The association between low birth weight and the development of hypertension, coronary heart disease, stroke and type 2 diabetes has led to the hypothesis that pathological processes can be set in motion by poor fetal nutrition (for a review, see Barker, 2001). Several animal models have been developed to test the idea that, in the face of inadequate nutrient supply or inappropriate access of glucocorticoid to the fetal compartment, growth, as well as development and function of the cardiovascular system and metabolism, is ‘programmed’.

The term ‘programming’ is now widely used in this context to describe the permanent alteration of fetal or neonatal physiological and metabolic processes by either a stimulus or an insult during a critical period of development, the action of a factor during such a ‘window’ of development thus exerting permanent organizational effects (for reviews, see Hales and Barker, 1992; Barker, 2001). However, while this might ensure survival under suboptimal conditions, these adaptations could be detrimental if the adult environment is not as unfavourable as ‘predicted’. Unbalanced maternal nutrition is one of the major environmental factors suggested to drive fetal programming, and several studies using rats, guinea-pigs and sheep show that diverse dietary restrictions during pregnancy reduce birth weight and produce permanent hypertension and hyperglycaemia in adult offspring (for a review, see Langley Evans et al., 1999a). The fact that different maternal nutritional insults result in a similar outcome indicates that there may be a common underlying mechanism.

The epidemiological studies of populations worldwide show that low birth weight and thinness at birth strongly predict the subsequent occurrence of disorders included in the ‘metabolic syndrome’ (hypertension, dyslipidaemia, insulin resistance, type 2 diabetes) associated with increased risk of cardiovascular disease (CVD) in adult life. These studies include birth weights within the normal range at term, rather than specifically those babies who were small due to intrauterine growth retardation, multiple or premature births (for a review, see Hales and Barker, 2001). Further studies have shown that placental size and body proportions also predict later CVD risk (for a review, see Barker, 2001). Transitions in populations, especially the increase in obesity against a background of low birth weight in third world countries, are now producing an epidemic of the ‘metabolic syndrome’ and type 2 diabetes of enormous proportions (for a review, see Zimmet et al., 2001).

Fetal growth is partly determined by genetic factors, although the genetically defined growth trajectory may be modified by maternal body composition and nutritional status, as well as genomic imprinting processes (Levin, 2000). Of these factors, nutritional status is highly variable within the population and may be the principal influence responsible for the intrauterine programming of cardiovascular risk. Severe maternal undernutrition in animals has long been associated with fetal growth retardation (Woodall
et al., 1996), but it is now also clear that subtle variations in intakes of specific nutrients within the normal range may produce programming even without an overt impact on fetal growth (for a review, see Hoet and Hanson, 1999). In a study of normal pregnancies in Southampton, women with the highest intakes of carbohydrate in early pregnancy and lowest intakes of animal protein in late pregnancy gave birth to the babies of lowest birth weight, whereas other studies have shown that increased protein intake in early gestation is associated with adult hypertension (Godfrey et al., 1996; Sheill et al., 2001).

Against this background, much interest has been focused over the last 5 years on the role of glucocorticoids in programming (for a review, see Benediktsson et al., 1993). For example, in rats, administration of synthetic glucocorticoids during the last week of pregnancy decreased birth weight as well as increasing adult blood pressure (Levitt et al., 1996) and causing glucose intolerance (Nyirienda et al., 1998) in adult offspring. Increasing the exposure of rat fetuses to maternal glucocorticoids by inhibiting 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) with carbenoxolone also causes postnatal development of hyperglycaemia, increased blood pressure in offspring and increased glucocorticoid receptor density (Lindsay et al., 1996; Bertram et al., 2001). In humans, a common practice is to administer antenatal glucocorticoids to mothers to promote maturation of organs in fetuses at danger of preterm delivery. The undoubted short-term benefits have until recently apparently outweighed the fact that not only are the mechanisms of action poorly understood but also that potential long-term adverse effects have not been studied (for a review, see Matthews, 2001).

Role of the HPA axis

Studies using a number of animal models point to the involvement of the hypothalamo–pituitary–adrenal (HPA) axis in programming. This is not surprising as glucocorticoids produced in the adrenal cortex in response to signals from the HPA axis have wide-ranging effects on a number of systems both in fetal and adult life, playing key roles in regulation of salt and water homeostasis, blood pressure, immunological responses and metabolism. The HPA axis is controlled by a classic negative feedback system, in which glucocorticoids released into the circulation by the adrenal gland interact with glucocorticoid receptors (GRs) located in the pituitary, hypothalamus and hippocampus. Thus over-activity at any stage along this pathway should result in negative feedback to the corticosteroid releasing hormone (CRH) corticotrophs in the hypothalamus, reducing CRH release (Fig. 1). Most circulating glucocorticoid is bound to corticosteroid binding globulin (CBG) and only free glucocorticoid can enter cells. It is taken into individual cells and attaches to the cytoplasmic GRs, which dimerize, translocate into the nucleus and attach to glucocorticoid response elements (GREs) on the DNA, thus acting as a transcription factor for any gene in possession of a GRE (Fig. 2).

Postnatal and adult HPA axes

The importance of glucocorticoids can be appreciated by study of clinical examples of deficiency (Addison’s disease/hypopituitarism) or excess (Cushing’s syndrome). Addison’s disease results in postural hypotension, weight loss and hypoglycaemia, whereas Cushing’s syndrome presents as hypertension, central obesity and glucose intolerance. These effects are, in part, brought about by the opposing effect of cortisol on insulin action. Glucocorticoids act via intracellular mineralocorticoid receptors (MRs) and GRs, and access to these receptors is determined by the presence of tissue-specific 11βHSD isoforms that catalyse the interconversion of active cortisol/corticosterone and inert cortisone/11-dehydrocorticosterone. There are at least two isoforms: 11βHSD1, which is a bidirectional enzyme that

Fig. 1. Activation of the hypothalamo-pituitary-adrenal (HPA) stress response is centrally regulated: corticosteroid releasing hormone (CRH) is secreted by the hypothalamus in response to hippocampal signals or pituitary/adrenal feedback messages. CRH is carried by the hypophysial portal vein to the pituitary, initiating expression of pro-opiomelanocortin (POMC) in pituitary corticotrophs. Several post-translational cleavage events occur, resulting in the release of several peptides, one of which is adrenocorticotropic hormone (ACTH). ACTH reaches the adrenal cortex via the systemic circulation, and initiates the biosynthesis and subsequent release of adrenal glucocorticoids into the bloodstream, 90% of which are complexed with corticosteroid binding globulin (CBG). Over-activity at any stage along this pathway should result in negative feedback to the CRH corticotrophs in the hypothalamus, reducing CRH release. GR: glucocorticoid receptor; PVN: paraventricular nucleus; AVP: arginine vasopressin.
acts predominantly as a reductase (activating cortisone to cortisol); and 11βHSD2, a high affinity dehydrogenase, a major task of which is to inactivate glucocorticoids that would otherwise compete with aldosterone for occupation of MRs. Deficiency of this enzyme causes apparent mineralocorticoid excess (AME) (for a review, see Stewart and Krozowski, 1999).

The carrier protein, CBG, may also have a part to play in programming, although little work on it has been undertaken to date. In high local concentrations, CBG acts as a buffering system preventing over-occupancy of both MRs and GRs by glucocorticoid. It is possible that chronically reduced expression of CBG, due to programming of its synthesis by the liver, could alter the dynamics of the HPA feedback system. During fetal life, glucocorticoids up-regulate expression of CBG mRNA in fetal liver, and circulating CBG concentrations increase in the fetus during late pregnancy such that a relatively low free cortisol concentration is maintained (for a review, see Challis et al., 2001).

Excessive activity of glucocorticoids, whether by increased circulating concentrations of cortisol, increased GR density to cortisol or altered cortisol metabolism, is a possible contributor to insulin resistance and could explain its association with hypertension, central obesity, dyslipidaemia and endothelial dysfunction; hence the link between low birth weight and subsequent ‘metabolic syndrome’.

Plasma cortisol concentrations and the HPA axis. Early morning plasma cortisol concentrations are higher in adult men who were born with lower birth weight, and are associated with relative hypertension, insulin resistance, glucose intolerance and hypertriglyceridaemia (Reynolds et al., 2001). More recent data confirm that these men have evidence of chronically increased activation of the HPA axis (Reynolds et al., 2001). As cortisol secretion is also increased in young men with a familial predisposition to essential hypertension (but not those with a similarly increased blood pressure whose parents had lower blood pressure), it may be that increased cortisol secretion is an early feature of essential hypertension (Matthews, 2000).

Glucocorticoid receptor. Assessment of GR sensitivity in humans is difficult. Dexamethasone suppression tests are used to assess central negative-feedback suppression of adrenocorticotropic hormone (ACTH) and cortisol secretion, but although there are altered responses to dexamethasone in obesity, no reports of abnormality have been reported in essential hypertensive or in lean insulin-resistant subjects. Dermal vasoconstrictor tests indicate that the response to glucocorticoids is increased in men with relative glucose intolerance and insulin resistance. Studies in rats and sheep suggest that GR sensitivity may be increased in peripheral tissues after nutritional deprivation in utero, but not in central tissues responsible for negative feedback (Dodic et al., 1999; Bertram et al., 2001a).

Fig. 2. Free corticosteroid from the circulation enters the cell and binds to intracellular glucocorticoid receptors (GRs). Movement of corticosterone from cytoplasm to nucleus is regulated by number of GRs and by 11β-hydroxysteroid dehydrogenase (11βHSD) isoforms. After translocation of the active steroid–receptor complex to the nucleus it binds to glucocorticoid response elements (GREs) located along the genome and interacts with RNA poly II (repression/initiation of transcription), after which transcription of specific genes increases or decreases and the resulting mRNA is translated into specific proteins. TF: transcription factor.

Role of the placenta

Glucocorticoids in the fetus can be derived from three sources: (i) de novo, through increasing basal secretion as the adrenal matures, or in response to fetal stress; (ii) from the mother by transplacental transfer; or (iii) by local production within the chorion trophoblasts and amnion epithelium. Availability is regulated by the 11βHSD isozymes. Decreased 11βHSD2 expression in the placenta would be expected to increase the amount of maternal glucocorticoid crossing into the fetal compartment, with deleterious effects on fetal development. Maternal undernutrition during
pregnancy, synthetic glucocorticoid administration to the mother or maternal carbenoxolone administration (to block placental 11βHSD2 activity) are all associated with reduced birth weight and subsequent increased blood pressure (Matthews, 2000; Bertram and Hanson, 2001).

Placental 11βHSD2 catalyses the conversion of maternal glucocorticoids to their inactive 11-keto forms (Brown et al., 1996). Although this barrier is not 100% effective, it ensures that the tenfold higher concentration in the maternal circulation does not adversely affect the fetus. A relative deficiency of placental 11βHSD2 may retard growth and have deleterious postnatal effects by allowing inappropriate glucocorticoid access to the fetal compartment (Edwards et al., 1993). In rats, reduced 11βHSD2 activity in larger placentae is associated with smaller fetuses in late gestation (Langley Evans et al., 1996). Similar associations have been proposed in humans (Stewart et al., 1995), although not all studies confirm this finding (Rogerson et al., 1997).

It has been recognized for many years that glucocorticoids have a vital role in preparing the full-term fetus for life outside the uterus (Liggins and Howie, 1972). Placental 11βHSD2 mRNA concentrations are significantly decreased in intrauterine growth-retarded (IUGR) babies compared with gestationally matched appropriately-grown babies, a change that is not attributable to alterations in trophoblast mass, 11βHSD2 gene mutations or gene imprinting. These data highlight the important role of placental 11βHSD2 in regulation of fetal growth and subsequent development of cardiovascular disease in adulthood (Shams et al., 1998; McTernan et al., 2001).

Placental 11βHSD2 inhibition with substances such as carbenoxolone results in hypertension and hyperglycaemia in the adult, effects that can also be produced by dexamethasone administration (a poor substrate for 11βHSD2) or by maternal dietary restriction (for a review, see Bertram and Hanson, 2001). This finding may be a valid argument for a role for glucocorticoids in programming, but it must be remembered that carbenoxolone targets other dehydrogenases in addition to all 11βHSD isoforms. In addition, 11βHSD2 null mice are of normal birth weight, but as mice undergo a loss of placental 11βHSD2 expression at mid-gestation (whereas human 11βHSD2 increases with increasing gestational age), this may not be evidence against the involvement of 11βHSD2 (Holmes et al., 2001).

Furthermore, placental 11βHSD2 mRNA content is indeed decreased in the placenta of rats fed a low protein diet in utero (Bertram et al., 2001), whereas in studies in sheep, Whorwood et al. (2001) showed that maternal nutrient restriction during the period of rapid placental growth (days 28–77 of gestation; term = day 147) resulted in undetectable 11βHSD2 mRNA in term placenta, although it was abundant in placenta at mid-gestation.

Thus, small changes in placental 11βHSD2 activity may have far-reaching effects on the fetus. By allowing the high glucocorticoid concentrations to cross the placenta, the fetal HPA feedback system that regulates the fetal adrenal output may be overwhelmed. Not only will this have an immediate effect on development, but it may also result in long term ‘resetting’ of the fetal axis, which may persist into adulthood, altering the system’s response to normal homeostatic regulation as well as to stress.

The fetal HPA axis

Ontogeny. From mid-gestation to term the human fetal adrenal gland synthesizes not only dehydroepiandosterone (DHEA), but also cortisol and aldosterone, at increasingly higher rates. Moreover, both the CRH–ACTH–cortisol and renin–angiotensin feedback systems appear to be operative. Immunoactive ACTH and other pro-opiomelanocortin (POMC)-derived peptides can be detected in the fetal pituitary by week 8 of gestation, and, through development of vascular communication with the hypothalamus, are responsive to neurohormonal agents such as CRH and arginine vasopressin (AVP) (for a review, see Matthews, 2000).

As the fetal HPA axis regulates the response of the fetus to acute episodes of intrauterine stress (for example, hypoxaemia, haemorrhage, hypotension) and is central to other processes such as organ maturation, growth and cardiovascular regulation, any disturbance is likely to affect a wide range of body systems. Human size at birth has been linked to HPA axis function: lower birthweight babies have increased urinary glucocorticoid excretion as children, and basal plasma cortisol concentrations and adrenocortical responsiveness to ACTH are high in adulthood (Phillips et al., 2000). In sheep, surgical restriction of placental size produces a decrease in POMC mRNA in the fetal pituitary (Phillips et al., 1996). Both exposure to dexamethasone and 11βHSD inhibition in utero increase basal plasma glucocorticoid concentrations in adult rats (for a review, see Welberg and Seckl, 2001), possibly due to decreased GR and MR expression in the hippocampus. As this has the highest density of glucocorticoid binding sites in the brain it exerts important control of the HPA axis (Levit et al., 1996; Welberg et al., 2000), although Langley Evans et al. (1997) reported increased hippocampal and decreased hepatic GR binding and number of receptors in male rats whose dams had a restricted protein diet (isocaloric 9% versus 18% casein) during pregnancy (maternal low protein; MLP).

Diaz et al. (1998) elegantly demonstrated that 11βHSD2 is highly expressed in all regions of the central nervous system during mid-gestation, although expression decreases markedly at the start of the final third of gestation (except in the thalamus and cerebellum), and also that GR mRNA is highly expressed throughout the brain from mid-gestation onwards, indicating that 11βHSD2 may protect the developing brain from glucocorticoids until late gestation, thereby allowing key glucocorticoid-dependent neuronal and glial maturation to occur. Any perturbation of this ontogeny is likely to have wide-ranging effects on a number of postnatal functions of the central nervous system.

Possible effects of inappropriate glucocorticoid concentrations on the fetus. Although most endogenous gluco-
corticoids are prevented from crossing the placenta by 11βHSD2, synthetic glucocorticoids such as dexamethasone, as they are poor substrates for 11βHSD2, transfer to the fetus easily; hence, they have been used in a number of animal models to study the effects of unhindered passage of endogenous glucocorticoids into the fetus (for a review, see Seckl, 1997).

In the fetus, glucocorticoids inhibit tissue expansion and growth at the same time as promoting maturation and cellular differentiation. Fetal plasma cortisol concentrations are low until late gestation, when the HPA axis is activated, producing increased secretion of cortisol from the fetal adrenal gland and a progressive increase in cortisol concentrations, resulting in the marked cortisol surge preceding parturition (for a review, see Challis et al., 2001).

The rate of fetal growth decreases towards term, which may be linked to the increase in plasma cortisol that occurs at this time, as fetal adrenalectomy results in an increase in body weight in the last week of pregnancy, whereas high fetal glucocorticoid concentrations reduce fetal size. Glucocorticoids also regulate the insulin-like growth factor (IGF) axis, and can downregulate expression of IGF-II mRNA in the liver and adrenal gland (Li et al., 1998). Glucocorticoids act as transcription factors with wide-ranging effects during development. Many genes have GREs, which are activated by glucocorticoid, leading to their transcription. Thus, any perturbation of the HPA axis can have subtle or overt effects on development of many tissues in the cardiovascular, pulmonary, renal and central nervous systems (for a review, see Byrne, 2001). For example, pre-term lambs exposed to betamethasone at the start of the final third of gestation had enhanced lung function but altered postnatal growth and endocrine function (Ikegami et al., 1997). Dexamethasone treatment programmes an increased postnatal blood pressure, which persists into adult life (Dodic et al., 1999, 2001), and high-altitude hypoxia from day 30 to day 120 of gestation reduces fetal adrenocortical responsiveness (Harvey et al., 1993). In rats, handling stress during early postnatal life permanently alters the HPA axis response to stress in adult life (Meaney et al., 1993).

In addition to the effects of glucocorticoid in the programming of adult hypertension and other manifestations of the ‘metabolic syndrome’, fetal glucocorticoid exposure due to prenatal stress appears to increase the possibility of psychiatric syndromes such as depression, eating disorders and anxiety (Diaz et al., 1998). Prenatal glucocorticoid exposure permanently programmes several central nervous system functions such as dopamine and serotonin sensitivity, as well as hippocampal GR gene expression. Studies of brain and neuronal development in sheep (for a review, see Newnham, 2001) show that prenatal administration of glucocorticoids was associated with restricted fetal growth, delayed myelination of the central nervous system, altered blood pressure after birth and decreased insulin sensitivity in adulthood. Barbazanges et al. (1996) proposed that stress-induced increases in maternal glucocorticoids might be a mechanism by which the function of the HPA axis is altered in adulthood. In rats, Barbazanges et al. (1996) found that prenatal stress (restraint) in the final third of gestation caused decreased expression of hippocampal mineralocorticoid receptors, but not glucocorticoid receptors. As this effect was not observed in adrenalectomized dams, these authors concluded that maternal glucocorticoid was implicated. In humans, prenatal stress has been reported to induce mental retardation and sleep disturbances (Shell, 1981; Barbazanges et al., 1996). Barbazanges et al. (1996) also reported that such stress decreased sexual activity and increased emotional reactivity in male offspring.

Severe (70%) global dietary restriction in pregnant rats produces low birthweight offspring, catch-up growth by week 30 of age and adult hypertension (Woodall et al., 1996). However, high postnatal blood pressure is also observed in the offspring of dams subjected to moderate (30–50%) dietary restriction throughout gestation. These offspring show impaired nitric oxide-mediated responses in small arteries in vitro, enhanced responses to a thromboxane A2 receptor agonist and enhanced sensitivity to K+, indicating impaired sensitivity of fetal vascular smooth muscle to nitric oxide (Ozaki et al., 2001). In sheep, mild (15%) reduction in maternal global nutrition for the first half of gestation produces postnatal hypertension and perturbed cardiovascular responses in adult life (Hawkins et al., 2000).

The extensive epidemiological, physiological and molecular studies now being undertaken to investigate the fetal origins of adult disease indicate that synthetic glucocorticoids slow fetal growth and may alter the size of the placenta, depending on the dose and timing of exposure. Furthermore, these effects persist after parturition. Thus, if a
pregnant rat is given a moderate dose of dexamethasone, the growth of the fetus is retarded (on average by about 14%) with no effect on the duration of gestation or fetal viability, and the individual has high blood pressure in adulthood. Glucocorticoids affect maturation of tissues involved in the control of blood pressure, such as glomerular number and kidney size (Langley Evans et al., 1999b), but also expression of catecholamine receptors, and second messenger systems in renal and vascular tissue. Glucocorticoids may also affect blood pressure by inducing growth factors, such as IGF, or via indirect effects on carbohydrate and fat homeostasis. By potentiating vasoconstrictor effects on the vasculature and by regulating the synthesis of catecholamines, nitric oxide and angiotensinogen, glucocorticoids also affect the blood pressure directly as well as having actions on the central nervous system (for a review, see Byrne, 2001).

The MLP diet in rat dams produces offspring with a low birth weight:placental mass ratio and high blood pressure up to week 44 of age (Langley Evans et al., 1999a). This hypertension is accompanied by impaired responses to endothelium-dependent and -independent vasodilators in small resistance arteries, indicating reduced nitric oxide release and vascular smooth muscle responses to it (Brawley et al., 2002). In rats fed a low protein diet, dysfunction of normal pregnancy-associated changes in uterine artery blood flow (Ni et al., 1997) is coupled to reduced uterine artery vascular endothelial growth factor (VEGF) responsiveness, which is also mediated in part via altered nitric oxide mechanisms (Itoh et al., 2002). In sheep, moderate reduction (30% isocaloric) of maternal protein intake during early gestation also results in impairment of responses to endothelium-dependent and -independent vasodilators (Ozaki et al., 2000).

Hypertensive offspring of MLP rats do not have high plasma corticosteroid concentrations, although the high blood pressure is dependent on an intact adrenal gland. The hypertension is coupled to tissue-specific increases in GR expression and downregulation of the corticosteroid inactivating enzyme 11βHSD2 activity in the placenta, kidney and adrenal, which will increase sensitivity and overexpose organs to cortisol, respectively. Indeed, inhibition of 11βHSD2 with the drug carbenoxolone in protein-replete pregnant rats overexposes the fetus to corticosteroids, producing small hypertensive offspring (Langley Evans, 1997a), with increases in GR similar to those found in rats fed a low protein diet (Bertram et al., 1999).

Type 2 diabetes and obesity are also associated with poor prenatal nutrition (Hales and Barker, 2001), as well as with prenatal glucocorticoid treatment. In a study by Moss et al. (2001), rats were found to have glucose intolerance in adulthood and Nyirienda et al. (1998) found altered glucose metabolism and increased hepatic phosphoenolpyruvate carboxykinase (PEPCK) concentrations.

Sloboda et al. (2000) studied the effects of repeated maternal doses of glucocorticoid on ovine fetal growth and HPA axis function, and found that antenatal betamethasone administration resulted in decreased birth weight and altered basal cord concentrations of plasma ACTH and CBG, although the changes did not reflect alterations in steady-state concentrations of POMC and CRH mRNA in the fetal pituitary or hypothalamus. In a follow-up study, Sloboda et al. (2002) found that the developmental changes in HPA function occurring after parturition are influenced by prenatal glucocorticoid exposure, reinforcing the hypothesis that adult health is programmed in utero.

‘Resetting’ of the HPA axis

The expression ‘resetting of the HPA axis’ has been used frequently with regard to programming. But what does it mean? The activities or concentrations of each component of the system (CRH, POMC, ACTH, GC, GR and CBG) are candidates. Work by Williams et al. (1999) suggests that the ‘resetting’ is not at the hypothalamus, as CRH concentrations and activity are not altered in prenatally stressed rats that are subjected to isolation stress at 3 weeks after parturition. However, Williams et al. (1999) found that ACTH concentrations were reduced in these rats, which is indicative of pituitary involvement. We have conducted similar experiments in which the prenatal stressor was a low protein diet throughout gestation and the postnatal stressor was isolation from the dam at the time of weaning. Although there was no significant shift in plasma concentrations, GR expression was increased in a tissue-specific manner, indicating that there is probably altered ligand–receptor affinity or an alteration in the feedback system that initiates GR expression (Bertram et al., 2001b). In sheep, Hawkins et al. (2001) found reduced GR mRNA expression in the fetal pituitary but not the paraventricular nucleus, although unlike Williams et al. (1999), they reported decreased CRH mRNA expression. Recent work also provides evidence that the rat and human GR gene promoter has multiple tissue-specific alternate first exons, which would allow further control of peripheral GR expression (McCormick et al., 2000).

Although the ‘programmability’ of the HPA axis, the role of glucocorticoids in fetal growth and their effect on postnatal blood pressure make the axis a strong candidate in the early origins of adult cardiovascular disease, the molecular mechanisms operating at the level of gene expression are not known. Children who were small at birth have higher plasma and urinary glucocorticoid concentrations (Clark 1998), which continue into adulthood (Phillips et al., 2000) and, thus, could predict disease (Levitt et al., 2000). Reynolds et al. (2001) and Levitt et al. (2000) have demonstrated that low birthweight offspring have exaggerated responses to stimulation of the HPA axis using the ACTH test, which suggests that there is long-term alteration of HPA function.

High dose glucocorticoid therapy during pregnancy is detrimental in terms of birth weight (Reinisch et al., 1978; Novy and Walsh, 1983), brain structure (Uno et al., 1994) and altered postnatal cortisol concentrations (Sapolsky,
Lower doses do not have an effect on birth weight (Mercado et al., 1995), but the long-term consequences of these have not been so widely researched, although treatment during the final third of gestation has been shown to increase blood pressure in adolescent offspring (Doyle et al., 2000). Current data indicate that single-dose treatment has few lasting effects, and that any side effects are far outweighed by the benefits (including reduction of incidence of brain damage, cerebral palsy and respiratory distress syndrome). However, over the last few years more fetuses have been exposed to multi-dose regimens, and evidence is accruing to suggest that these are deleterious to later health. Most evidence cited is from animal models, but longitudinal studies are now showing altered blood pressure (Doyle et al., 2000), reduced birth weight, head circumference and more severe chronic lung disease (French et al., 1999) in children who were treated with multi-dose glucocorticoids in utero. Furthermore, a retrospective analysis by Banks et al. (1999) showed that multiple courses did not improve outcome and were associated with increased mortality, decreased growth and prolonged adrenal suppression.

Thus, it has been demonstrated that the HPA axis is programmable by altered nutrition in utero, whereby the sensitivity of the axis to exogenous stimulation is reduced during fetal life (Lingas et al., 1999; Hawkins et al., 1999, 2000, 2001) and modified in early postnatal life (Hawkins et al., 2000; Lingas and Matthews, 2001). This programming effect is maintained in part into adult life. Its magnitude is sex-specific and it can be exacerbated by postnatal influences such as obesity and diabetes. In elderly men, low birth weight is linked to high fasting cortisol concentrations, which could underlie the high blood pressure in these individuals (Phillips et al., 2000). Considerably more research is needed in this important area to uncover the specific mechanisms by which altered glucocorticoid exposure in utero leads to degenerative disease in offspring. Only when these causes have been established will it be possible to devise methods for their prevention.

Conclusion

Fetal over-exposure to increased concentrations of glucocorticoids may influence development and have profound effects on the incidence of postnatal and adult disease. The access of glucocorticoids, whether endogenous or exogenous, to the fetal compartment is governed by the activity of the enzyme 11βHSD2 in the placenta. Fetal exposure is easily explained in the case of synthetic glucocorticoid, as it is a poor substrate for 11βHSD2. However, the issue becomes more complicated when considering the movement of endogenous glucocorticoids to the fetus: it is suggested that unbalanced maternal nutrition or other stressors cause reduced expression of the enzyme, allowing maternal glucocorticoid to pass to the fetus and affect the ‘setting’ of the HPA axis. In addition, genetic factors may influence 11βHSD2 expression, so that stressors such as nutrition can increase fetal glucocorticoid concentrations.

Animal and human studies indicate that glucocorticoid-induced disruption of the HPA axis can occur at all levels, as shown by altered ACTH expression, plasma glucocorticoid concentrations, glucocorticoid metabolism and tissue GR density. These perturbations can all be linked to adult disorders such as type 2 diabetes, cardiovascular disease and other manifestations of the ‘metabolic syndrome’, which, in turn, have been linked by epidemiological studies with low birth weight.

Fetal growth is slowed and placental size is altered by glucocorticoids, depending on the dose and timing of exposure. Glucocorticoids have important effects on the maturation of tissues involved in the control of blood pressure, as well as effects on adrenergic receptor expression, second messenger systems in renal and vascular tissue, growth factors such as IGF, and carbohydrate and fat homeostasis. Glucocorticoids also affect blood pressure by promoting vasoconstrictor effects and regulate the synthesis of catecholamines, nitric oxide and angiotensin, as well as acting on the central nervous system.

Investigations into the effects of therapeutic use of synthetic glucocorticoids have, together with the wealth of epidemiological research and extensive animal studies, increased our knowledge of the programming events. However, the molecular and cellular mechanisms underlying the fetal origins of adult disease remain to be clarified. Much research into the interactions of glucocorticoids, the renin–angiotensin system and various vasoactive compounds remain to be performed to determine how physiological adaptations that ensure the short-term survival of the fetus and newborn can predispose the individual to adult hypertension, cardiovascular and metabolic disease.

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