Prenatal nutritional influences on growth and development of ruminants

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Summary

Intrauterine growth retardation (IUGR) results from inadequate nutrient supply to the foetus due to placental insufficiency and/or low maternal circulating metabolite concentrations during late gestation if nutrient intake and body reserves are limited. In our recent study of postnatal consequences of IUGR, growth–retarded newborn lambs tended to be hypoglycaemic and exhibited 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 matching those of normal lambs. However, increased fatness at any given weight resulted, apparently related to high energy intakes soon after birth, low maintenance energy requirements, and limited capacity for bone and muscle growth. These growth characteristics were accompanied by higher plasma levels of GH and leptin, and lower levels of IGF–1 during the first week or two of postnatal life, and higher levels of insulin during subsequent growth to 20 kg. Emerging evidence suggests that in sheep, as in rodents, foetal programming of postnatal cardiovascular and metabolic dysfunctions is associated with IUGR and may be mediated partly by foetal overexposure to cortisol. Similar postnatal responses can be elicited by maternal undernutrition or cortisol treatment in early–mid pregnancy without changes in foetal or placental growth.

Keywords: sheep, cattle, foetus, placenta, birth weight, nutrition

Introduction

The Australian environment can result in prolonged periods of severe nutritional constraints for ruminant livestock during gestation and early postnatal life, primarily due to drought and/or regional climatic characteristics. High levels of mortality and morbidity in low birth–weight offspring remain a major problem, particularly in sheep flocks, despite decades of research on the multifaceted aetiology of intrauterine growth retardation (IUGR). Excessive foetal growth due to maternal nutrition also increases perinatal mortality. Emerging evidence suggests that foetal metabolic disturbance can lead to 'programming' of increased predisposition to various disease syndromes during later postnatal life, possibly with ramifications for long–term health and productivity of livestock. This review focuses on the causes and consequences of IUGR in ruminant livestock. Our own recent studies on early postnatal metabolic development and capacity for growth of key tissues in lambs suffering severe, natural IUGR are summarized. Other, recent studies on incipient or actual pathophysiological consequences of prenatal nutritional insufficiency and IUGR in neonatal and older sheep, which include experimental evidence for the concept of 'foetal programming', are also discussed.

Normal conceptus metabolism and growth

Patterns of prenatal growth

Patterns of foetal and placental growth in the normal and growth–retarded sheep conceptus are illustrated in Figure 1. In sheep, as in other placental mammals, post–embryonic growth becomes quantitatively significant only after mid–gestation. However, this is preceded by rapid hyperplastic growth of the placenta which attains all or most of its mass of dry tissue, protein, and DNA by mid–gestation (Ehrhardt and Bell 1995). Foetal growth then follows its familiar, flattened sigmoid pattern during the latter half of gestation as it proceeds from an early exponential phase through a rapid, linear phase, and then, as term approaches, begins to diminish in rate. In most species, there is little or no increase in placental weight during this period; the ovine placenta actually diminishes in weight, mostly due to loss of extracellular water (Ehrhardt and Bell 1995). However, the placenta undergoes extensive tissue remodelling after mid–gestation, including major proliferative growth of the umbilical vasculature (Teasdale 1976),

which is associated with a progressive increase in its functional capacity. Relations between placental size and function, and implications for foetal growth are discussed below.

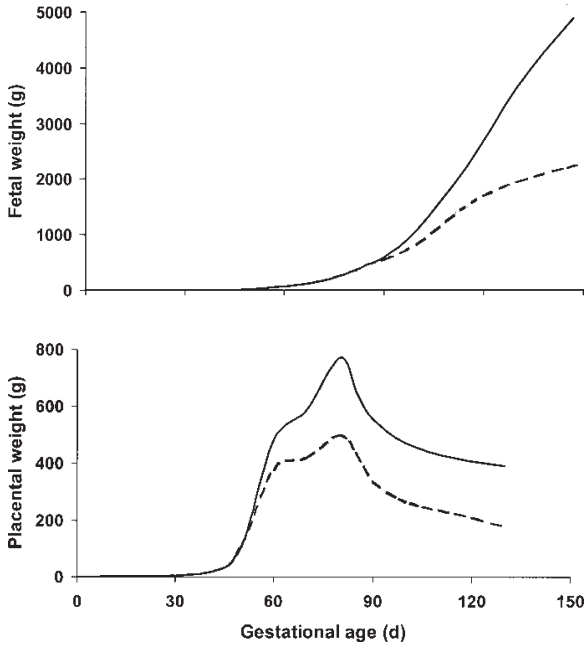

Figure 1 Patterns of foetal and placental growth in the normal (—) and growth–retarded (– –) sheep conceptus. Adapted from the data of Ehrhardt and Bell (1995) and Greenwood *et al.* (2000a). Reproduced with permission of Elsevier Science B.V., Amsterdam (Bell *et al.* 2003).

General features of foetal metabolism and its regulation

Foetal macronutrient requirements and metabolism in sheep and cattle have been quantitatively described in terms of umbilical exchanges of oxygen, nutrients, and metabolites (see Bell *et al*. 2003). During late pregnancy in these species, 35–40 % of foetal energy is taken up as glucose and its foetal–placental metabolite lactate, and a further 55% is taken up as free amino acids. In contrast to its importance as an energy source in the maternal ruminant, umbilical uptake of acetate is estimated to account for only 5–10% of foetal energy consumption. In ruminants, placental capacity for transfer of long–chain, non–esterified fatty acids (NEFA) and ketoacids is even more limited (see Bell and Ehrhardt 2002), making these maternal substrates trivial contributors to foetal metabolism. Almost all of the nitrogen acquired by the foetus is in the form of amino acids, but a small net umbilical uptake of ammonia is derived from placental deamination of amino acids during the latter half of gestation (Holzman *et al*. 1977; Bell *et al*. 1989). About 60% of these amino acids are used for tissue protein synthesis, which accounts for ~18% of foetal energy expenditure (Kennaugh *et al*. 1987). The remaining 40% are rapidly catabolized, accounting for at least 30% of the oxidative requirements in the well–nourished sheep foetus (Faichney and White 1987) or, in the case of glutamate and serine, taken up and metabolised by the placenta (Battaglia and Regnault 2001).

Gestational changes in conceptus metabolism

The many–fold increase in foetal mass from mid to late gestation is accompanied by increased absolute rates of uterine and umbilical uptake of oxygen and nutrients and of urea export by conceptus tissues, and of foetal whole–body protein synthesis in sheep and cattle (Bell *et al.* 1986; Reynolds *et al.* 1986; Kennaugh *et al.* 1987; Bell *et al.* 1989; Ferrell 1991). When expressed on a weight–specific basis these rates are considerably greater in mid than in late gestation, concomitant with greater relative rates of growth in the immature foetus. In sheep, the gestational decline in weight–specific foetal whole–body metabolic rates is associated with allometric growth patterns of metabolically active vital organs, such as the liver, versus that of less active skeletal tissues (Bell *et al.* 1987a), as well as a decline in the weight–specific rate of foetal hepatic oxygen consumption (Vatnick and Bell 1992).

Intrauterine growth retardation

Placental size and nutrient transport capacity

Placental weight and associated capacity for maternal–foetal nutrient transfer are powerful determinants of foetal growth during late gestation in all species studied. This has been most persuasively demonstrated by controlled manipulation of placental size and/or functional capacity using pre–mating caruncletomy (Alexander 1964), heat–induced placental stunting (Alexander and Williams 1971), or uteroplacental vascular embolisation (Creasy *et al.* 1972). Natural variations in foetal weight due to varying litter size in prolific ewes are strongly correlated with placental mass per foetus (Rhind *et al.* 1980; Greenwood *et al.* 2000a). Recently, the quite profound growth retardation of foetuses in overfed, primiparous ewes has been attributed to a primary reduction in placental growth (Wallace *et al.* 2000). Placental weight and birth weight are also highly correlated in cattle (Anthony *et al*. 1986; Echternkamp 1993; Zhang *et al*. 1999).

The probably common aetiology of IUGR in experimentally–induced and natural cases of placental insufficiency is illustrated by the similar patterns of association between foetal and placental weights in pregnant ewes with varying conceptus weights due to caruncletomy, heat stress, litter size, and overfeeding of primiparous dams (Figure 2). In each case, severe growth retardation was associated with chronic foetal

hypoxaemia and hypoglycaemia during late gestation (Creasy *et al*. 1972; Harding *et al*. 1985; Bell *et al*. 1987b; Wallace *et al*. 2002). A detailed assessment of influences on placental transport of nutrients is beyond the scope of this review, but is provided in Bell *et al.* (2003).

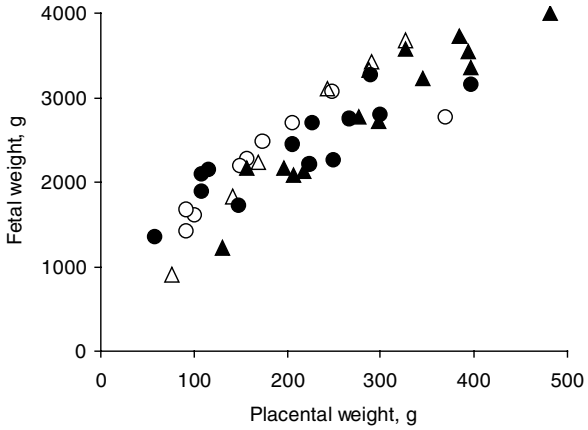

Figure 2 Relation between foetal and placental weights in ewes representing different models of placental insufficiency during late pregnancy. Variation in placental weight was achieved by premating carunclectomy (●; Owens *et al.* 1986), chronic heat treatment (○; Bell *et al.* 1987b), natural variation in litter size (▲; Greenwood *et al.* 2000a), and overfeeding of adolescent ewes (△; Wallace *et al.* 2000). Reproduced with permission from the Society for Reproduction and Fertility (Greenwood and Bell 2003).

Maternal nutrition

Maternal nutrition influences growth of the foetus and size of the newborn either directly as a result of the adequacy of nutrient intake and circulating substrate concentrations, or indirectly due to effects on the capacity of the placenta to transport nutrients to the foetus.

Chronic and acute nutritional effects on foetal growth in sheep occur mainly during the final two months of pregnancy, when foetal nutrient requirements increase rapidly (Wallace 1948; Mellor 1983). These effects can be substantial and have been demonstrated using an *in vivo* technique to measure curved crown–rump length and thoracic girth circumference. Commencing at 112 to 120 days of gestation, acute nutritional restriction of ewes reduced foetal growth rate by 30 to 47% within 3 days, including some foetuses that eventually reached growth stasis (Mellor and Matheson 1979; Mellor and Murray 1981). When ewes that had been severely undernourished for 9 or 16 days were realimented to normal levels, there was an immediate increase in foetal growth rate, but not in foetuses of ewes undernourished for 21 days (Mellor and Murray 1982b). Similarly, foetal intravenous nutritional supplementation overcame experimentally induced foetal growth retardation during late gestation (Charlton and Johengen 1987). Chronic, moderate undernutrition of ewes between 90 d and 140 d of pregnancy resulted in a progressive decline in foetal growth rate, with foetuses of undernourished ewes being 22% lighter than those of well–nourished ewes at 142 d (Mellor and Murray 1982a).

The adverse effects of chronic undernutrition throughout pregnancy or of severely restricted nutrition during late gestation on foetal growth and birth weight can be variable. Moderating influences include maternal body condition (McNeill *et al.* 1999) and plane of nutrition during late pregnancy (Oddy and Holst 1991) when growth of the foetus is normally constrained. Nevertheless, a high plane of nutrition during the final four weeks of pregnancy could not totally compensate for the effect on birth weight of severe undernutrition of ewes from mating to four weeks pre–partum, indicating that following prolonged foetal growth retardation, an extended period of nutritional rehabilitation is also required to normalise birth weight (McClymont and Lambourne 1958).

Effects of adverse nutrition during early to mid pregnancy on foetal growth (Everitt 1964) or birth weight (Nordby *et al.* 1987) have been demonstrated. However, these required extremely severe maternal undernutrition, to the extent that some ewes died (Everitt 1965), or prolongation of feed restriction from one month prior to breeding until 100 days of pregnancy (Nordby *et al.* 1987). In general, maternal nutritional restriction during early (Parr *et al.* 1986; Krausgrill *et al.* 1999) and/or mid pregnancy (Oddy and Holst 1991; McCrabb *et al.* 1992; Fogarty *et al.* 1992; Cronje and Adams 2002; Jopson *et al.* 2002) has only small, if any, effect on weight of the foetus or newborn if adequate nutriment is restored during the final 2 months or so of pregnancy.

In contrast to the limited effects of moderate nutritional restriction during early to mid pregnancy on birth weight, shearing during early to mid gestation enhances mobilisation of maternal body tissues (Jopson *et al.* 2002) and has increased the birth weight of single or twin lambs by up to 17%, although results have been inconsistent (Morris, *et al.* 2000; Jopson *et al.* 2002; Kenyon *et al.* 2002a; Revell *et al.* 2000, 2002). This has led to the proposal that the foetal growth response to shearing occurs in ewes that would otherwise give birth to a low birth weight newborn, and the ewe must have adequate maternal reserves and/or be fed adequately to support increased foetal growth (Kenyon *et al.* 2002b).

In cattle, severe nutritional restriction for at least the last half to one–third of pregnancy is required to reduce foetal growth (Holland and Odde 1992). Birth weight was unaffected by nutritional restriction of heifers from mating to 140 days gestation (Cooper *et al.* 1998) or of mature cows for the second trimester (Freetly *et al.* 2000). However, significant reductions in birth weight were caused by prolonged underfeeding of heifers from weaning until parturition (Wiltbank

et al. 1965), and underfeeding of heifers and cows during the second and third trimesters (Freetly *et al.* 2000; Hennessy *et al.* 2002), or during late pregnancy only (Hight, 1966; Tudor 1972; Bellows and Short 1978; Kroker and Cummins 1979). The effect of nutritional restriction on birth weight was more pronounced in heifers than cows when the period of restriction encompassed mid and late gestation (Hennessy *et al.* 2002) rather than late gestation only (Tudor 1972). Interestingly, birth weight of calves of Hereford dams sired by double–muscled Piedmontese bulls was more affected by restricted nutrition during mid and late pregnancy than those sired by Wagyu bulls (Hennessy *et al.* 2002), indicating that foetal growth capacity can interact with available nutrition in determining whether foetal growth is retarded. When assessed within parity and sire–breed, nutritional restriction resulted in reduced birth weights of Piedmontese–sired calves from heifers and cows, but only of Wagyu–sired calves from heifers. Effects of foetal growth potential, or foetal nutrient demand, on the nutritional reserves of pregnant cows were also evident (Greenwood *et al.* 2002b). Dams mobilized more muscle to support growth of male compared to female foetuses and tended to mobilize more muscle to support growth of Piedmontese–sired compared to the Wagyu–sired foetuses, while heifers mobilized less fat and muscle to support foetal growth than cows.

Because placental growth precedes foetal growth on a weight specific basis (Ehrhardt and Bell 1995), residual effects of nutrition during early and mid pregnancy on subsequent foetal growth may be mediated, at least in part, by effects on placental size. This has stimulated interest in understanding how nutrition may be used during early to mid pregnancy to increase placental capacity for nutrient transport in sheep (Davis *et al.* 1981; McCrabb *et al.* 1992; Clarke *et al.*, 1998; Heasman *et al.* 1998; Cooper *et al.* 1998; Wallace *et al.* 1999b) and cattle (Cooper *et al.* 1998; Perry *et al.* 1999) prior to the period of maximal foetal growth potential during late pregnancy. However, effects of nutrition on placental growth during early to mid pregnancy are highly variable, and may be influenced by a range of factors that uncouple the normally tight association between placental and foetal weights, including nutritional status of the dam prior to mating (Kelly 1992). For example, evidence supports the proposition that ewe fatness during early gestation influences the placental growth response to nutrition (Bell and Ehrhardt 2000). Ewes that were fatter during early pregnancy responded to restricted nutrition during early to mid pregnancy with increased placental size, while placental size was reduced following undernutrition of ewes that were thinner during early pregnancy (McCrabb *et al.* 1992). These results appear consistent with retarded placental growth in overfed pregnant adolescent ewes (Wallace *et al.* 1996, 1999a) being overcome by restricting nutrition of these ewes from 50 to 100 days of pregnancy, during which time enhanced placental growth was associated with maternal body tissue mobilization (Wallace *et al*. 1999b). Furthermore, ewe body condition during early to mid gestation was inversely related to placental weight when maternal nutrient requirements were met (Greenwood *et al.* 2000a).

Taken overall, the above findings emphasise that practices which affect the dam's capacity to mobilize peripheral body tissues or partition nutrients towards the gravid uterus may influence birth weight by altering placental development during early to mid gestation and/or the supply of nutrients available to the foetus during late gestation. For example, cold stress of ewes during late gestation increased maternal glucose, glycerol and nonesterified fatty acid concentrations and foetal glucose concentration, and increased birth weight by 15% (Thompson *et al.* 1982). Similarly, following isolation stress of ewes for 1 h on 10 occasions during late pregnancy, birth weight of lambs was increased by 12% (Roussel and Hemsworth 2002).

Coordination of foetal metabolism and growth

The mechanisms relating nutrient supply to expression of endocrine and local regulatory factors, and thence tissue metabolism and growth, can be illustrated by integration of the present knowledge on IUGR, whether caused by placental insufficiency, maternal undernutrition, or insulin–induced maternal hypoglycaemia. Effects on the local expression of trophic factors and the cellular growth of skeletal muscle will serve as an example of tissue responses to an altered extracellular milieu. The putative relationships discussed below are schematically represented in Figure 3.

Placental insufficiency during late gestation is generally characterized by foetal hypoxaemia and hypoglycaemia, whether caused by surgical reduction (carunclectomy; Harding *et al.* 1985), placental embolisation (Creasy *et al.* 1972), maternal heat stress (Bell *et al.* 1987b), or overfeeding of adolescent ewes (Wallace *et al.* 2002). Associated endocrine changes include decreased foetal plasma concentrations of insulin (Robinson *et al.* 1980) and IGF–1 and –2 (Owens *et al.* 1994), and increased concentrations of cortisol (Phillips *et al.* 1996). All of these changes can be elicited by maternal undernutrition or insulin–induced hypoglycaemia, implicating foetal glycaemia as an important primary signal (Mellor *et al.* 1977; Osgerby *et al.* 2002). However, it must be recognized that hypoxaemia may reinforce these responses through its stimulation of foetal adrenal secretion of cortisol and catecholamines, and the inhibitory influence of the latter on foetal insulin secretion.

It seems likely that hypoinsulinaemia is a primary, coordinating mediator of the numerous metabolic and trophic consequences of reduced foetal nutrient supply. Disruption of foetal pancreatic insulin secretion has a potent, negative effect on foetal growth (Fowden 1995), associated with decreased foetal tissue uptake and

metabolism of glucose (Fowden and Hay 1988), decreased uptake of amino acids and increased proteolysis (Carver *et al.* 1997), and reduced circulating levels of IGF–1 (Gluckman *et al.* 1987).

However, although circulating IGF–1 may be of increasing importance during late gestation, it is likely that local tissue expression and actions of this and other growth factors are more significant mediators of tissue growth responses to altered nutrient supply. For example, foetal muscle strongly expresses IGF–1 throughout gestation (Dickson *et al.* 1991; Lee *et al.* 1993) and disruption of the IGF–1 gene causes lethal abnormalities in muscle development (Liu *et al.* 1993), consistent with the extensive evidence for the role of IGF–1 in regulation of myogenesis (Florini *et al.* 1996). It therefore seems likely that the reduced mitotic activity of myosatellite cells and growth of skeletal muscle in acutely undernourished or placentally growth–retarded sheep foetuses (Greenwood *et al.* 1999) was mediated, at least partly, by reduced local expression of IGF–1, possibly caused by elevated plasma levels of cortisol (Li *et al.* 2002).

Finally, although this section has focused on IUGR to illustrate aspects of the coordination of nutrient supply with growth in the foetus, it should be recognised that even in optimally fed, healthy, animals the foetal growth is constrained by placental capacity for nutrient transfer during late pregnancy. This phenomenon ensures that the unborn animal's demands upon its dam's nutrient reserves are not excessive, and reduces the possibility of birth injury to itself and its mother. The capacity for increased growth in response to increased nutrient supply was demonstrated by the almost 20% increase in birth weight of singleton lambs that had been infused directly with glucose for the last 30 days of gestation in ewes that were extremely well fed (Stevens *et al.* 1990).

Postnatal consequences of altered conceptus metabolism and growth

We recently compared postnatal growth, body composition, tissue development, metabolites and hormones, and gene expression in normally grown and

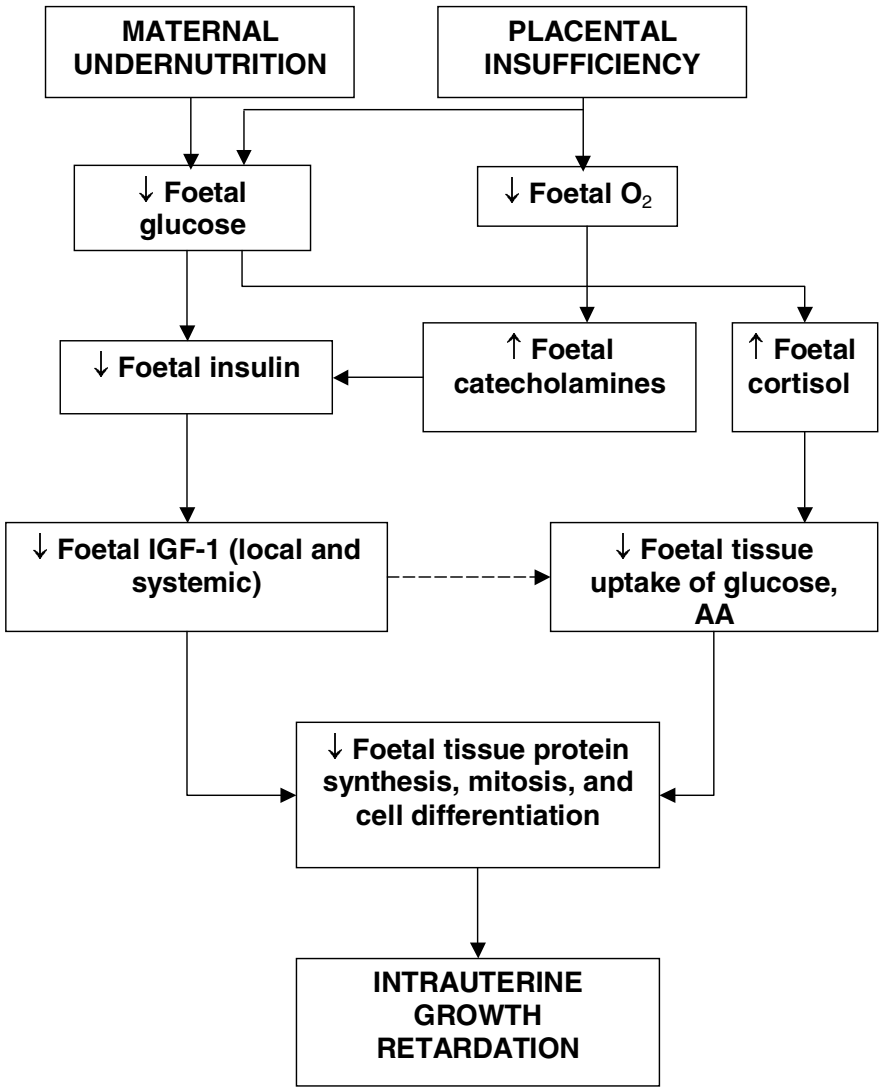

Figure 3 Schematic outline of some important factors linking maternal undernutrition and placental insufficiency to intrauterine growth retardation. Reproduced with permission of Elsevier Science B.V., Amsterdam (Bell *et al.* 2003).

severely growth–retarded male Suffolk x (Finnsheep x Dorset) lambs at birth and during postnatal growth to a nominal live weight (LW) of 20 kg (Greenwood *et al.* 2002a; Greenwood and Bell 2003). 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–milk replacer as described by Greenwood *et al.* (1998). The following section deals with these and other influences of metabolism and growth during foetal life on postnatal metabolism, growth and body composition, with some emphasis on muscle development and growth. Interactions between prenatal and early–postnatal development and their potential consequences for longer–term growth and development are also highlighted.

Metabolic and endocrine characteristics at birth

Transition from prenatal to postnatal life is characterized by an abrupt increase in the supply of nutrients and changes in glucose and lipid metabolism compared to prenatal life (Girard *et al.* 1992). Associated with this increase is a shift in the quality of the supply of nutrients from primarily glucose and amino acids, to less carbohydrate and more fat. Immediately post–partum, catabolism of brown adipose tissue occurs to support thermoregulation of the newborn outside of the uterine environment (Alexander 1979). Plasma glucose concentration in the newborn increases rapidly, and induction of expression of genes for key regulatory enzymes important in gluconeogenesis and lipid metabolism occurs during transition to postnatal life (Girard *et al.* 1992; 1997). Survival of newborns is inversely related to birth weight, until weights that result in dystocia are reached (Alexander 1974). A major contributing factor to post–partum mortality is inadequate energy stores to meet the requirements of the growth–retarded newborn for heat production via shivering in skeletal muscle and non–shivering thermogenesis in brown adipose tissue (Alexander 1979).

Data for lambs sampled before feeding and within 2 h of birth are summarised in Table 1 (Greenwood *et al*. 2002a). The moderately elevated levels of plasma urea nitrogen in growth–retarded lambs could have been due to greater rates of amino acid catabolism and/or lesser capacity for renal clearance of urea, both of which are foetal characteristics and might be regarded as signs of immaturity. The small lambs also tended to be more hypoglycaemic than their normal counterparts, possibly extending from the chronic hypoglycaemia that is typical of late–gestation foetuses suffering placental insufficiency (Bell *et al.* 1999). However, the most striking feature of these observations is the apparent immaturity of the somatotropic axis in the growth–retarded lambs. This is indicated by very high levels of growth hormone (GH) and low levels of insulin–like growth factor (IGF)–1 more reminiscent of the late–gestation foetus 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 growth–retarded newborn lambs (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–1. Other indices of hepatic GH responsiveness, including expression of mRNA for the GH receptor, IGF–1, 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–1 was discernible as early as 130 d of gestation in growth–retarded foetuses, despite the much lower absolute levels of expression of these genes in foetal versus neonatal lambs (Rhoads *et al.* 2000b). These data are consistent with decreases in foetal plasma IGF–1 that were highly correlated with decreases in placental weight and apparent delivery of glucose and

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)	2.63 ± 0.95	1.42 ± 0.23	ns
Urea N (mmol/L)	6.39 ± 0.32	8.31 ± 0.25	<0.01
Insulin (µg/L)	0.13 ± 0.06	0.09 ± 0.02	ns
Growth hormone (µg/L)	10.8 ± 4.3	49.1 ± 17.0	<0.05
IGF–1 (µg/L)	158 ± 22	36 ± 7	<0.001
Leptin (µg/L)	3.8 ± 0.3	4.1 ± 0.3	ns

Values are means ± SEM; ns, not significant
Data from Ehrhardt *et al.* (2001) and Greenwood *et al.* (2002a)

oxygen in carunclectomized ewes during late pregnancy (Owens *et al.* 1994), given that, in both cases, foetal growth retardation 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, plasma concentration of which is elevated in the placentally retarded foetus (Phillips *et al.* 1996). However, treatment with cortisol appears to advance rather than retard the development of GH–dependent hepatic expression of IGF–1 in the late–gestation sheep foetus (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 metabolism and growth

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 in Table 2 and described in detail elsewhere (Greenwood *et al.* 2002a). 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 two days of birth but remained significantly higher than levels in normal lambs for about two weeks. During the same period, plasma IGF–1 increased steadily in both groups but remained significantly lower in the small lambs (Greenwood *et al.* 2002a). These observations suggest that the apparent immaturity of the GH/IGF axis in growth–retarded newborn lambs persists for several weeks after birth. Interestingly, only during this early postnatal phase did the absolute growth rates of low birth weight lambs (248 g/d) lag significantly behind those of normal birth weight lambs (353 g/d) (Greenwood *et al.* 1998). Thereafter, during rapid growth from about 2 weeks of age to slaughter at 20 kg (attained at 6.5 to 8 weeks of age), plasma IGF–1 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 (~132 days of age) and adulthood (~378 days of age) in low birth weight male lambs from carunclectomized ewes compared to 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 levels of energy intake. Then, from about two weeks of age until slaughter at 20 kg, plasma insulin concentrations were persistently higher in low compared with normal birth weight lambs (Table 2). We speculate that this relative hyperinsulinaemia may be due to the predisposition of growth–retarded neonates to develop insulin resistance (Hales *et al.* 1996).

Plasma leptin concentrations were somewhat higher in rapidly fattening, low birth weight lambs during the first week post partum, but not thereafter (Ehrhardt *et al.* 2001), despite the fact that at any subsequent liveweight up to 20 kg these lambs were significantly fatter than their normal birth weight counterparts (Greenwood *et al.* 1998). These findings also suggest that relatively low levels of plasma leptin during the immediate post–partum period may support high weight–specific levels of feed intake to enable rapid accretion of energy (lipid) stores to enhance later survival. This appears to be particularly relevant to the survival of the very small newborn.

The adverse longer–term consequences of greater fatness and a degree of insulin resistance (see Hales *et al.* 1996) in small newborn animals may, therefore, arise due to adaptations to enhance survival during early

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[1]		Age 2 — 8 weeks[2]	
Plasma concentration	**Normal**	**Low**	**Normal**	**Low**
Glucose (mmol/L)	6.8	7.5	7.3	7.2
Urea N (mmol/L)	5.7	3.9	5.6	5.2
Insulin (μg/L)	2.5	1.7	3.1	4.2
Growth hormone (μg/L)	3.2	7.0	4.8	5.2
IGF–1 (μg/L)	559	400	480	616
Leptin (μg/L)	4.6	4.3	5.9	5.8

[1]Values are means of measurements made at days 5, 7, 9, 11, and 13 after birth
[2]Values are means of five or six weekly measurements made between 2 and 8 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.* (2002a)

postnatal life. During the immediate post–partum period, there is increased propensity for very small newborn lambs to deposit more adipose tissue than their larger counterparts (Greenwood *et al.* 1998), reminiscent of results for pigs following long–term, chronic growth retardation from birth that resulted in smaller muscles with heavy infiltration of adipose tissue following nutritional rehabilitation (Widdowson 1973). Greater fatness in the growth retarded newborn lambs during early postnatal life resulted from consumption of about 20% more feed on weight–specific basis, coupled with reduced maintenance energy requirements and limited capacity to accrete muscle or lean tissue (Greenwood *et al.* 1998, 2000b). In relation to the latter, muscle from these lambs was 57% lighter and contained 67% and 60% less DNA and RNA, respectively, at birth compared to the larger newborns (Greenwood *et al.* 2000b). As described above, circulating concentrations of insulin were also persistently higher in the small newborns during the period to weaning (Greenwood *et al.* 2002a), presumably a consequence of greater relative feed intake coupled with limited clearance by peripheral tissues during the post–partum period, and suggesting a degree of insulin resistance.

Clearly, there are potential implications of nutrition during the post–partum period for health during later life that may result from adaptations to enhance prospects for survival of the low birth weight newborn. Therefore, the concept of long–term deleterious influences of adaptations to enhance postnatal survival previously proposed by Fowden *et al.* (1998), in relation to the period immediately pre–partum, should be extended to include adaptations during the early post–partum period.

Tissue growth and functional development

Livestock have a remarkable ability to recover body mass following prenatal nutritional insult. However, it is well recognised that prenatal development can influence postnatal growth and mature size (reviewed by Everitt 1968; Allden 1970; Widdowson 1977; Bell 1992). Influences of prenatal nutrition on postnatal growth to mature size in sheep are evident when severe, chronic nutritional restriction is imposed throughout gestation (Schinckel and Short 1961), or during late but not necessarily early gestation (Everitt 1967). Early postnatal growth capacity is reduced among low birth weight lambs (Schinckel and Short 1961; Taplin and Everitt 1964; Greenwood *et al.* 1998) and pigs (Powell and Aberle 1980), and additive adverse effects of inadequate prenatal and postnatal nutrition on growth and body size have been reported (Schinckel and Short 1961; Gunn 1977).

It appears that when maternal, social and/or nutritional, and environmental disadvantages (Mellor 1988) are minimised, neonatal growth potential is little affected by prenatal growth restriction *per se*. As described above, artificially reared, growth–retarded lambs born to prolific ewes grew more slowly than normal lambs, in absolute terms, during the first two weeks of postnatal life, despite higher relative rates of gain (Greenwood *et al.* 1998). Thereafter, however, their absolute growth rates to 20 kg LW almost exactly matched those of the normal birth weight lambs when both groups were fed unlimited amounts of a high quality milk replacer (Figure 4). Therefore, it appears that direct prenatal effects on capacity for growth of neonates are somewhat ameliorated or exacerbated depending upon the postnatal environment into which they are born (Schinckel and Short 1961; Gunn 1977; Greenwood *et al.* 1998).

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 (EBW) during growth to ~20 kg liveweight. At any given EBW, low birth weight male lambs had a larger spleen and testes, and a greater total visceral mass than normal birth weight lambs (P.L. Greenwood and A.W. 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). Also, at any given weight during postnatal growth, the semitendinosus muscle contained less DNA (Figure 5). This suggests 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 foetal myosatellite cells during late gestation (Greenwood *et al.* 1999) and low muscle DNA content at birth (Greenwood *et al.* 2000b).

Consistent with other signs of apparent immaturity at birth, growth–retarded lambs suffered more from 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 foetus (Avila *et al.* 1989; Trahair *et al*. 1997). The attainment of aggressive feeding behaviour and very high intakes of milk replacer by small lambs within a week of birth suggests that the nutritional consequences of perinatal gastrointestinal immaturity were short–lived. Therefore, in the newborn lamb, severe foetal growth retardation does not appear to adversely affect appetite and voluntary feed intake, as shown by Sibbald and Davidson (1998), in contrast to reported effects in species including rodents, guinea pigs, pigs and humans (Widdowson 1977). Certainly, the mass of stomach, small and large intestines, separately and in aggregate, were not adversely affected by birth size at any given empty body weight during rearing to 20 kg liveweight (P.L. Greenwood and A.W. 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.

The timing of myogenesis also raises important questions about the potential of prenatal nutrition to alter postnatal muscle growth capacity. It has been proposed that the earlier the gestational nutritional influence on myogenesis, which appears to be completed by about two–thirds gestation in sheep (Greenwood *et al.* 1999), the greater the potential effects on postnatal muscle growth capacity (Stickland *et al.* 2000; Hocquette *et al.* 2001). While this hypothesis may apply in theory, in as much as increased or reduced myofibre and/or myosatellite cell number can alter growth capacity, it is not supported by experimental evidence in sheep (Everitt *et al.* 1967; Parr *et al.* 1986; Nordby *et al.* 1987; Krausgrill *et al.* 1999). Although possible, in reality it is difficult to significantly alter growth of the early– to mid–gestational foetus in non–litter bearing species (for examples, see Everitt 1965; Krausgrill *et al.* 1999) due to early gestational nutrient requirements of the foetus being quantitatively small and to the capacity of the dam to mobilize body tissues in support of foetal nutrient requirements (see earlier sections, and Bell 1992).

Severe prenatal growth–retardation has resulted in greater fatness during postnatal life (Powell and Aberle *et al.* 1980; Villette and Theriez 1981; Greenwood *et al.* 1998), and is associated with reduced mass of muscle, protein, bone and/or ash (Widdowson 1971; Powell and Aberle 1980; Villette and Theriez 1981; Greenwood *et al.* 1998, 2000b). Increased fat content at any given body weight in lambs with low birth weight was offset more by reduced ash content than protein content, suggesting that bone was more limited than lean soft tissues in its capacity to respond to the rapid postpartum increase in nutrient supply (Greenwood *et al.* 1998). These early responses may contribute to the smaller mature size of sheep born to ewes severely undernourished during pregnancy (Schinckel and Short 1961; Everitt 1967).

Few experimental results have been published on effects of IUGR on body composition at mature size of livestock or other species. Bone and muscle mass were reduced 17% and 13%, respectively, in a runt pig compared to its larger littermate at three years of age (Widdowson 1971). Severe restriction of maternal protein intake throughout pregnancy reduced body mass of pigs at 119 weeks of age (Pond *et al*. 1990). However, no significant effects on carcass composition were observed, despite a reduction in absolute mass of muscle. Compositional differences were not evident in the whole body or carcass of Hereford steers or heifers grown to 370 to 400 kg liveweight following restricted or adequate nutrition of their dams from 180 days of pregnancy to parturition that resulted in a difference in calf birth weight of 6.8 kg or 22% (Tudor *et al*. 1980). This may reflect the less extreme variation in birth weight of these cattle relative to those in studies of other species.

Growth–retarded newborn lambs also tended to have shorter and sparser birth coats than normal lambs, due to the failure of secondary skin follicles to mature and produce wool fibres during late gestation (Alexander 1974). This 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).

Feed efficiency of low birth weight lambs (Greenwood *et al.* 1998) and pigs (Ritacco *et al.* 1997) is greater during the first week post–partum compared to larger newborns due to reduced maintenance requirements associated with their smaller size, and to

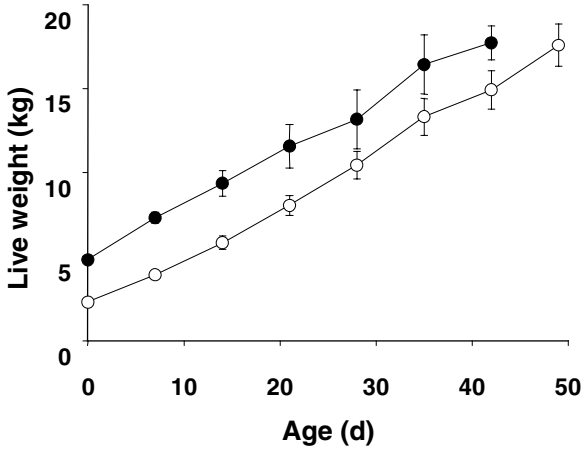

Figure 4 Growth of lambs of normal (●, n = 12) and low (○, n = 16) birth weight, artificially reared from birth to approximately 20 kg liveweight, with unlimited access to a high quality milk replacer. Values are means ± SEM for birth weight and weekly measurements of liveweight (data from Greenwood *et al.* 1998).

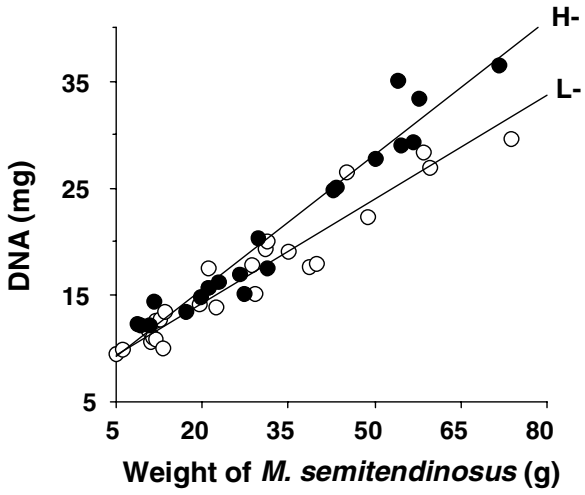

Figure 5 Total DNA (mg) in semitendinosus muscle of lambs of normal (●, n = 20) and low (○, n = 28) birth weight reared from birth to a live weight of approximately 20 kg (from Greenwood *et al.* 2000b).

the apparent reduction in their weight–specific maintenance energy requirements (Greenwood *et al.* 1998). During subsequent growth to 20 kg liveweight, feed efficiency of lambs was not affected by size at birth (Greenwood *et al.* 1998) although, in the longer–term, feed efficiency was reduced in IUGR pigs (Powell and Aberle 1980). There do not appear to be published results for long–term consequences of prenatal nutrition or birth weight on feed efficiency in ruminants.

Overall, research on postnatal consequences of prenatal nutrition on growth and body composition are consistent with the reality that non litter–bearing species, such as ruminants, have evolved to maximise survival of relatively few offspring in their lifetime compared to litter bearing species. However, possible influences during late gestation and early postnatal life may have a role in modulation of postnatal growth potential and mature size in these species, in accordance with the availability of nutrients.

Foetal programming of postnatal pathophysiology

Effects of intrauterine growth retardation

The human epidemiological evidence for foetal programming has implicated IUGR as an important risk factor for onset of diseases including hypertension and type II diabetes during adulthood (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 age 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 one 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 suggested that this long term response may involve cortisol–induced foetal 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 foetus, and of the direct effects of cortisol infusion on foetal blood pressure and vascular responses to angiotensin II (Tangalakis *et al.* 1992). During placental insufficiency, these effects may be exacerbated through down–regulation of placental activity of 11β–hydroxysteroid dehydrogenase type 2 (11βHSD2) by increased foetal cortisol secretion, thereby increasing foetal exposure to maternal cortisol (Clarke *et al.* 2002).

Persuasive evidence that prenatal growth retardation leads to postnatal development of insulin resistance in ruminants has yet to be obtained. Glucose

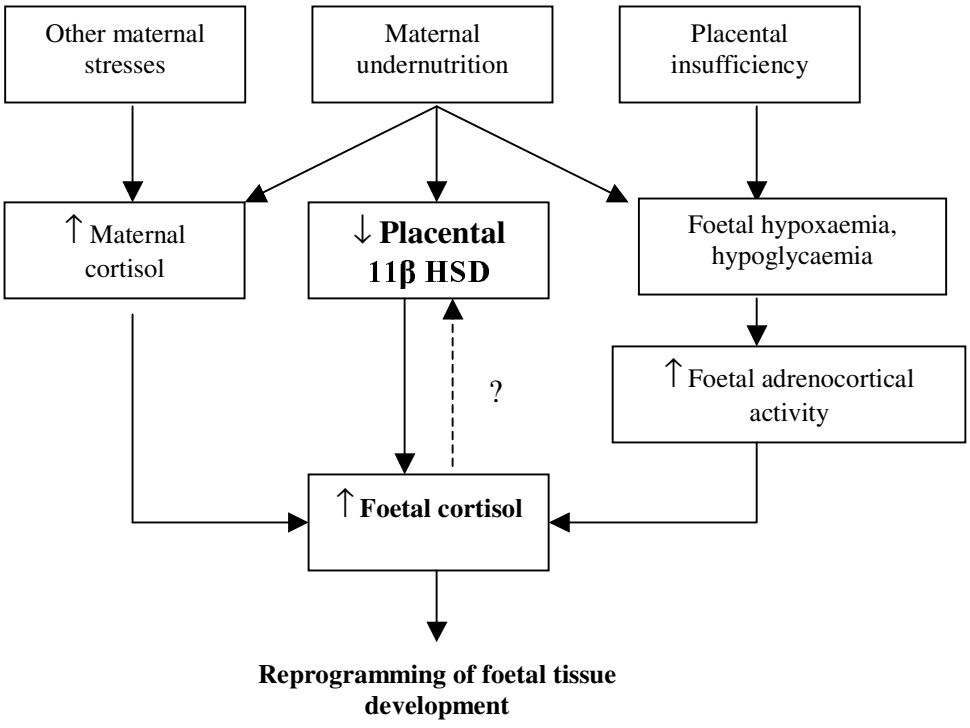

Figure 6 Schematic diagram showing how foetal plasma cortisol concentrations in sheep are increased by conditions associated with intrauterine growth retardation that are believed to exert effects on reprogramming of foetal tissue development (modified from Fowden *et al.* 1998). Reproduced with permission from Society for Reproduction and Fertility (Greenwood and Bell 2003).

and insulin tolerance at one, three, and six months of age were unimpaired in twin lambs that were ~20% lighter than their co–twins at birth (Clarke *et al.* 2000). However, in this study the growth penalty may have been insufficient to elicit an effect because even the lighter twins were relatively large (~4 kg) at birth. The persistent relative hyperinsulinaemia of more severely growth–retarded lambs during growth to 20 kg (Table 2; Greenwood *et al.* 2002a) is suggestive 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 foetuses also could influence the development of insulin resistance in the liver and peripheral tissues, with implications for postnatal metabolic health (Figure 6). Circulating concentration of cortisol was increased in the placentally restricted sheep foetus during late gestation (Phillips *et al.* 1996). Also, hepatic exposure may be increased locally by up–regulation of the liver's capacity to convert cortisone to cortisol, consistent with the observation of increased expression of 11βHSD1 in liver of placentally retarded foetuses (McMillen *et al.* 2000). In the only published study on postnatal consequences of foetal overexposure to cortisol in sheep, treatment of foetal lambs 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 (HPA) axis at 12 months but not 6 months of age, in ways that varied according to the timing of prenatal glucocorticoid treatment, and whether it was administered to dam or foetus (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 foetal programming can involve long–term sequelae to changes in the early prenatal environment that do not necessarily cause changes in foetal gross morphology (Morley *et al.* 2002). For example, modest undernutrition of ewes during the first half of pregnancy had no effect on growth of lambs during foetal 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 adrenals, kidney, liver, lungs, and perirenal adipose tissue of the foetus at term (~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 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 foetal responses were evident as early as 77 days of gestation. However, no effects on the insulin or glucose response to a glucose challenge were evident in offspring at 8 months of age following nutrition of ewes at a level that reduced body condition during early– to mid–pregnancy compared to lambs born to ewes that maintained body condition during the same period (Cronje and Adams 2002). Birth weights of these groups of lambs did not differ (mean 5.7 kg), but lower basal glucose concentration of lambs from the undernourished ewes was evident, which resulted in a smaller glucose response to an insulin challenge.

A central role for corticosteroids in the mediation of foetal programming was further implicated by the remarkable finding that exposure of ewes to high levels of dexamethasone for only two 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). Further details of the consequences of foetal exposure to endogenous and exogenous glucocorticoids in humans and experimental animals are provided by Bertram and Hanson (2002).

Recent studies have attempted to further elucidate the potential role of nutrition during the periconceptual period and early gestation in programming the hypathalamo–pituitary adrenal axis and the cardiovascular system in sheep. Mean arterial blood pressure and plasma ACTH concentrations were elevated during late pregnancy following restricted periconceptual nutrition, while the cortisol response to corticotropin releasing hormone was greater in twin foetuses compared to singletons and there was a positive correlation between blood pressure and plasma ACTH concentration (Edwards and McMillan 2002a,b). Development of corticotrophic cells in the foetal pituitary were also shown to be altered as a result of the uterine environment during both early and late pregnancy in carunclectomized ewes (Butler *et al*. 2002).

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 thermoregulatory and nutritional challenges soon after birth (Alexander 1974). Placental insufficiency and/or low maternal circulating metabolite concentrations during late gestation due to restricted nutrient intake coupled with inadequate body reserves result in reduced foetal growth and low birth

weight. Maternal nutrition during early to mid pregnancy appears to interact with maternal body reserves to influence the size of the placenta, while factors that affect the capacity to mobilise body tissues during late pregnancy also influence birth weight. 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 foetal life has grown out of landmark research on epidemiological associations between birth size and incidence of mature–onset diseases in humans (Barker 1998). Our own recent evidence also suggests that in growth retarded newborns, the early post–partum period may be important in determining longer–term compositional and metabolic characteristics (Greenwood and Bell 2003). In addition to its importance in agricultural production, the sheep offers an excellent biomedical model for investigation of the underlying mechanisms of foetal programming because of its amenability to experimental manipulation during foetal and postnatal life and its combination of a relatively long gestation period with rapid postnatal maturation. It is certain that such investigations also will 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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