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Consequences of intra-uterine growth retardation for postnatal growth, metabolism and pathophysiology

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Intra-uterine growth retardation (IUGR), caused by maternal undernutrition or placental insufficiency, is usually associated with disproportionately large reductions in the growth of some fetal organs and tissues (thymus, liver, spleen, thyroid) and impaired cellular development of other tissues (small intestine, secondary wool follicles, skeletal muscle). Growth of other tissues, most notably brain, is relatively unimpaired. In our recent study of postnatal consequences of IUGR in the offspring of prolific ewes, growth-retarded newborn lambs tended to be hypoglycaemic and showed sluggish postnatal engagement of the growth hormone (GH)–insulin-like growth factor (IGF) system. When artificially reared in an optimum environment, low birth weight lambs grew at rates similar to those of normal lambs. However, low birth weight lambs were fatter at any given weight, apparently related to their high energy intakes, especially soon after birth, had low maintenance energy requirements, and limited capacity for bone and muscle growth. These growth characteristics were accompanied by higher plasma concentrations of GH and leptin, and lower concentrations of insulin-like growth factor I (IGF-I) during the first 2 weeks of postnatal life, and higher concentrations of insulin during subsequent growth up to 20 kg body weight. Emerging evidence indicates that in sheep, as in rodents, fetal programming of postnatal cardiovascular and metabolic dysfunctions is associated with IUGR and may be mediated partly by overexposure of the fetus to cortisol. Similar postnatal responses can be elicited by maternal undernutrition or cortisol treatment in early to mid-pregnancy without changing the growth of the fetus or placenta.

Introduction

A decade ago we noted the continuing validity of an earlier complaint by Everitt (1968) that 'the extent to which [events of later life] may be modified by factors operating during

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the intra-uterine formative stages appears to be insufficiently appreciated' (Bell, 1992). At about the same time, epidemiological evidence for the notion of 'fetal programming' began to accumulate, on the basis of the postulate that prenatal nutritional experience can have indelible influences on postnatal development and later incidence of systemic diseases in humans (Barker, 1998). Animal experiments have replicated and sought to explain mechanistically the epidemiological associations that have now been confirmed in several human populations (Langley-Evans, 2001). Much of this work has been confined to rodents but is now being extended to other species, including sheep.

This review focuses on the postnatal consequences of intra-uterine growth retardation (IUGR) in sheep. Our recent work on early postnatal metabolic development and the capacity for growth of key tissues in lambs with severe, natural IUGR is summarized. Other, recent studies on incipient or actual pathophysiological consequences of prenatal nutritional insufficiency and IUGR in neonatal and older sheep are discussed too.

Natural causes and experimental models of IUGR

Maternal nutrient deprivation

Acute effects of fasting and longer term effects of more prolonged undernutrition on patterns of fetal growth in sheep have been described in a series of studies reviewed by Mellor *et al.* (1983). These studies demonstrated that fetal growth is sensitive to even a few days of maternal feed deprivation and is especially responsive to maternal glycaemia. This finding is consistent with the established role of glucose as a primary source of energy for fetal growth and the known effects of maternal energy intake on glucose supply to the conceptus (Bell *et al.*, 1999). Maternal protein deprivation, uncomplicated by energy restriction, also predictably reduces growth of sheep fetuses, despite compensatory responses in maternal tissues (McNeill *et al.*, 1997).

Placental insufficiency

Placental mass and associated capacity for maternal–fetal nutrient transfer are powerful determinants of fetal growth during late gestation in sheep and cattle. This finding has been most persuasively demonstrated by controlled manipulation of placental size or functional capacity using pre-mating carunclectomy (Alexander, 1964), heat-induced placental stunting (Alexander and Williams, 1971) or uteroplacental vascular embolization (Creasy *et al.*, 1972). Natural variations in fetal weight as a result of varying litter size in prolific ewes are strongly correlated with placental mass per fetus (Rhind *et al.*, 1980; Greenwood *et al.*, 2000a). The profound growth retardation of fetuses in overfed, primiparous ewes too has been attributed to a primary reduction in placental growth (Wallace *et al.*, 2000).

The probably common aetiology of IUGR in experimentally induced and natural cases of placental insufficiency is illustrated by the similar patterns of association between fetal and placental weights in pregnant ewes with varying conceptus weights due to carunclectomy, heat stress, litter size and overfeeding of primiparous dams (Fig. 1). In each of these cases, severe growth retardation is associated with chronic fetal hypoxaemia and hypoglycaemia during late gestation (Harding *et al.*, 1985; Bell *et al.*, 1987; Wallace *et al.*, 2002).

Growth of fetal organs and tissues

Effects of IUGR on allometric growth of individual organs and tissues vary with the severity and gestational timing of growth restriction. Nevertheless, some very consistent relationships

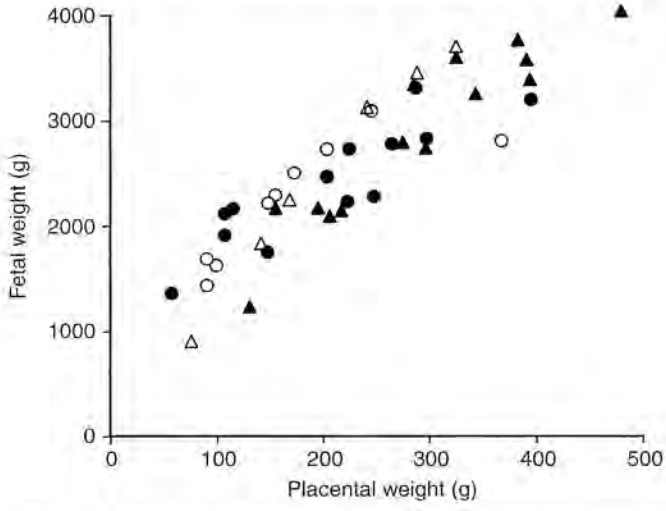

Fig. 1. Relationship between fetal and placental weights in ewes representing different models of placental insufficiency during late pregnancy. Variation in placental weight was achieved by pre-mating caruncleclectomy (●; Owens *et al.*, 1986), chronic heat treatment (○, Bell *et al.*, 1987), natural variation in litter size (▲; Greenwood *et al.*, 2000a) and overfeeding of adolescent ewes (△; Wallace *et al.*, 2000).

between relative size of anatomical parts and birth weight are evident in Alexander's (1974) summary of data from some 250 newborn lambs with birth weights ranging from 1 to 5 kg. These results were collected in nine series of experiments in which fetal growth was influenced by greatly differing levels of maternal nutrition, chronic maternal heat stress, caruncleclectomy or natural variation in litter size. In general, the IUGR-related growth penalty was disproportionately large in liver, spleen, thyroid and, most especially, thymus. The development of secondary wool follicles was also reduced disproportionately in small lambs. Conversely, growth of the brain, other head parts and the adrenal glands was relatively unimpaired in small newborn lambs. There was a tendency for alimentary tissues and the kidneys to be relatively larger, and for skeletal muscles to be somewhat smaller in relation to birth weight, whereas the masses of most bones, pulmonary and adipose tissues were proportionately related to body weight. These data are generally consistent with those of others who have examined effects of maternal undernutrition (Wallace, 1948), caruncleclectomy (Harding *et al.*, 1985), placental embolization (Creasy *et al.*, 1972), overfeeding of adolescent ewes (Wallace *et al.*, 2000), and extreme natural variation in litter size (P. Greenwood and A. Bell, unpublished) on patterns of ovine fetal growth during late gestation.

Developmental and physiological characteristics of the growth-retarded neonate

Greenwood *et al.* (2002) compared plasma concentrations of metabolites and hormones in normally grown and severely growth-retarded male Suffolk × (Finnsheep × Dorset) lambs at birth and during postnatal growth to a nominal live weight of 20 kg. Well-grown (birth weight > 4.3 kg) and growth-retarded (birth weight < 2.9 kg) lambs were removed from their dams at birth and reared artificially on sheep's milk replacer as described by Greenwood

Table 1. Plasma concentrations of metabolites and hormones in normally grown and severely growth-retarded newborn lambs

Variable	Normally grown ($n=4$)	Growth-retarded ($n=4$)	Significance of difference (P)
Birth weight (kg)	4.89 ± 0.21	2.24 ± 0.26	–
Plasma concentration			
Glucose (mmol l^{-1})	2.63 ± 0.95	1.42 ± 0.23	n.s.
Urea N (mmol l^{-1})	6.39 ± 0.32	8.31 ± 0.25	< 0.01
Insulin (μg l^{-1})	0.13 ± 0.06	0.09 ± 0.02	n.s.
Growth hormone (μg l^{-1})	10.8 ± 4.3	49.1 ± 17.0	< 0.05
IGF-I (μg l^{-1})	158 ± 22	36 ± 7	< 0.001
Leptin (μg l^{-1})	3.8 ± 0.3	4.1 ± 0.3	n.s.

Values are means ± SEM.
IGF-I: insulin-like growth factor I; n.s.: not significant.
Data from Ehrhardt *et al.* (2001) and Greenwood *et al.* (2002).

et al. (1998). The duration of gestation of growth-retarded lambs was similar to that for normal lambs. Influences of prenatal growth retardation on aspects of postnatal growth, body composition, tissue development and gene expression were also studied.

Metabolic and endocrine characteristics at birth

Data for lambs sampled before feeding and within 2 h of birth are summarized (Table 1). The moderately high plasma concentrations of urea nitrogen in growth-retarded lambs could have been due to greater rates of amino acid catabolism or lower capacity for renal clearance of urea, both of which are fetal characteristics and might be regarded as signs of immaturity. The small lambs also tended to be more hypoglycaemic than lambs of normal birth weight, possibly extending from the chronic hypoglycaemia that is typical of late-gestation fetuses that experience placental insufficiency (Bell *et al.*, 1999). However, the most striking feature of these observations is the apparent immaturity of the somatotrophic axis in the growth-retarded lambs, which is indicated by very high concentrations of growth hormone (GH) and low concentrations of insulin-like growth factor I (IGF-I) that are more reminiscent of the late gestation fetus than of the normal, well-grown lamb immediately after birth (Gluckman *et al.*, 1999). It is notable that hepatic expression of the gene for the acid-labile subunit (ALS), which is GH dependent and is greatly increased at or soon after birth in normal lambs (Rhoads *et al.*, 2000a), was reduced in naturally growth-retarded newborn lambs from prolific ewes (Rhoads *et al.*, 2000b). An early postnatal reduction in the hepatic synthesis and secretion of ALS would delay the normal postnatal shift in size of circulating IGF complexes from 50 kDa to 150 kDa (Butler and Gluckman, 1986) and the consequent major increases in half-life and concentration of circulating IGF-I. Other indices of hepatic GH responsiveness, including expression of mRNA for the GH receptor, IGF-I and IGF-binding protein (IGFBP)-3 were not significantly affected by birth weight (Rhoads *et al.*, 2000b).

It is notable that reduced hepatic expression of both ALS and IGF-I was discernible as early as day 130 of gestation in growth-retarded fetuses, despite the much lower absolute expression of these genes in fetal versus neonatal lambs (Rhoads *et al.*, 2000b). These data are consistent with decreases in fetal plasma IGF-I that were highly correlated with decreases in placental weight and apparent delivery of glucose and oxygen in carunclectomized ewes during late pregnancy (Owens *et al.*, 1994), given that, in both cases, fetal growth retardation

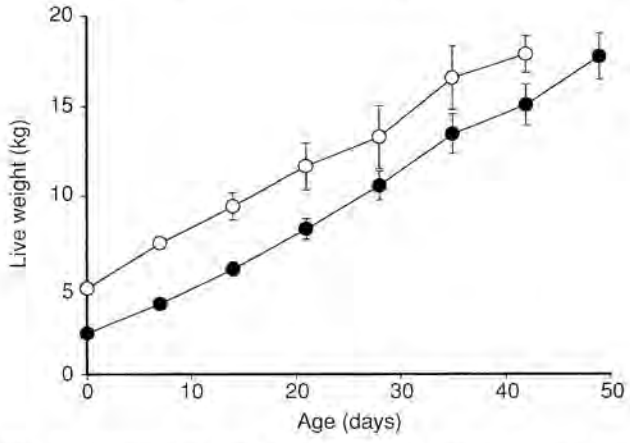

Fig. 2. Growth of low (●, $n = 16$) and normal (○, $n = 12$) birth weight lambs that were artificially reared from birth to approximately 20 kg live weight and had unlimited access to a high quality milk replacer. Values are means ± SEM for birth weight and weekly measurements of live weight (data from Greenwood *et al.*, 1998).

was due to placental insufficiency. The endocrine mediation of altered development of the GH–IGF system is unclear. A logical candidate for this role might be cortisol, the plasma concentration of which is increased in the placentally retarded fetus (Phillips *et al.*, 1996). However, treatment with cortisol appears to advance, rather than retard, the development of GH-dependent hepatic expression of IGF-I in the late gestation sheep fetus (Fowden *et al.*, 1998).

Plasma leptin concentrations were similarly low in small and normally grown newborn lambs (Table 1) (Ehrhardt *et al.*, 2001), consistent with their low and similar relative masses of adipose tissue and total body lipid (Greenwood *et al.*, 1998).

Postnatal growth and tissue development

Whole-body growth and composition. Artificially reared, growth-retarded lambs born to prolific ewes grew more slowly than normal lambs, in absolute terms, during the first 2 weeks of postnatal life, despite higher relative rates of gain. However, thereafter, their absolute growth rates to 20 kg live weight almost exactly matched those of the normal birth weight lambs when both groups were fed unlimited amounts of a high quality milk replacer (Fig. 2) (Greenwood *et al.*, 1998). Thus, it appears that when maternal, social and nutritional, and environmental disadvantages (Mellor, 1988) are minimized, neonatal growth potential is little affected by prenatal growth restriction *per se*.

Low birth weight lambs were somewhat fatter than normal birth weight lambs at all stages of postnatal growth up to 20 kg body weight. Their propensity for greater rates of fat deposition was most obvious during the first 2 weeks after parturition and apparently related to rapid relative rates of energy intake, lower maintenance energy requirements and limited capacity for lean growth (Greenwood *et al.*, 1998). Increased fat content at any given body weight in low birth weight lambs was offset more by reduction in ash content than in protein content, indicating that bone was more limited than lean soft tissues in its capacity to respond to the rapid increase in nutrient supply after birth. These early responses may contribute to the

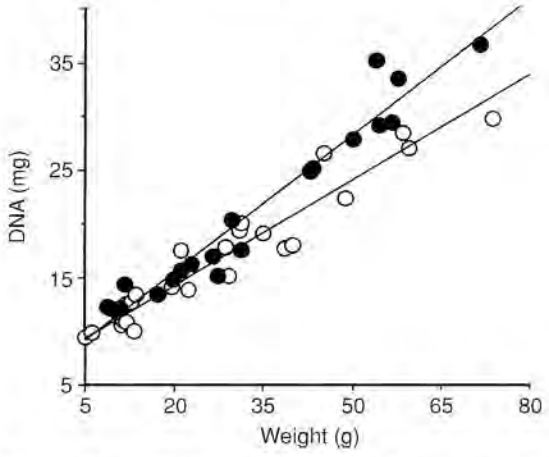

Fig. 3. Total DNA (mg) in semitendinosus muscle of low (○, $n=28$) and high (●, $n=20$) birth weight lambs that were reared from birth to a live weight of approximately 20 kg (data from Greenwood *et al.*, 2000b).

smaller mature size of sheep born to ewes that are severely undernourished during pregnancy (Schinckel and Short, 1961; Everitt, 1967).

Tissue growth and functional development. Effects of IUGR on postnatal relative growth of organs and tissues were assessed by comparing lambs of normal and low birth weight at common empty body weights (live weight minus gut contents) during growth to approximately 20 kg live weight. At any given empty body weight, low birth weight male lambs had a larger spleen and testes and a greater total visceral mass than normal birth weight lambs (P. Greenwood and A. Bell, unpublished). Conversely, the rates of gain in several skeletal muscles, including the semitendinosus, were persistently slower in low birth weight lambs, as were rates of gain in DNA, RNA and protein in the semitendinosus muscle (Greenwood *et al.*, 2000b). In addition, at any given weight during postnatal growth, the semitendinosus muscle contained less DNA (Fig. 3). This finding indicates that although myofibre number per anatomical muscle is unaffected by IUGR (Greenwood *et al.*, 1999, 2000b), the capacity for postnatal growth of muscle is constrained by decreased mitotic rates of fetal myosatellite cells during late gestation (Greenwood *et al.*, 1999) and low muscle DNA content at birth (Greenwood *et al.*, 2000b).

Growth-retarded newborn lambs tended to have shorter and sparser coats at birth than normal lambs, due to the failure of secondary skin follicles to mature and produce wool fibres during late gestation (Alexander, 1974). This failure could lead to a lifelong penalty in capacity for wool growth, as observed in growth-retarded lambs born to severely undernourished ewes (Schinckel and Short, 1961).

Consistent with other signs of apparent immaturity at birth, growth-retarded lambs experienced more digestive dysfunction and were harder to train to suck than normally grown lambs during the first few days after birth. Although digestive capacity was not measured objectively, our subjective observations are consistent with reports of decreased digestibility of milk replacer in low birth weight lambs (Houssin and Davicco, 1979) and impaired intestinal development in the growth-retarded ovine fetus (Avila *et al.*, 1989). The attainment of

Table 2. Plasma concentrations of metabolites and hormones in lambs of normal and low birth weight during early (< 2 weeks) and later (2–8 weeks) neonatal life

	Age < 2 weeks[a]		Age 2–8 weeks[b]	
Plasma concentration	Normal birth weight ($n = 10$)	Low birth weight ($n = 10$)	Normal birth weight ($n = 6$)	Low birth weight ($n = 6$)
Glucose (mmol l^{-1})	6.8	7.5	7.3	7.2
Urea N (mmol l^{-1})	5.7	3.9	5.6	5.2
Insulin ($\mu g\ l^{-1}$)	2.5	1.7	3.1	4.2*
Growth hormone ($\mu g\ l^{-1}$)	3.2	7.0*	4.8	5.2
IGF-I ($\mu g\ l^{-1}$)	559	400*	480	616*
Leptin ($\mu g\ l^{-1}$)	4.6	4.3	5.9	5.8

[a]Values are means of measurements taken at days 5, 7, 9, 11 and 13 after birth.
[b]Values are means of five or six weekly measurements taken at 2–7 weeks of age; weekly samples were pooled from individual samples taken several times each week.
Data from Greenwood *et al.* (1998), Ehrhardt *et al.* (2001) and Greenwood *et al.* (2002).
*Significantly different from mean value for normal birth weight lambs within the same age group ($P < 0.05$).
IGF-I: insulin-like growth factor I.

aggressive feeding behaviour and very high intakes of milk replacer by small lambs within a week of birth indicates that the nutritional consequences of perinatal gastrointestinal immaturity are short-lived. Certainly, the mass of stomach, small and large intestines, separately and in aggregate, was unaffected by birth size at any given empty body weight during rearing to 20 kg live weight (P. Greenwood and A. Bell, unpublished).

The functional consequences of the relatively rapid postnatal growth of spleen and testes, and constraint of muscle growth in low birth weight lambs remain to be investigated. It is notable that testicular volume increased more slowly and puberty was delayed in growth-retarded ram lambs born to overfed adolescent ewes compared with lambs of normal birth weight (Da Silva *et al.*, 2001).

Postnatal metabolic and physiological development

Most of the data discussed in this section, dealing with effects of size at birth on plasma concentrations of metabolites and hormones in neonatal lambs, are summarized (Table 2) and described in detail elsewhere (Greenwood *et al.*, 2002). Postnatal changes in superficial indices of carbohydrate and protein metabolism were little affected by birth weight in small and normal lambs that were artificially reared with *ad libitum* access to milk replacer. The very high concentrations of plasma GH in small, newborn lambs decreased markedly within 2 days of birth but remained significantly higher than concentrations in lambs of normal birth weight for about 2 weeks. During the same period, plasma IGF-I increased steadily in both groups but remained significantly lower in the small lambs (Greenwood *et al.*, 2002). These observations imply that the apparent immaturity of the GH–IGF axis in growth-retarded newborn lambs persists for several weeks after birth. Only during this early postnatal phase did the absolute growth rates of low birth weight lambs (248 g per day) lag significantly behind those of normal birth weight lambs (353 g per day) (Greenwood *et al.*, 1998). Thereafter, during rapid growth from about 2 weeks of age to slaughter at 20 kg (attained at 6.5–8.0 weeks of age), plasma IGF-I concentrations were persistently higher but GH concentrations were not different in low versus normal birth weight lambs (Table 2). This study did not examine the consequences of low birth weight after weaning. However, plasma GH concentrations tended to be higher

during adolescence (approximately 132 days of age) and adulthood (approximately 378 days of age) in low birth weight male lambs from carunclectomized ewes compared with lambs of normal birth weight and were negatively correlated with indices of birth size (Gatford *et al.*, 2002).

Plasma insulin concentrations increased rapidly during the early postnatal period in small lambs feeding *ad libitum*, consistent with their very high energy intake. From about 2 weeks of age until slaughter at 20 kg, plasma insulin concentrations were persistently higher in low compared with normal birth weight lambs (Table 2). It is possible that this relative hyperinsulinaemia is due to the predisposition of growth-retarded neonates to develop insulin resistance (Hales *et al.*, 1996).

The relatively rapid rates of fat deposition in low birth weight lambs feeding *ad libitum* were accompanied by significantly higher plasma concentrations of leptin during week 1 after birth, but not thereafter (Ehrhardt *et al.*, 2001).

Fetal programming of postnatal pathophysiology

Effects of IUGR

The epidemiological evidence for fetal programming in humans has implicated IUGR as an important risk factor for mature onset of diseases including hypertension and type II diabetes (Barker, 1998). These associations have been replicated in rodent models, usually involving maternal protein restriction (Langley-Evans, 2001) and, to a limited extent, in various models of IUGR in sheep (McMillen *et al.*, 2001). Consistent with some clinical observations on small for dates babies, low birth weight lambs from ewes subjected to placental embolization (Louey *et al.*, 2000) or glucocorticoid treatment (Moss *et al.*, 2001) during late pregnancy were relatively hypotensive during the first 2–3 months of postnatal life. However, McMillen *et al.* (2001) have cited their own preliminary evidence that by 1 year of age, systolic blood pressure was inversely related to indices of birth size in normal and placentally restricted lambs from carunclectomized ewes. The authors suggest that this long-term response may involve cortisol-induced fetal sensitization of the vasoconstrictor response to angiotensin II, based on observations of increased cortisol secretion (Phillips *et al.*, 1996) and vascular responsiveness to angiotensin (Edwards *et al.*, 1999) in the placentally retarded sheep fetus, and of the direct effects of cortisol infusion on fetal blood pressure and vascular responses to angiotensin II (Tangalakis *et al.*, 1992). During placental insufficiency, these effects may be exacerbated through downregulation of placental activity of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) by increased fetal cortisol secretion, thereby increasing exposure of the fetus to maternal cortisol (Clarke *et al.*, 2002). Putative mechanistic links between maternal nutrition, placental function, fetal cortisol status, and developmental consequences are outlined schematically (Fig. 4).

Persuasive evidence that prenatal growth retardation leads to postnatal development of insulin resistance in ruminants has yet to be obtained. Glucose and insulin tolerance at 1, 3 and 6 months of age were unimpaired in twin lambs that were approximately 20% lighter than their co-twins at birth (Clarke *et al.*, 2000). However, this growth penalty may have been insufficient to elicit an effect because even the lighter twins were relatively large (approximately 4 kg) at birth. The persistent relative hyperinsulinaemia of more severely growth-retarded lambs during growth to 20 kg (Table 2; Greenwood *et al.*, 2002) is indicative of insulin resistance as a postnatal consequence of IUGR.

In addition to its putative long-term effects on cardiovascular pathophysiology, increased exposure to cortisol in growth-retarded fetuses could also influence the development of insulin

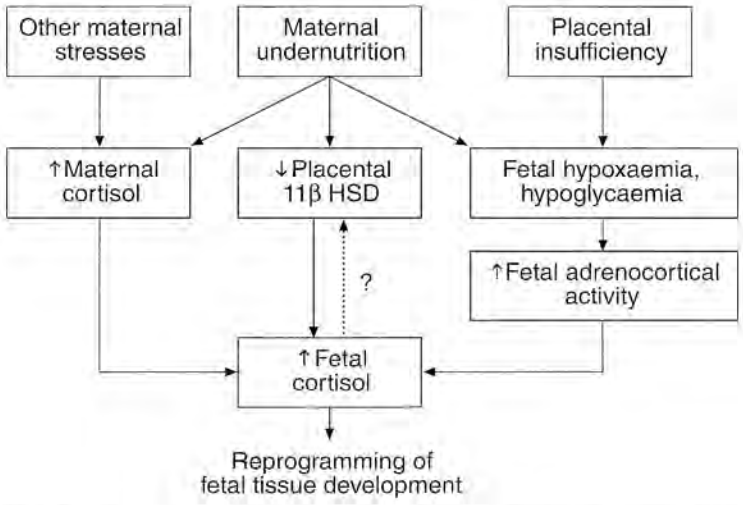

Fig. 4. Schematic diagram showing how fetal plasma cortisol concentrations in sheep are increased by conditions associated with intra-uterine growth retardation that are believed to exert effects on reprogramming of fetal tissue development (modified from Fowden *et al.*, 1998).

resistance in the liver and peripheral tissues, and have implications for postnatal metabolic health (Fig. 4). Plasma concentration of cortisol was increased in placentally restricted sheep fetuses during late gestation (Phillips *et al.*, 1996). In addition, hepatic exposure may be increased locally by upregulation of the capacity of the liver to convert cortisone to cortisol, consistent with the observation of increased expression of 11βHSD1 in liver of placentally retarded fetuses (McMillen *et al.*, 2000). In the only published study on postnatal consequences of fetal overexposure to cortisol in sheep, treatment of lamb fetuses with betamethasone during late pregnancy caused increased insulin responses to glucose challenges with no effect on glycaemic responses at 6 and 12 months of postnatal age (Moss *et al.*, 2001). These animals also displayed altered responsiveness of the hypothalamic–pituitary–adrenal axis at 12 months but not 6 months of age, in ways that varied according to the timing of prenatal glucorticoid treatment, and whether it was administered to the dam or fetus (Sloboda *et al.*, 2002).

Effects of maternal nutrition and other factors during early pregnancy

Growing evidence from studies on sheep and other species indicates that fetal programming can involve long-term sequelae to changes in the early prenatal environment that do not necessarily cause changes in gross morphology of the fetus. For example, modest undernutrition of ewes during the first half of pregnancy had no effect on growth of lambs during fetal or postnatal life but caused relative hypertension and increased activity of the HPA axis in lambs aged 12–13 weeks (Hawkins *et al.*, 2000). Consistent with these responses, maternal undernutrition between early and mid-gestation caused increased expression of the glucocorticoid receptor in adrenal gland, kidney, liver, lungs and perirenal adipose tissue of the fetus at term (approximately 145 days) (Whorwood *et al.*, 2001). At the same time, there was increased expression of 11βHSD1 in perirenal adipose tissue (but not in other tissues), marked decreases in expression of 11βHSD2 in the adrenal gland and kidney, and

increased expression of glucocorticoid-responsive angiotensin II type 1 receptor in tissues in which increased expression of the glucocorticoid receptor and/or decreased expression of 11βHSD1 was observed. Some of these tissue-specific fetal responses were evident as early as day 77 of gestation.

A central role for corticosteroids in the mediation of fetal programming was further implicated by the surprising finding that exposure of ewes to high doses of dexamethasone for only 2 days in early pregnancy resulted in hypertensive offspring at 3–4 months of age (Dodic *et al.*, 1998). This hypertension amplified with age to beyond three years and was associated with increased cardiac output (Dodic *et al.*, 1999) but no change in responsiveness of the HPA axis (Dodic *et al.*, 2002). Glucose metabolic responses to insulin were unaltered but the ability of insulin to suppress net fatty acid release from adipose tissue (plasma non-esterified fatty acid concentration) was moderately enhanced (Gatford *et al.*, 2000).

Conclusions

The problem of low birth weight in domestic ruminants, especially sheep, has long been appreciated in terms of perinatal mortality related to the diminished capacity of small neonates to withstand themoregulatory and nutritional challenges soon after birth (Alexander, 1974). Negative consequences for postnatal growth and productivity of surviving small neonates have also been documented (Bell, 1992). During the past decade, a new awareness of the possible long-term effects of nutritional insults during fetal life has grown out of landmark research on epidemiological associations between birth size and incidence of mature-onset diseases in humans (Barker, 1998). The sheep offers an excellent biomedical model for investigation of the underlying mechanisms of fetal programming because of its amenability to experimental manipulation during fetal and postnatal life and its combination of a relatively long gestation period with rapid postnatal maturation. It is certain that such investigations will also lead to a new understanding of the influence of prenatal experience on postnatal development of key tissues and functions important to animal productivity, including muscle growth, reproduction, lactation and disease resistance.

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