4. Glucocorticoid programming in animal models

Various strategies have been used in animal models to increase fetal glucocorticoid load and thus study the effects of prenatal glucocorticoid exposure on long-term pathophysiology. These include maternal administration of synthetic glucocorticoids such as dexamethasone or betamethasone, which are poor substrates for 11β-HSD2, and thus cross the placenta [16,17]. Likewise, fetal glucocorticoid exposure can be increased by inhibiting placental 11β-HSD2 using liquorice, or its derivatives, such as carbenoxolone [2,18]. As mentioned briefly above, fetal glucocorticoid levels are also increased in response to maternal undernutrition, placental insufficiency or restriction of placental blood flow. The majority of animal models examining glucocorticoid programming effects on metabolic outcomes described below have focused on effects mediated via GR. Potential programmed effects mediated via MR reported to date are limited to changes in MR in the brain associated with alterations in behaviour [19].

4.1. Glucose and insulin homeostasis

Programming of glucose intolerance may result from altered insulin sensitivity of target tissues, or altered development and insulin-secreting capacity of the endocrine pancreas. In rodent models, administration of dexamethasone or inhibition of 11β-HSD2 to increase fetal glucocorticoid load, results in permanent hyperglycaemia and hyperinsulinaemia in the offspring [17,18] with life-long elevations in phosphoenolpyruvate carboxykinase (PEPCK) mRNA and activity, the rate-limiting enzyme of gluconeogenesis [17]. The timing of glucocorticoid exposure is key in determining the outcome, and week 3 of gestation appears to be a critical 'window' resulting in long-term metabolic changes in the offspring. These effects are dependent on maternal glucocorticoids, as maternal adrenalectomy prevents the effects of carbenoxolone on birthweight and glucose metabolism [18]. Similar long-term disruption of glucose homeostasis secondary to maternal glucocorticoid administration have been reported in both sheep and non-human primates [16,20].

The molecular mechanisms underlying these programmed changes in offspring glucose metabolism have not been fully determined but alterations in HPA axis activity have been implicated as the animals have increased levels of circulating corticosterone [21], decreased GR expression in the hippocampus, the site of central negative feedback in the rodent [21] and increased peripheral GR expression in insulin-sensitive target tissues including liver and muscle [17,22]. Increased hepatic GR expression is also seen in other models of *in utero* programming of hyperglycaemia, such as maternal protein restriction or uterine artery ligation [23]. The mechanisms underlying the programmed increased PEPCK expression have been dissected in more detail. PEPCK expression is regulated by transcription factors, including members of the HNF (hepatocyte nuclear factor) and GR, that bind to the PEPCK gene promoter. In the dexamethasone-programmed rats, there is increased expression of both GR [17] and HNF 4α [24] in the liver, suggesting that the observed increase in PEPCK may be secondary to alterations in these transcription factors. Thus changes in key transcription factors may underlie permanent changes in glucose metabolism.

4.2. The endocrine pancreas

The neonatal period is a time of islet cell plasticity, and thus insults during this time can have life-long consequences for glucose homeostasis. Yet there are few studies reporting the effects of prenatal glucocorticoid exposure on the development of the pancreas. Glucocorticoid signaling is important in both pancreatic and beta cell development [25,26], with potential underlying mechanisms including interaction of glucocorticoids with other transcription factors that control proliferation and differentiation of the pancreas [27]. For example, glucocorticoids decrease expression of key growth and transcription factors important in pancreatic development including IGF (insulin-like growth factor) 2, the IGF receptor, and several IGF binding proteins as well as *Pdx-1* [28]. In the adult pancreas, glucocorticoids inhibit insulin secretion and so the high levels of circulating glucocorticoids in offspring of 'programmed' mothers, may also contribute directly to the development of hyperglycaemia.

4.3. Obesity

Prenatal glucocorticoid exposure is also associated with alterations in fat distribution and function. Offspring of rats treated with dexamethasone during days 8, 10 and 12 of pregnancy have increased intra-abdominal fat depots, and a parallel increase in circulating leptin levels [29]. Treatment of rats with dexamethasone in the last week of pregnancy leads to an increase in GR expression in visceral adipose tissue and alterations in fat metabolism which may contribute to insulin resistance [22]. Maternal nutrient restriction during pregnancy in sheep also results in increased obesity and adipose tissue GR expression [30,31]. Recent evidence also shows that the activity of 11β-HSD type 1 (11β-HSD1), which reamplifies local tissue glucocorticoid levels, and has been implicated in the pathogenesis of obesity and the metabolic syndrome, may also be 'programmed' by the early life environment. A brief antenatal exposure to glucocorticoids in pregnant marmosets resulted in upregulation of 11β-HSD1 mRNA expression and activity in subcutaneous, but not visceral, fat of the offspring [32]. The increase in 11β-HSD1 occurred before the animals developed obesity or overt features of the metabolic syndrome. This upregulation of 11β-HSD1 following prenatal 'stress' hormone exposure suggests a novel mechanism underlying the fetal origins of obesity.

Importantly, evidence suggests that these programming effects on glucose intolerance and obesity may not be limited to first generation offspring. For example, prenatal dexamethasone treatment not only has metabolic effects in the immediate offspring (F1) as adults, but also elevates plasma levels of glucose, insulin and hepatic PEPCK in their own offspring (F2) [33]. Such peripheral metabolic programming effects transmit to a second generation without further manipulation, and this phenomenon appears to also occur in humans [9]. There is currently much interest in exploring potential epigenetic mechanisms underlying this phenomenon [10,34].

5. Glucocorticoid programming in humans

In humans there is now evidence that exogenous glucocorticoid administration and increasing evidence that endogenous glucocorticoids are implicated both as mediators of – and targets of – programming.

5.1. Exogenous glucocorticoids as mediators of programming

Antenatal glucocorticoids are given to 7–10% of women in Europe and North America during preterm labour, to mature the

fetal lungs and reduce the risk of neonatal morbidity and mortality [35]. While there is no doubt that treatment with synthetic glucocorticoids greatly improves survival [36], this may not be without adverse effects. The consequences in terms of long-term metabolic effects have not been described in detail. This is party due to small study sizes and short duration of follow-up, or studies that have focused on neurodevelopmental sequelae [37]. The largest studies with the longest duration of follow-up are from New Zealand.

The first and largest Auckland Steroid Trial in which women were randomized to a single course (2 doses of betamethasone) has now followed the offspring to age 30 years [38]. Exposure to antenatal betamethasone had no effect on body size, fasting lipids, blood pressure, plasma cortisol, prevalence of diabetes or history of cardiovascular disease but there was evidence of increased insulin resistance. Although this is of no clinical significance at this age, it may have implications on health with increasing age. In contrast, in the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS), women were randomly assigned to repeat doses of corticosteroids as compared to a single course. The *z*-scores for weight and head circumference were lower at birth in babies in the repeat-dose group, although there were no significant differences by the time of hospital discharge [39]. In follow-up studies, there were also no differences in either blood pressure or body size at 2 years [40]. Recent data in a non-human primate model suggest dose-associated programming of cardiometabolic parameters by dexamethasone [16], implying that the lowest dose of glucocorticoid possible should be used to avoid long-term adverse side effects.

5.2. Endogenous glucocorticoids as mediators of programming

Evidence that endogenous glucocorticoids influence birthweight in humans remains limited. Human fetal blood cortisol levels are increased in pregnancies complicated by intrauterine growth retardation, implicating endogenous cortisol in retarded fetal growth [41]. Lower placental 11β-HSD2 activity is seen in babies of low birthweight [18,42,43], suggesting that increased exposure to maternal cortisol may be a critical factor during development. Further, observational studies suggest that women who consume large amounts of liquorice (which inhibits 11β-HSD2) during pregnancy deliver smaller babies [44]. Although humans with 11β-HSD2 deficiency are rarely reported, babies homozygous for deleterious mutations of the HSD11B2 gene are of lower birthweight, averaging 1.2 kg less than their heterozygote siblings [45]. To date, however, there are no studies linking polymorphisms of the HSD11B2 gene with low birthweight. A recent study showed that higher early morning maternal urine cortisol was associated with smaller fetal size, as measured by ultrasound, during the second trimester [46], but other studies linking detailed cortisol measurements in pregnancy with offspring outcomes are lacking. There is some evidence that maternal cortisol levels are related to offspring cortisol levels. For example, in women with post-traumatic stress disorder, maternal cortisol levels, particularly during the third trimester, were associated with the babies' cortisol levels at 1 year of age [47]. There was no effect on birthweight, though the incidence of intrauterine growth retardation was increased and head circumference reduced. Although the precise programming 'insult' is unknown, there may be changes in activity of the maternal HPA axis influenced by, for example, maternal diet [48–50], maternal stress [47], placental 11 β-HSD2 activity leading to increased exposure of the developing fetus to cortisol [2], or epigenetic modification affecting transcription of GR [10,33]. However, the extent to which variation in endogenous glucocorticoid production in the mother influences fetal growth and subsequent metabolic and obesity risk in the offspring is not known.

5.3. Glucocorticoids as targets of programming

The first evidence for possible programming of the HPA axis in humans was suggested by a study in children reporting a U-shaped relationship between birthweight and glucocorticoid metabolite excretion in 24-h urine samples [51]. Then in 1998, Phillips et al. reported an inverse association between birthweight and fasting morning cortisol levels in a population of elderly men [52]. Subsequent studies indicated that this association was seen in both men and women, and spanned across the ages, ranging from young adults aged 20 years, through to elderly individuals aged 70 years [53]. A recent meta-analysis of 11 studies (with data on 2301 subjects) of the relationship between birthweight and cortisol concentrations reported that cortisol concentrations fell on average by 25.3 (95% CI, 5.9–44.8) nmol/l/kg increase in birthweight [54]. Low birthweight has also been associated with increased urine cortisol metabolites in children and adults [51,55,56].

A single fasting measurement of cortisol is an imprecise measurement of HPA axis activity, but it is thought that the combination of fasting and the novel clinic setting in which the samples were taken may act as a form of 'stress' test. Interestingly there is no association of birthweight with cortisol if the measurements are taken in the unstressed state either by sampling over 24 h in blood [57] or saliva [58]. It has therefore been proposed that low birthweight is associated with enhanced biological responses to stress secondary to central activation of the HPA axis. This is supported by studies in men and women showing increased plasma cortisol responses to synthetic ACTH [56,59,60] and increased salivary cortisol responses to stress tests, including the Trier Pyschosocial Stress Test (TSST) [61,62] and cold-pressor test [63]. Alternatively, the association between high fasting cortisol and low birthweight could be explained by impaired central negative feedback sensitivity of the HPA axis. Studies using dexamethasone suppression which tests the GR component of central negative feedback, have suggested there are no differences in central negative feedback sensitivity [56,60] in association with birthweight. However, further detailed studies, dissecting different components of central negative feedback including the contribution of both GR and MR, as has been described in obesity [64], are required.

5.4. Do the programmed changes in HPA axis activity result in diabetes and obesity?

The evidence discussed above indicates that subtle variations in HPA axis activity appear to be an outcome of programming. While it is well recognized that cortisol overproduction in Cushing's syndrome is associated with abdominal obesity and impaired glucose tolerance, it is now apparent that more subtle variations in HPA axis activity are also associated with these outcomes. It is therefore plausible that programmed changes in HPA axis activity contribute to the risk of developing diabetes and obesity. A series of studies have examined the relationship between aspects of cortisol secretion and tissue action and glucose intolerance. In case–control and cross-sectional studies higher glucose levels and insulin resistance are associated with higher fasting cortisol levels [52,65,66], increased adrenal responsiveness to synthetic ACTH [48,56,67], increased urinary cortisol metabolites [56], elevated salivary cortisol [68] and altered responsiveness to dexamethasone suppression [69].

In people with diabetes, early studies of HPA axis regulation showed inconsistencies. This was partly caused by inclusion of individuals with type 1 and type 2 diabetes [70], or a failure to control for other factors influencing cortisol levels such as obesity and gender [71]. In studies that included subjects with type

2 diabetes alone, elevated basal plasma cortisol levels [72–74] and late night salivary cortisol levels [75] have been reported. Elevated ACTH levels [76,77], increased cortisol levels following overnight dexamethasone suppression [70,78] and impaired habituation of cortisol levels to repeated stress [65] are consistent with a 'central' dysregulation of the HPA axis in type 2 diabetes. Higher cortisol concentrations are not just associated with an adverse metabolic profile, but in people with established type 2 diabetes mellitus, higher circulating cortisol and increased urine cortisol excretion is associated with more severe complications from type 2 diabetes mellitus [79] and fatty liver [80], the hepatic manifestation of the metabolic syndrome.

Many of the studies relating variations in HPA axis activity to glucose intolerance do not adequately control for differences in adiposity between individuals which is important, as obesity may have independent effects in predicting glucose intolerance. In addition, obesity is also associated with dysregulation of the HPA axis [81]. Morning plasma or salivary cortisol levels are normal or low [68,82] while studies measuring 24-h urinary cortisol excretion, responsiveness to ACTH or other stimuli, suggest cortisol secretion rate is enhanced in obesity [81,83,84]. This paradox may be explained by either a central dysregulation of the HPA axis with blunting of the diurnal rhythm [68], impaired central negative feedback [64,85] or by enhanced peripheral metabolic clearance of cortisol [71]. Ultimately in glucose intolerance with associated obesity there are opposing influences on plasma cortisol levels. The effect of obesity on cortisol levels (i.e., to lower plasma circulating levels) may obscure underlying positive associations between plasma cortisol and glucose intolerance.

There are few studies in humans exploring whether glucocorticoids may mediate the link between low birthweight and glucose intolerance. In the studies reporting birthweight, HPA responses, and metabolic outcomes, both elevated cortisol levels [52] and increased adrenal responsiveness to ACTH [48,56,59,60,67] are associated with an adverse metabolic profile including glucose intolerance in adulthood. Associations with urinary glucocorticoid metabolites are less consistent [56,60]. In a small study using the TSST [50], we also found no association of cortisol responses to psychosocial stress with fasting glucose (Reynolds, unpublished), although in these young adults, there were only limited assessments of glucose tolerance available. Larger studies have suggested that psychosocial factors including increased work stress are associated with increased HPA axis activity and the metabolic syndrome [86,87]. Studies measuring cortisol responses using formal stress tests such as the TSST in birthweight cohorts to examine associations with glucose intolerance or obesity are probably not practical on a large scale.

6. Conclusions

A wealth of animal data and translational evidence in humans supports a role for glucocorticoids as both mediators of – and targets of – programming of glucose intolerance, diabetes and obesity (see Fig. 1). These effects appear to be transmitted across generations leading to a potential intergenerational cycle of low birthweight, obesity and diabetes. Detailed studies in humans may be difficult due to various factors such as the diurnal rhythm of cortisol secretion, but the existing literature is supportive of data from animal studies in which detailed mechanistic studies are possible. Future studies should identify targets of glucocorticoid programming which are suitable for intervention. Such understanding of the mechanisms underlying glucocorticoid programming may have a profound impact on public health strategies for the prevention of diabetes and obesity.

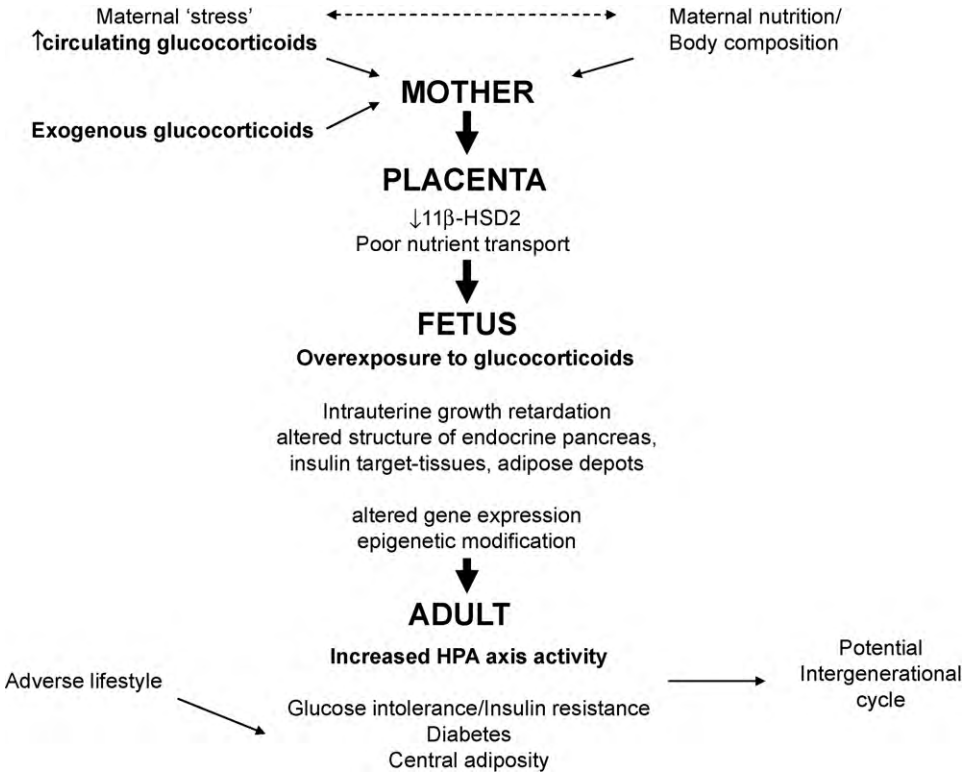

Fig. 1. Role of glucocorticoids in programming diabetes and obesity. An adverse *in utero* environment resulting from maternal and/or placental factors leads to over-exposure of the developing fetus to excess glucocorticoids. The fetus responds to this in a number of ways including reducing fetal growth and altering structure and function of insulin target tissues, as well as altering gene expression. The 'programmed' adult has increased activity of the HPA axis and develops glucose intolerance, diabetes and obesity. Adverse lifestyle factors in adulthood may contribute to the development of diabetes and obesity. These findings are potentially transmittable to the next generation leading to an intergenerational cycle of low birthweight, obesity and diabetes (11-βHSD2—11 beta hydroxysteroid dehydrogenase type 2 and HPA—hypothalamic–pituitary–adrenal).

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