Glucocorticoids and the preparation for life after birth: are there long-term consequences of the life insurance?

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In mammals, survival both before and after birth depends on a number of key physiological processes such as the provision of O_2, a supply of oxidative substrates and a means of removing the waste products of metabolism. In adults these processes are carried out by a number of different tissues, whereas in the fetus they are carried out primarily by the placenta. The successful transition from intra- to extra-uterine life, therefore, depends on the ability of specific tissues and organ systems to take over the functions of the placenta at birth. Consequently, organs such as the lungs, liver, kidneys and gut undergo maturational changes during late gestation in preparation for extra-uterine life. Most of these changes are glucocorticoid dependent and can be induced prematurely by exogenous glucocorticoid administration (Silver, 1990; Liggins, 1994; Fowden, 1995). As a consequence, synthetic glucocorticoids are now routinely administered to women in threatened preterm labour to improve neonatal viability (NIH Consensus Development Conference, 1995).

In all species studied so far, there is an increase in the circulating glucocorticoid concentration in the fetus towards term (Fig. 1). The magnitude and timing of this cortisol surge vary between species, as does the precise mechanism by which it occurs (Fig. 1; Fowden & Silver, 1995; Wood & Cudd, 1997). In most species, the prepartum cortisol surge is due to increased adrenal cortisol output, but in certain animals, such as the rat and horse, its effect is enhanced by a fall in the level of plasma corticosteroid-binding globulin (Challis *et al.* 1993; Wood & Cudd, 1997). In normal conditions, therefore, fetal tissues are exposed to increasing levels of bioactive glucocorticoid for periods of up to 10–15 d before delivery.

Maturational effects of the glucocorticoids

Glucocorticoids have been shown to have a wide range of maturational effects *in utero* (Table 1). They induce both structural and functional changes in a variety of different fetal tissues and activate many of the biochemical processes which have little or no function in fetal life (Table 1). They affect not only those tissues essential for survival immediately at birth, but also organs involved in the more long-term adaptation to extra-uterine life (Liggins, 1994).

Specific tissues

Lung. The lung is the tissue on which immediate neonatal survival most depends and its maturation is highly glucocorticoid dependent (Kitterman *et al.* 1981). Structurally, cortisol increases lung compliance by accelerating alveolarization, thinning the septae and by increasing the pulmonary content of collagen and elastin (Crone *et al.* 1983; Schellenberg *et al.* 1987; Warburton *et al.* 1988). In fetal rats, glucocorticoids increase both the number of cells in the lung expressing the tropoelastin gene and the amount of expression per cell (Pierce *et al.* 1995). Glucocorticoids also act functionally to prepare the fetal lung for gas exchange. They increase synthesis of both the lipid and

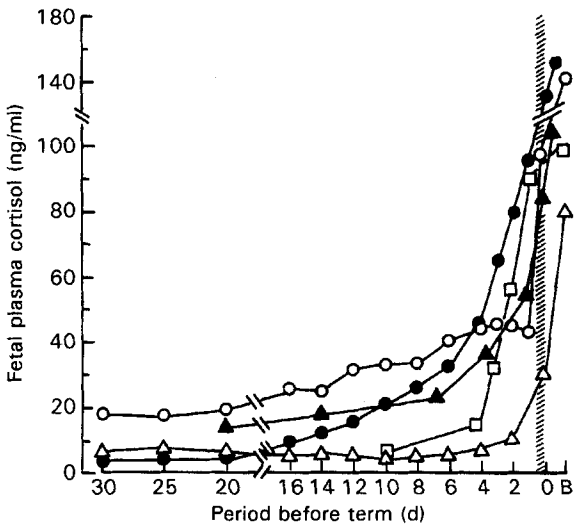

Fig. 1. Mean fetal concentrations of plasma cortisol with respect to time period (d) from delivery in the sheep (●), pig (○), man (▲), guinea-pig (□), and horse (△). (▨), Labour; B, birth. (Data from Silver & Fowden, 1988.)

Abbreviations: GH, growth hormone; GRE, glucocorticoid response elements; HPA, hypothalamic–pituitary–adrenal; IGF, insulin-like growth factor; 11βHSD, 11β-hydroxysteroid dehydrogenase.

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Table 1. Some of the maturational changes induced by cortisol in fetal ovine tissues essential for neonatal survival (Data from Silver, 1990; Liggins, 1994; Fowden, 1995; Segar *et al.* 1995; Li *et al.* 1996*b*; Phillips ID *et al.* 1997).

Tissue	Maturational change
Lung	Surfactant production and release
	Collagen and elastin synthesis
	β-Adrenoreceptor induction
	Lung liquid re-absorption
	Structural maturation of alveoli
Liver	Glycogen deposition
	Gluconeogenic enzyme induction
	IGF-gene expression
	β-Adrenoreceptor induction
	Prolactin-receptor induction
	GH-receptor induction
	CBG synthesis
	Angiotensinogen-gene down-regulation
Kidney	Increased glomerular filtration rate
	Tubular Na re-absorption
	Ion-exchange-pump induction
	Erythropoietin-gene down-regulation
	AT_1-receptor-gene down-regulation
	Renin-gene down-regulation
Gut	Mucosal growth
	Acid secretion
	Digestive-enzyme induction
	Gastrin secretion
Adrenal	Cytoarchitecture of *zona fasciculata*
	Induction of P450 cytochromes
	Induction of PNMT enzyme
	Induction of ACTH receptors

IGF, insulin-like growth factor; GH, growth hormone; CBG, corticosteroid-binding globulin; AT_1, angiotensin I; renin, *EC* 2.4.23.15; PNMT, phenylethanolamine *N*-methyltransferase (*EC* 2.1.1.28); ACTH, adrenocorticotrophic hormone.

protein components of surfactant and enhance its release from the type II pneumocytes into the alveoli (Kitterman *et al.* 1981). Surfactant synthesis is enhanced partially by induction of the rate-limiting enzymes involved in phosphatidylcholine synthesis, and partially by activation of glycogenolysis which provides substrate for phospholipid synthesis (see Liggins, 1994). In addition, glucocorticoid enhances the liquid resorptive capacity of the fetal lung (Wallace *et al.* 1995) by inducing ion channels in the pulmonary epithelium and by increasing the density of the alveolar β-adrenoreceptors which activate these channels (Warburton *et al.* 1988; Ingbar *et al.* 1997).

Liver. In the liver, the maturational effects of cortisol appear to be primarily functional (Silver, 1990). Cortisol increases the synthesis of a wide range of proteins in the fetal liver including receptors, enzymes, binding proteins and growth factors (Table 1). It also increases the deposition of hepatic glycogen by enhancing the activity of glycogen synthetase (*EC* 2.4.1.21; Jones & Rolph, 1985). In all species studied so far, there is an increase in hepatic glycogen deposition towards term which closely parallels the normal prepartum rise in fetal plasma glucocorticoids (Shelley, 1961; Fowden *et al.* 1991). When this glucocorticoid surge is prevented by fetal adrenalectomy or hypophysectomy, glycogen levels in the fetal liver remain low (Fig. 2). Conversely, raising plasma cortisol at

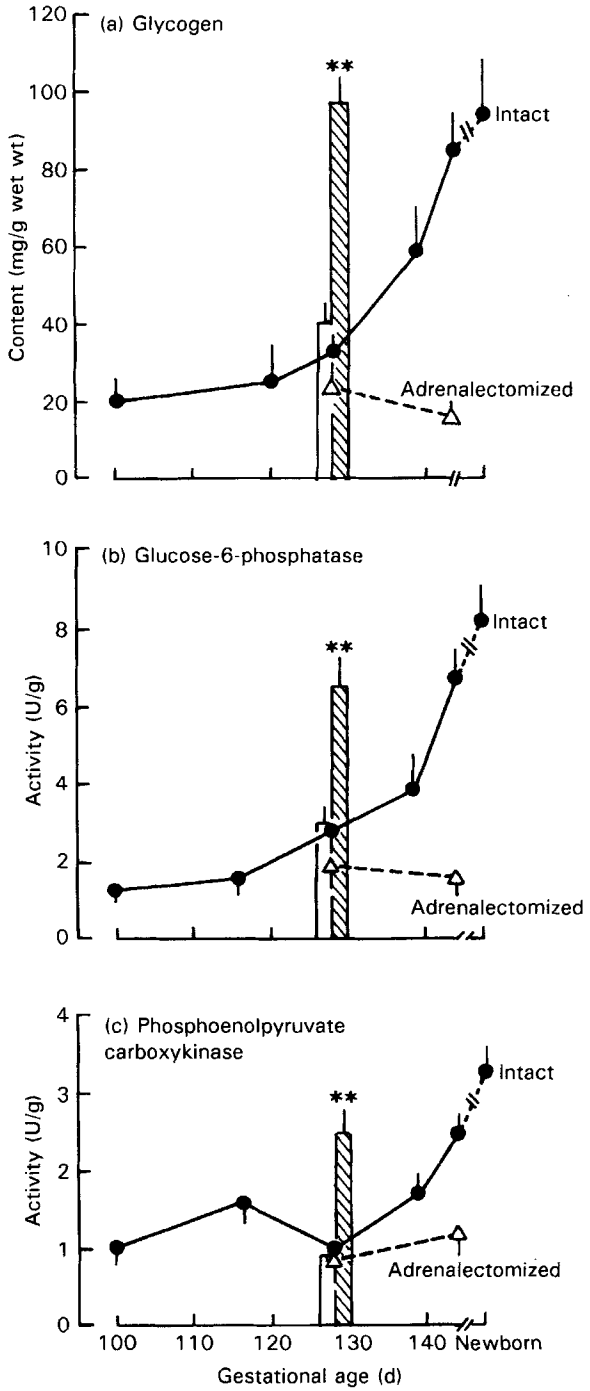

Fig. 2. Values for hepatic glycogen (a), glucose-6-phosphatase (*EC* 3.1.3.9; b) and phosphoenolpyruvate carboxykinase (*EC* 4.1.1.38; c) in liver from intact (●) and adrenalectomized (△) sheep fetuses with respect to gestational age and in intact fetuses infused with cortisol (2–3 mg/kg per d; ▨) or saline (9 g NaCl/l; □) for 5 d before delivery. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for saline-infused fetuses: $^{**}P < 0{\cdot}01$. (Data from Barnes *et al.* 1978; Fowden *et al.* 1993.)

a time when concentrations are normally low leads to a premature increase in glycogen deposition in a number of species, including the rat, sheep, pig and monkey (Fig. 2; Jones & Rolph, 1985; Klepac, 1985; Fowden *et al.* 1995).

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Glucocorticoids also induce the activity of several other rate-limiting enzymes in the fetal liver (Liggins, 1994). In particular, they increase the levels of fatty acid synthase (*EC* 2.3.1.85), aminotransferases and all the key gluconeogenic enzymes (Fig. 2; Jones & Rolph, 1985; Fowden *et al.* 1993). Cortisol has also been shown to be responsible for the normal prepartum rise in corticosteroid-binding globulin synthesis in the liver and in the hepatic activity of the 5′-monodeiodinase which stimulates outer-ring deiodination of thyroxine to triiodothyronine (thyroxine deiodinase; *EC* 3.8.1.4; Wu *et al.* 1978; Jeffray *et al.* 1995). The ontogenic up-regulation in receptor density for growth hormone (GH), prolactin and β-adrenoreceptors in the ovine fetal liver is also dependent on the fetal plasma cortisol surge (Li *et al.* 1996*b*; Barnes, 1997; Phillips ID *et al.* 1997).

Glucocorticoids do not only up-regulate protein synthesis in the liver. They also suppress gene expression for a number of specific proteins including angiotensinogen, insulin-like growth factor (IGF)-II and certain of the IGF-binding proteins (Olson *et al.* 1991; Price *et al.* 1992; Li *et al.* 1993). The maturational effects of cortisol on the fetal liver, therefore, affect the functioning of several fetal endocrine systems (e.g. the renin–angiotensin II, somatotrophic, thyroid and pituitary–adrenal axes) which will have widespread effects elsewhere in the body.

Gut. Glucocorticoids have both structural and functional effects on the gut (Table 1). In the fetal pig and sheep, they affect villus–crypt architecture in the stomach and small intestine and induce digestive enzymes in all parts of the gastrointestinal tract (Table 1). In fetal sheep, cortisol increases villus height and density and thins the *musculari externa* in the small intestine (Trahair *et al.* 1987*b*). It also increases the rate of migration of enterocytes up the villi (Trahair *et al.* 1987*b*). These changes mimic those seen close to term, which suggests that the prepartum cortisol surge is responsible for the normal sequence of development observed in the fetal gut towards term (Trahair & Sangild, 1997). Certainly, these changes in gut morphology are abolished by adrenalectomizing the fetus (Trahair *et al.* 1987*a*). Similarly, fetal adrenalectomy prevents the normal prepartum increases in the activity of abomasal pepsinogen and prochymosin and of pancreatic amylase (*EC* 3.2.1.1) and chymotrypsin (*EC* 3.4.21.1) in the sheep fetus (Sangild *et al.* 1995*b*). In the pig, intra-fetal cortisol administration during late gestation has been shown to stimulate digestive activity in the stomach, pancreas and small intestine (Sangild *et al.* 1994*a,b,c*, 1995*a*). In the stomach, cortisol increases gastrin release, acid secretion and the number and distribution of the prochymosin-containing cells in the fundic glands (Sangild *et al.* 1994*a,b*). In the pancreas, there are increases in the amylase and trypsin (*EC* 3.4.21.4) content in response to elevating cortisol levels for 6 d before delivery (Sangild *et al.* 1994*c*). In the small intestine, activities of all the major brush-border hydrolases are increased in cortisol-treated fetal pigs (Fig. 3; Sangild *et al.* 1995*a*). In both the fetal sheep and pig, the maturational effects of cortisol on the gut proceed in a proximal to distal direction, with the most pronounced effects in the stomach and proximal small intestine (Trahair & Sangild, 1997).

Kidney. In comparison with other fetal tissues, relatively little is known about the maturational effects of glucocorticoids on renal development (Lumbers, 1995). In late gestation, glucocorticoids appear to have functional rather than structural effects on the fetal kidneys, although earlier in gestation they may affect nephrogenesis (Wintour & Moritz, 1997). Near term, glucocorticoid administration has been shown to increase tubular re-absorptive capacity and reduce the fractional Na excretion in fetal rats and lambs (Stonestreet *et al.* 1983; Slotkin *et al.* 1992). In the lamb, these changes are accompanied by increases in the glomerular filtration rate and total renal blood flow (Stonestreet *et al.* 1983). The cortisol-induced fall in fractional Na excretion is due primarily to an increase in distal tubular Na re-absorption and is associated with a rise in Na^+/K^+-ATPase (*EC* 3.6.1.37) mRNA abundance in the fetal ovine kidney (Towstoless *et al.* 1989; Celsi *et al.* 1993). Increases in Na^+–H^+ exchanger activity and in the mRNA abundance for this transporter have also been observed in proximal tubules from cortisol-treated fetal sheep (Guillery *et al.* 1995).

Maturation of the endocrine functions of the kidney also appears to be influenced by glucocorticoids. Renal erythropoietin-gene expression normally declines towards term and can be down-regulated prematurely by preterm cortisol infusion (Lim *et al.* 1996). Conversely, the normal prepartum suppression of this gene is prevented by fetal adrenalectomy (Lim *et al.* 1996). Preterm cortisol infusion into fetal sheep also reduces renal angiotensin II type 1-receptor mRNA abundance and lowers basal plasma renin (*EC* 2.4.23.15) and renal renin mRNA levels (Wood *et al.* 1987; Carbone *et al.* 1995; Segar *et al.* 1995). However, renin responses to specific and haemorrhage-induced hypotension are enhanced in sheep fetuses pretreated with cortisol (Wood *et al.* 1984; Carbone *et al.* 1995). Glucocorticoids, therefore, appear to adapt the kidney from a salt-losing to a salt-conserving organ during the perinatal period.

Physiological systems

Many of the processes essential for postnatal survival in the long term, such as thermoregulation, fluid and metabolic balance, require the coordinated development of several different tissues and organ systems. For instance, maintaining a supply of oxidative substrates during the transition from parenteral to enteral nutrition involves the liver, gut, muscle and various other tissues (see Silver, 1990). During the period between placental separation and the establishment of nutritive suckling, the endogenous fuel reserves provide the nutrients, but once lactation and suckling begin, the gut takes over as the principal source of oxidizable substrates. The mechanisms regulating substrate utilization and the circulating metabolite concentrations must also adapt at birth from the continuous but finite supply of nutrients *in utero* to the more plentiful yet intermittent pattern of postnatal nutrition. Coordination of these and many of the other complex perinatal adaptations depends heavily on the glucocorticoids.

Cortisol acts through a number of different mechanisms to ensure a supply of nutrients immediately after birth (Fowden, 1995). It increases the storage of glucose as

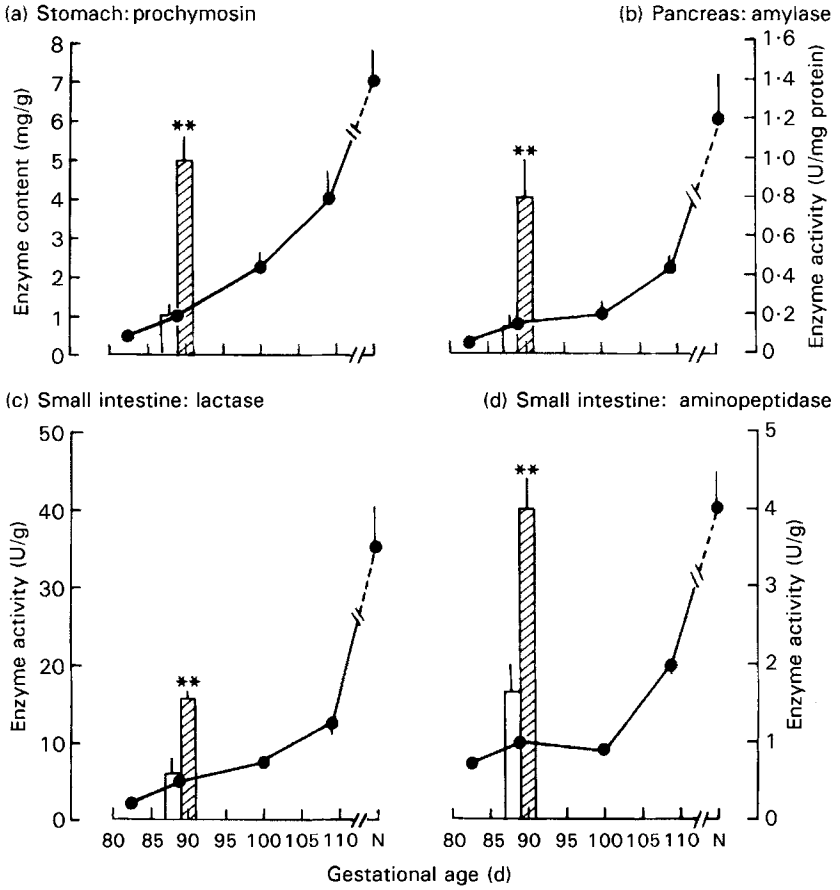

Fig. 3. Values for (a) stomach prochymosin, (b) pancreatic amylase (*EC* 3.2.1.1), (c) lactase (*EC* 3.2.1.108) and (d) aminopeptidase (*EC* 3.4.11.11) in the small intestine of the fetal pig with respect to gestational age (●; $n > 4$ in each group) and in fetuses infused with cortisol (1–3 mg/kg per d; ▨) or saline (9 g NaCl/l; □) for 6 d before delivery. N, newborn. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for saline-infused fetuses: $^{**}P < 0.01$. (Data from Sangild *et al.* 1994*b*,*c*, 1995*a*.)

glycogen in a variety of tissues and induces the enzymes responsible for producing circulating glucose from both glycogen and other precursors such as lactate and amino acids in the fetal liver and kidney (Fowden *et al.* 1993, 1995). Cortisol, therefore, helps maintain the circulating glucose level by enhancing the glucogenic capacity of the liver and kidneys and by providing specific glucose reserves in tissues, such as cardiac and skeletal muscle, which can meet their glucose requirement in the short term without drawing on the circulating glucose pool (Fowden *et al.* 1991, 1993). In addition, by stimulating hepatic β-adrenergic receptors, cortisol may enhance the capacity for sympatho-adrenal activation of hepatic glucose production (Fowden *et al.* 1995). Indeed, cortisol has been shown to stimulate hepatic glucose production in sheep fetuses close to term (Townsend *et al.* 1991; Barbera *et al.* 1997). Furthermore, the maturational effects of cortisol on the adrenal medulla increase the availability of adrenaline which, in turn, can activate the glucogenic and lipolytic pathways (Table 1; Barnes, 1977). The prepartum cortisol surge, therefore, has a key role both in ensuring that there are adequate fuel reserves at birth and in initiating their mobilization once delivery has occurred.

Glucocorticoids are also involved in the adaptations to enteral feeding. In stimulating structural and functional changes in the proximal regions of the gut, cortisol ensures that nutrients delivered to the gut can be digested and absorbed efficiently shortly after birth (Trahair & Sangild, 1997). Growth factors present in the milk can then complete the process of gastrointestinal maturation, particularly in the distal regions, via both luminal and systemic mechanisms (Trahair & Sangild, 1997). The effects of cortisol on the secretion of gastrin and other gut peptides indicate that it may also have an important role in the onset of the local and endocrine control mechanisms characteristic of postnatal gastrointestinal function (Trahair, 1993). Certainly, gastrointestinal function is poor in animals delivered prematurely before the final cortisol surge (Moog, 1979).

Less is known about the effects of glucocorticoids on the mechanism regulating the utilization and circulating concentrations of nutrients. Cortisol is known to depress umbilical glucose uptake and alter amino acid uptake and utilization by the sheep fetus *in utero* (Milley, 1996; Barbera *et al.* 1997), but the effects of prenatal glucocorticoid exposure on substrate utilization after birth remain

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unknown. Recent studies have suggested that the prenatal cortisol surge initiates a switch in the nutritional regulation of growth by activating the GH dependence of the somatotrophic axis (Li *et al.* 1996*b*). Cortisol infusion into the sheep fetus before term induced hepatic GH-receptor-gene expression while, conversely, abolition of the cortisol surge by fetal adrenalectomy prevented the normal upregulation of this gene towards term (Li *et al.* 1996*b*).

Excessive glucocorticoid *in utero* has also been shown to alter the subsequent sensitivity of the hypothalamic–pituitary–adrenal (HPA) axis to physiological challenges such as fasting (Seckl, 1997*a*). This effect is mediated, at least in part, via alterations in glucocorticoid-receptor-gene expression in brain regions involved in the feedback control of the HPA axis (Levitt *et al.* 1996). Since glucocorticoid-receptor-gene expression is known to change in these regions of the fetal brain towards term (Matthews *et al.* 1995), it is possible that the endogenous rise in cortisol before birth resets the HPA axis for the new nutritional and other environmental conditions that prevail after birth.

Mechanisms of glucocorticoid action

Glucocorticoids stimulate tissue maturation via several different direct and indirect mechanisms which alter the balance between tissue accretion and differentiation. They have been shown to inhibit fetal growth in the rat, sheep, monkey and man (see Seckl, 1994; Fowden, 1995). In the sheep fetus, growth rate, measured as crown–rump increment, decreases by 50% over the period of late gestation during which fetal cortisol levels rise (Fowden *et al.* 1996). This prepartum decline in growth rate is prevented by fetal adrenalectomy and can be stimulated prematurely by raising cortisol levels to prepartum values by exogenous cortisol infusion (Fowden *et al.* 1996). Adrenalectomized sheep fetuses are also heavier at term and have changes in protein : DNA in certain individual tissues that are indicative of maintained cell division (Barnes *et al.* 1978; Fowden *et al.* 1996; Wallace *et al.* 1996). Glucocorticoids, therefore, appear to trigger maturation by switching the cell cycle from proliferation to differentiation.

This action of the glucocorticoids is mediated, at least in part, by alterations in gene expression and tissue content of the IGF. These IGF genes are known to be developmentally regulated and have been shown to be essential for normal intra-uterine growth (see Gluckman, 1995). Expression of the IGF-II gene, in particular, is high *in utero* compared with postnatal values (Delhanty & Han, 1993). In late gestation, expression of both IGF genes is directly related to the circulating cortisol concentration *in utero* (Li *et al.* 1993, 1996*b*). In fetal sheep, cortisol suppresses IGF-II mRNA abundance in the fetal liver, muscle and adrenal, and is responsible for the developmental down-regulation of this gene towards term (Fig. 4; Li *et al.* 1993, 1996*b*; Lü *et al.* 1994). It also reduces IGF-I-gene expression in ovine skeletal muscle independently of any change in GH-receptor-gene expression (Fig. 4). This cortisol-induced suppression of IGF-gene expression will reduce the drive for fetal growth and may act as a specific signal for cell differentiation. Certainly, in fetal sheep, the prepartum changes in muscle IGF-gene expression are coincident with the final stages of secondary myofibre differentiation (see Dauncey & Gilmour, 1996).

In contrast to muscle, cortisol up-regulates total IGF-I mRNA abundance in fetal ovine liver (Li *et al.* 1996*a*, 1997). This effect appears to be mediated by the increment in hepatic GH-receptor abundance and is accompanied by a preferential increase in the GH-sensitive transcript of the IGF-I gene (Li *et al.* 1996*b*). By inducing the switch from IGF-II to GH-dependent IGF-I-gene expression in the liver, cortisol initiates the transition from local to endocrine IGF production and, thereby, ensures that rapid tissue accretion can resume after birth despite the changed pattern of nutrition.

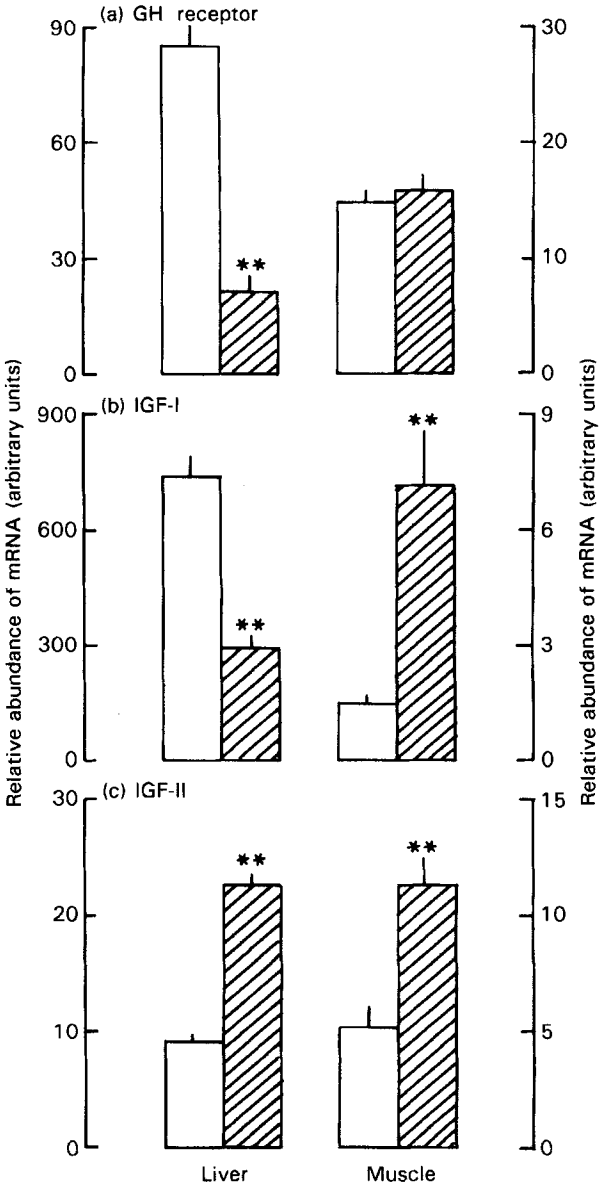

Fig. 4. Relative abundances of (a) growth hormone (GH)-receptor mRNA, (b) total insulin-like growth factor (IGF)-I mRNA and (c) IGF-II mRNA in liver and skeletal muscle from intact (□) and adrenalectomized (▨) sheep fetuses at 142–145 d of gestation (term 145 ± 2 d). Mean value significantly different from that observed in the intact animals: $^{**}P < 0.01$. (Data from Li *et al.* 1993, 1996*b*, 1997.)

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At a molecular level, glucocorticoids affect a number of different processes. They can act on transcription, mRNA stability, translation and/or on the post-translational processing of the protein products (Burnstein & Cidlowski, 1989; Venkatesh & Ballard, 1991). Several of the genes known to be regulated by glucocorticoids *in utero* (e.g. IGF-II, angiotensinogen, tropoelastin, erythropoietin) have the necessary glucocorticoid response elements (GRE) in their promotor regions to allow direct transcriptional control of the gene by cortisol (Olson *et al.* 1991; Li, 1994; Pierce *et al.* 1995; Lim *et al.* 1996). However, other genes which are apparently glucocorticoid sensitive (e.g. IGF-I) do not appear to have recognizable GRE consensus sequences (Dickson *et al.* 1991). In these instances, the effects of cortisol must be mediated indirectly either by post-transcriptional control of steady-state levels of mRNA or through other transcription factors with full-length or half-site GRE sequences (Venkatesh & Ballard, 1991; Lim *et al.* 1996). Alternatively, cortisol may act through triiodothyronine. Genes without GRE sequences often have triiodothyronine consensus sequences and plasma triiodothyronine is known to rise concomitantly with plasma cortisol as a result of the cortisol-induced deiodination of thyroxine to triiodothyronine (Wu *et al.* 1978; Venkatesh & Ballard, 1991). Indeed, synergism between plasma triiodothyronine and cortisol has been observed in a number of prepartum maturational processes including lung liquid reabsorption and down-regulation of hepatic IGF-II-gene expression (Barker *et al.* 1991; Forhead *et al.* 1996). In genes which have multiple transcripts derived from alternate exon slicing and promotor usage, the effects of glucocorticoids may be specific to certain leader exons in the 5′ untranslated region. In the IGF-II gene, cortisol down-regulates exon 7-containing but not exon 6-containing transcripts (Li, 1994). Similarly, cortisol preferentially increases the class 2 transcript of the IGF-I gene and switches on the adult, liver-specific leader exon of the GH receptor (exon 1a) in the liver of fetal sheep close to term (Li *et al.* 1996*a*,*b*). Thus, part of the maturational effect of the glucocorticoids may be to initiate use of specific promotors which, in turn, alters the nature of the gene product and its potential for translation (Roberts, 1997).

Some of the maturational effects of cortisol appear to be specific to particular periods of development. For instance, cortisol down-regulates hepatic IGF-II-gene expression in fetal sheep at 130 d of gestation but not in younger animals (Li *et al.* 1993; Li, 1994). Similarly, cortisol leads to tubular Na re-absorption in fetal sheep close to term, but causes naturiesis in fetuses at 110 d of gestation (Towstoless *et al.* 1989). The ability of exogenous cortisol to induce digestive enzymes in the small intestine of the fetal pig also appears to be confined to the period of late gestation just before the endogenous cortisol level normally rises (Trahair & Sangild, 1997). These time-dependent effects of the glucocorticoids may be due partially to ontogenic changes in glucocorticoid-receptor density and partially to alterations in the isoform and activity of 11β-hydroxysteroid dehydrogenase (*EC* 1.1.1.146; 11β HSD). This enzyme is present in many fetal tissues and converts cortisol to its inactive metabolite, cortisone, and vice versa depending on the specific isoform present in the tissue (Yang, 1992). It therefore regulates the bioavailability of cortisol to the fetal tissues (Chapman *et al.* 1997). In turn, both 11β HSD and glucocorticoid-receptor-gene expression can be regulated by cortisol (Yang, 1992; Matthews *et al.* 1995). The precise maturation effects induced by cortisol, therefore, depend on the duration, magnitude and developmental timing of the increment in plasma cortisol.

The long-term consequences of intra-uterine glucocorticoid exposure

In normal conditions, glucocorticoid concentrations only rise just before term as a signal for tissue maturation (see Silver, 1990). In these circumstances, prenatal glucocorticoid exposure appears to have few adverse sequalae, as the fetal tissues have proliferated normally up to a point at which the prepartum cortisol surge triggers differentiation. However, in stressful intra-uterine conditions such as placental insufficiency, undernutrition or restricted blood flow (Fig. 5), the fetal HPA axis is activated earlier in development and fetal cortisol levels become elevated well before term (Challis *et al.* 1993; Wood & Cudd, 1997). Although glucocorticoid exposure in these circumstances will ensure survival should delivery occur, the early switch from cell proliferation to differentiation may lead to an inappropriate pattern of growth for the stage of development, with adverse consequences much later in life (see Barker, 1997). Similarly, in human infants treated antenatally with dexamethasone for threatened preterm delivery or congenital adrenal hypoplasia, over-exposure to glucocorticoids at a time in development when cortisol levels are normally low may have important implications for the subsequent development and long-term health of the child (Seckl, 1997*b*).

In experimental animals, preterm dexamethasone treatment reduces fetal body weight at delivery and produces persistently elevated blood pressure in the adult offspring (Benediktsson *et al.* 1993; Dodic *et al.* 1997). In rats, this treatment also impairs adult glucose tolerance (Lindsay *et al.* 1996*a*). Increasing fetal glucocorticoid exposure by inhibiting placental 11β HSD has also been shown to lead to hypertension and glucose intolerance in the adult rat (Lindsay *et al.* 1996*b*). Although it is not known whether prenatal over-exposure to glucocorticoids in the human infant has similar long-term effects, it does retard intrauterine growth (Reinisch *et al.* 1978; Buescher *et al.* 1992). Epidemiological studies in man have recently shown that impaired growth *in utero* is associated with a substantially increased risk of hypertension, insulin resistance, non-insulin-dependent diabetes mellitus and IHD in adult life (see Barker, 1997). Since fetal cortisol levels are elevated in growth-retarded human infants (Goland *et al.* 1993), glucocorticoids are also likely to have an important role in the early-life programming of adult cardiovascular and metabolic disease in man.

Glucocorticoids are well placed to have a pivotal role in the prenatal programming of adult disease. Their concentration *in utero* is increased in response to all the environmental and experimental conditions known to have programming effects in early life (Fig. 5). Prenatally, they

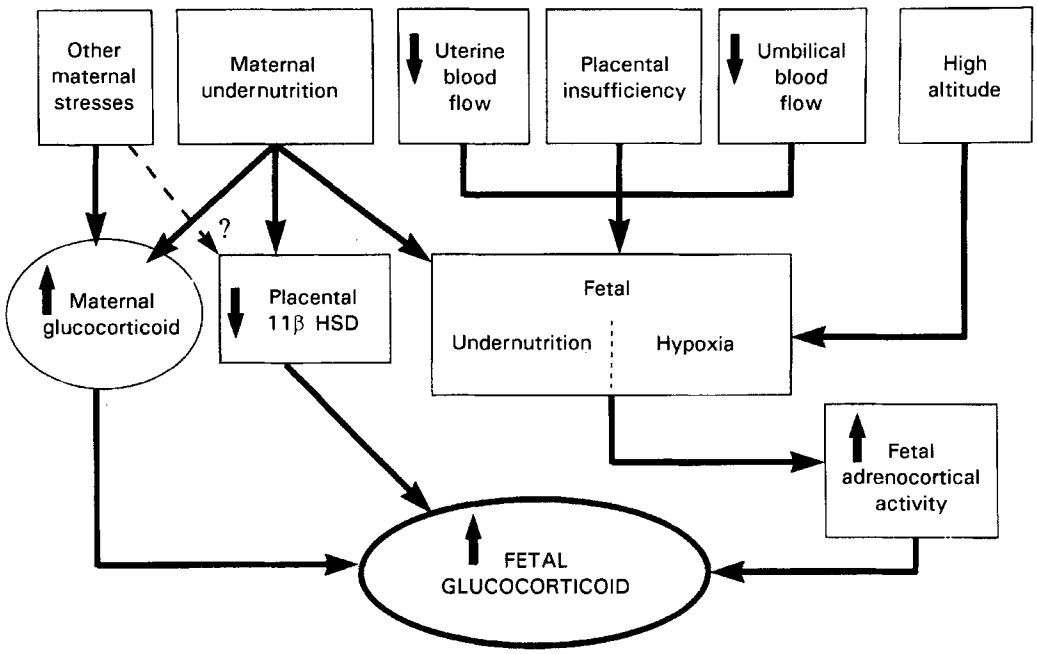

Fig. 5. Schematic diagram to show how fetal cortisol levels are raised by various environmental and experimental conditions believed to exert programming effects during intrauterine development. 11β HSD, 11β-hydroxysteroid dehydrogenase (*EC* 1.1.1.146). (Data from Silver 1990; Challis *et al.* 1993; Fowden *et al.* 1995; Barker, 1997; Seckl, 1997*a*.)

also affect development of the tissues that subsequently show pathophysiology in adult life (see Liggins, 1994). In addition, the observation that the duration, severity and timing of the exposure to glucocorticoids are critical in determining the precise developmental responses are consistent with the epidemiological findings that specific types of intra-uterine growth retardation are related to particular diseases in later life (Barker, 1997).

Inappropriate exposure to glucocorticoids in early life could affect the subsequent functioning of the cardiovascular system in several different ways. First, glucocorticoids may affect the development of the blood vasculature itself. Fetal glucocorticoid administration is known to raise fetal blood pressure, femoral resistance and vascular sensitivity to angiotensin II (Tangalakis *et al.* 1992; Derks *et al.* 1997). It also induces permanent changes in adrenergic-receptor expression, and in the intracellular coupling of these receptors which might alter subsequent vascular sensitivity to vasoconstrictors (Seckl, 1997*a*). There may also be morphological changes in the fetal heart and blood vasculature in response to glucocorticoid administration which contribute to the fetal hypertension and increase the risk of adult cardiovascular disease (Barker, 1997). Second, glucocorticoids may alter the sensitivity of the hypothalamus and HPA axis to feedback from hormones and peripheral chemo- and baroreceptors involved in cardiovascular control (Levitt *et al.* 1996; Phillips DIW *et al.* 1997). Third, glucocorticoids may alter cardiovascular function via their effects on renal morphogenesis and the renin–AII system (see p. 115). Glucocorticoids, therefore, have the potential to permanently alter the neural, endocrine and morphological contributions to blood-pressure control in the adult.

Similarly, there are several mechanisms by which overexposure to glucocorticoid *in utero* may lead to adult glucose intolerance and insulin resistance. Glucose production may be permanently enhanced by the cortisol-induced up-regulation of gluconeogenic activities in the liver and kidney (Fowden *et al.* 1993; Desai & Hales, 1997). Alternatively, there may be changes in pancreatic β cell function in response to glucocorticoid exposure, although there is little direct evidence, at present, for changes in insulin secretion following manipulation of fetal plasma cortisol (see Fowden, 1985). Finally, glucocorticoids may alter expression of the glucoregulatory genes in tissues, such as skeletal muscle, which make a major contribution to insulin-sensitive glucose disposal. Changes in the availability of glucose transporters and hormone receptors induced *in utero* may influence the efficiency with which insulin acts in later life and lead to insulin resistance and type 2 diabetes in the long term.

Conclusions

Glucocorticoids are essential at term for the normal process of prepartum tissue maturation. They stimulate tissue differentiation and coordinate the various adaptations needed to survive the transition from intra- to extra-uterine life. Raising glucocorticoid levels in experimental animals earlier in gestation accelerates this maturational sequence and has led to the routine use of synthetic glucocorticoids in the treatment of preterm delivery in man. While neonatal mortality and morbidity are improved in these circumstances, the stimulation of tissue differentiation at the expense of proliferation may permanently alter cell number

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and function with adverse consequence much later in life. Clearly in treating premature human infants, the potential long-term costs of the life insurance provided by glucocorticoids should be considered carefully.

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