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Placental transport of nutrients and its implications for fetal growth

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Placental growth during early and mid-pregnancy has a powerful, constraining influence on fetal growth during late pregnancy. Studies involving surgical and environmental reduction of placental size in sheep have shown an associated reduction in capacity to transport oxygen, glucose and amino acids. Oxygen transport is limited by placental blood flow but transport of glucose and amino acids is determined by the abundance and activity of specific transport proteins. Glucose transporters include the GLUT1 and GLUT3 isoforms previously identified in brain and other tissues; systems for active transport of amino acids have been inferred but not characterized. Placental metabolism of glucose and amino acids has major effects both on the quantity of carbon and nitrogen delivered to the fetus, and on the composition of substrates involved. For example, the uteroplacental tissues consume more than 60% of uterine glucose uptake during late pregnancy, and the placenta substantially modifies the pattern of amino acids delivered to fetal blood. The placenta also participates in the array of metabolic adaptations of maternal and conceptus tissues to altered maternal nutrient supply. Placental capacity for glucose transport in moderately undernourished ewes is upregulated, partly by increased expression of the GLUT3 transport protein. During more severe glucose deprivation, placental transfer and fetal uptake of glucose are constrained in proportion with maternal supply, leading to fetal growth retardation.

Introduction

The placenta is a unique organ of pregnancy of higher animals, including domestic ruminants. Its various, highly specialized functions include exchange of nutrients and excreta between mother and fetus, endocrine regulation of numerous pregnancy-specific physiological and metabolic adaptations in fetal and maternal tissues, and immunological protection of the conceptus from its maternal host. This review will address only the nutrient transport functions of the placenta.

Domestic ruminants, principally sheep, have provided most of the experimental evidence regarding placental nutrient transfer and the importance of placental influence on prenatal growth (Alexander, 1974; Battaglia and Meschia, 1988; Ferrell, 1989; Robinson *et al.*, 1995). Unless stated otherwise, examples in this review will be confined to studies on sheep, particularly those focussed on the integration of placental function and fetal response. Major themes include relations between placental growth and capacity for nutrient transport, and placental adaptations to changing fetal nutrient requirements during gestational development and altered maternal nutrition.

Placental Influences on Fetal Growth

Growth patterns of conceptus tissues

In ruminants as in most other mammals, the major phase of placental growth occurs during the first half of gestation, substantially preceding that of fetal growth during later gestation. In the

sheep, polycotyledonary, epitheliochorial placentation is fully established by about 30 days after conception, and the number of placentomes attached to each fetus is fixed at or soon after this time. Rapid hyperplastic growth then occurs until about day 55, before declining to minimal rates by mid-pregnancy at approximately 75 days (Ehrhardt and Bell, 1995). Placental mass (that is, total mass of placentomes) declines appreciably between mid-pregnancy and term, due to tissue dehydration, associated with loss of hyaluronic acid and related glycosaminoglycans, and extensive tissue remodelling. This pattern contrasts somewhat with that in cows, in which modest placental growth, confined to the maternal (caruncular) component, continues into the third trimester (A. W. Bell and R. A. Ehrhardt, unpublished).

Effect of placental size on fetal growth

During the latter half of pregnancy, positive correlations between fetal and placental weights become progressively stronger, such that within a few weeks of term, variation in placental weight accounts for more than 80% of variation in fetal weight (Stegeman, 1974). Such statistical associations have been used to imply, but do not necessarily prove, placental cause and fetal effect. Persuasive evidence that placental weight is indeed a powerful determinant of fetal growth during late gestation was first obtained by the deceptively elegant carunclectomy experiments of Alexander (see Alexander, 1974). In other studies, chronic heat stress, sufficient to cause persistent hyperthermia in pregnant ewes, caused a profound reduction of placental weight that was followed by fetal growth restriction (Alexander, 1974; Vatnick *et al.*, 1991; McCrabb *et al.*, 1993). Premating carunclectomy and maternal heat stress result in similar patterns of association between fetal and placental weights near term (Bell and Ehrhardt, 1998), suggesting that they may provide comparable models of placental insufficiency during late pregnancy.

Effects of maternal nutrition on placental growth are usually more variable and subtle than those caused by physical ablation or heat stress. Undernutrition of ewes during early and mid-pregnancy has caused conflicting positive (Faichney and White, 1987; McCrabb *et al.*, 1992) and negative (McCrabb *et al.*, 1992; Clarke *et al.*, 1998) effects on placental growth. Variation in body condition during early pregnancy may partly explain this confusion, in that fatter ewes are more likely to respond to underfeeding with a compensatory increase in placental growth, whereas the opposite occurs in lean ewes (Bell and Ehrhardt, 1998). In contrast, recent, novel studies have shown that overfeeding and rapid maternal growth of primiparous ewes during early–mid- pregnancy causes profound reductions in placental and fetal weights at term (Wallace *et al.*, 1996; Table 1). Early indications are that the fetal growth retardation in this model of adolescent pregnancy is a consequence of placental insufficiency that is due to a primary failure of cotyledonary growth (J. M. Wallace, personal communication).

Functional correlates of placental size

In both carunclectomized and heat-treated ewes, reduction in placental size is highly correlated with decreases in several important determinants and indices of placental transport, and with consequent changes in fetal metabolic characteristics during late gestation (see reviews by Bell, 1987; Owens *et al.*, 1989; Robinson *et al.*, 1995; Bell and Ehrhardt, 1998). These include reductions in uterine and umbilical blood flows, consistent with reduced placental clearance of highly diffusible, flow-limited materials such as antipyrine or ethanol, and metabolic consequences such as reduced placental oxygen uptake and transport, and development of fetal hypoxaemia.

Placental capacity for glucose transport also was reduced substantially, as were uteroplacental glucose consumption rate and fetal glycaemia in carunclectomized (Owens *et al.*, 1989) and heat-treated ewes (Bell, 1987; Thureen *et al.*, 1992). At least part of the absolute reduction in glucose transport capacity is presumed to be due to a reduction in exchange surface area of the trophoblastic membrane, as also shown in carunclectomized ewes (Robinson *et al.*, 1995). In previously heat-

Table 1. Fetal weight and placental variables at term in normally grown and rapidly grown adolescent ewes

Variable	Normally grown	Rapidly grown	Significance of difference (P)
Number of ewes	11	8	
Duration of gestation (days)	143 ± 0.3	140 ± 0.9	< 0.01
Fetal weight (kg)	4.34 ± 0.27	2.74 ± 0.25	< 0.001
Placental weight (g)	438 ± 44.6	263 ± 16.8	< 0.01
Number of placentomes	90 ± 7.5	74 ± 5.4	ns

Values are means ± SEM. ns: not significant
Data from Wallace *et al.* (1996)

treated (Thureen *et al.*, 1992), but not in carunclectomized (Owens *et al.*, 1989) ewes, placental weight-specific glucose transport capacity also was reduced. This implies that chronic heat stress, which reduces average weight but not total number of placentomes, additionally reduces number or activity of specific glucose transport proteins at maternal or fetal exchange surfaces. In contrast, carunclectomy, which reduces placentome number but may stimulate a compensatory increase in average weight of individual placentomes, caused a modest increase in the placental weight-specific clearance of the nonmetabolizable glucose analogue, 3-*O*-methyl glucose (Owens *et al.*, 1989). This implies that glucose transporter expression was preserved or increased in the remaining placentomes.

Placental insufficiency in heat-treated ewes also extends to impaired capacity for amino acid transport, including major reductions in placental uptake and fetal transfer of leucine, and in the normally extensive placental catabolism of this branched-chain amino acid (Ross *et al.*, 1996). The molecular basis for the reduction in placental weight-specific transfer of leucine, and perhaps, other essential amino acids, is unknown. Presumably there is decreased abundance of specific transporter proteins, especially those responsible for active transport and concentration of amino acids in trophoblast cells (Hay, 1998).

Conceptus Requirements and Placental Transport of Macronutrients

Glucose

Glucose is a principal energy substrate for fetal and placental metabolism in ruminants (Battaglia and Meschia, 1988; Ferrell, 1989; Bell, 1993). For example, in the well-nourished, late-pregnant ewe, glucose accounts for approximately 60% of the net uptake of carbon by the gravid uterus, as calculated from the data of Carver and Hay (1995) for non-nitrogenous substrates, and of Chung *et al.* (1998) for amino acids. Under these favourable conditions fetal glucose requirements are met entirely by placental transport and fetal uptake of glucose from the umbilical circulation. Oxidation of glucose, directly and via its fetoplacental metabolite, lactate, then accounts for about 60% of fetal ATP synthesis (see Hay, 1995).

Analysis of the kinetics of placental glucose transport *in vivo* has confirmed that in sheep and other species, this process is achieved by facilitated diffusion (see Hay, 1995). We have shown that the predominant glucose transporter protein isoforms in sheep placenta are GLUT1 and GLUT3, and that mRNA and protein abundance of these transporters, especially those of GLUT3, increase from mid- to late pregnancy (Ehrhardt and Bell, 1997; Table 2). This appears to account for much of the five-fold increase in glucose transport capacity of the ovine placenta *in vivo* over this period (Molina *et al.*, 1991). Our failure to detect placental expression of the insulin-responsive isoform, GLUT4, is entirely consistent with the lack of a direct effect of maternal or fetal insulinaemia on uteroplacental uptake and placental transport of glucose *in vivo* in the pregnant ewe (see Bell, 1993; Hay, 1995).

Table 2. Developmental changes in expression of GLUT 1 and GLUT 3 protein and RNA in the sheep placenta

Variable	Day of pregnancy		
	75	110	140
Protein abundance			
GLUT 1	1.0 ± 0.06^{a}	2.1 ± 0.19^{b}	2.4 ± 0.15^{b}
GLUT 3	1.0 ± 0.04^{a}	1.9 ± 0.09^{b}	2.9 ± 0.09^{c}
mRNA abundance			
GLUT 1	1.0 ± 0.07^{a}	1.6 ± 0.19^{b}	1.8 ± 0.21^{b}
GLUT 3	1.0 ± 0.05^{a}	2.3 ± 0.5^{b}	4.0 ± 0.17^{c}

Values are means ± SEM in arbitrary, densitometric units expressed relative to day 75 of pregnancy.
^{a,b,c} Values with different superscripts within rows are significantly different ($P < 0.05$).
Adapted from Ehrhardt and Bell (1997)

Other possible influences on placental glucose transport include uterine and umbilical blood flow and placental glucose metabolism. Consistent with its diffusion-limited transport mechanism, the placental delivery of glucose to the umbilical circulation is not responsive to physiological variations in uterine blood flow (Wilkening *et al.*, 1985).

Amino acids

Fetal requirements for amino acids are determined by rates of tissue growth and protein deposition that change with gestational age, and by fetal energy demands that result in extensive catabolism of amino acids throughout the latter half of gestation, even in well-nourished animals. Fractional rates of fetal tissue protein synthesis decline from approximately 25% per day at mid-gestation to < 10% per day near term (Kennaugh *et al.*, 1987), concomitant with a decline in fractional rate of protein deposition from 12% per day to approximately 4% per day (Van Veen *et al.*, 1987; Bell *et al.*, 1989). Throughout this period, the anabolic use of amino acids is accompanied by extensive oxidative deamination and fetal ureagenesis, sufficient to support 30–35% of fetal energy requirements (Faichney and White, 1987). Thus, placental transport of amino acid nitrogen into the umbilical circulation is considerably greater than that required for fetal synthetic purposes in sheep (Hay, 1998) and cows (Ferrell, 1989). The gestational decline in relative rates of umbilical uptake of amino acids (Bell *et al.*, 1989) is consistent with accompanying declines in fractional rates of fetal protein synthesis (Kennaugh *et al.*, 1987) and oxygen consumption (Bell *et al.*, 1987).

Most amino acids taken up by the placenta are transported against a fetal–maternal concentration gradient by energy-dependent mechanisms that have been elaborated in various mammalian tissues. These mechanisms, including identity and characterization of specific transporters, have not been studied in ruminant placentae. However, it is assumed that in ruminant as in human placental microvesicles, for example, there are at least ten sodium-dependent and sodium-independent transporter systems that have different levels of activity at different placental membrane surfaces. Hay (1998) has recently summarized the specific amino acids transported by each system, conditions favouring or inhibiting or affected by each system, and location (maternal or fetal trophoblast membrane) for each system.

Known mechanisms of placental amino acid transport imply diffusion-limited rather than flow-limited clearance, and, therefore, insulation against moderate fluctuations in placental blood flow. More severe restriction of placental perfusion, as can occur during exercise or acute heat stress (Bell, 1987), may indirectly affect amino acid transport through negative effects on placental energetics and ion gradients, as discussed by Hay (1998).

Fatty acids

Acetate and other derivatives of rumen fermentation, such as 3-hydroxybutyrate, are relatively abundant in maternal blood and are important energy sources for maternal tissues of ruminant animals (Bell, 1993). However, these short-chain fatty acids and keto acids are poorly transported by the ruminant placenta and make relatively minor contributions to fetal energy requirements in sheep and cattle (Battaglia and Meschia, 1988; Bell, 1993). The capacity for placental transport of long-chain, nonesterified fatty acids (NEFA), which are the primary vehicle for plasma delivery to other tissues of fatty acids mobilized from adipose tissue stores, is also extremely limited in sheep (Elphick *et al.*, 1979) and, presumably, other ruminants. Regarding the adequacy of fetal supplies of the C18 essential fatty acids, Noble *et al.* (1985) have identified active systems for desaturation and chain-elongation of linoleic and linolenic acids in the sheep placenta. In addition, the placenta takes up and metabolizes esterified lipids from maternal plasma (Hay, 1996), which, in ruminants, are richer than plasma NEFA in linoleic and linolenic acids. Thus, placental metabolism ensures an adequate fetal supply of the longer-chain ω6 and ω3 metabolites of the C18 polyunsaturated fatty acids, which are the forms ultimately required by tissues.

Impact of Placental Metabolism on Maternal–Fetal Nutrient Transfer

Oxygen consumption

The vital role of the placenta in transporting nutrients from the maternal to the fetal bloodstream, as well as functions such as peptide synthesis and maintenance of ion gradients, have a disproportionately high metabolic cost. This greatly affects the partitioning of nutrients within the gravid uterus, as well as adding substantially to the nutrient demands of pregnancy on the dam. In the late-pregnant ewe, the aggregate weight of placentomes is less than 15% that of the attached fetus. However, the weight-specific metabolic rate of the placenta is so great that the uteroplacental tissues (placentomes, endometrium, myometrium) consume 40–50% of oxygen taken up by the uterus in ewes (Bell and Ehrhardt, 1998) and cows (Ferrell, 1989). Estimates based on measurement of uteroplacental oxygen consumption *in vivo* and of placental oxygen consumption *in vitro* suggest that neither absolute nor dry weight-specific rates of placental energy expenditure change appreciably between mid- and late gestation (Vatnick and Bell, 1992). During mid-gestation, when fetal demands are small, much of this energy presumably is used to support active placental growth, whereas in late gestation the high rate of placental ATP synthesis must be related to functional demands.

Glucose metabolism

Uteroplacental consumption accounts for 60–70% of uterine net uptake of glucose during late pregnancy in ewes (Hay, 1995) and cows (Ferrell, 1989). Glucose uptake by the entire conceptus is determined directly by the maternal arterial glucose concentration, and glucose transport to the fetus is dependent directly on the maternal–fetal concentration gradient. The transplacental glucose concentration gradient, in turn, is directly related to both placental and fetal glucose consumption. Partitioning of the uterine glucose supply into placental and fetal rates of glucose consumption, however, is dependent on the fetal glucose concentration. For example, as fetal glucose concentration decreases relative to that of the mother, increasing the maternal–fetal gradient, glucose transport to the fetus increases at the expense of placental glucose consumption (Hay, 1995).

We have recently examined the metabolic fate of glucose consumed by the ovine placenta (Aldoretta *et al.*, 1994). Rapid metabolism to lactate (about 35%), fructose (about 4%), and CO_2 (about 17%) accounted for about 56% of uteroplacental glucose consumption in late-pregnant ewes with low or high maternal plasma glucose concentrations (Table 3). The metabolic fate of the remaining approximately 44% of glucose consumed is not known and requires investigation. Glucose oxidation accounted for 23–34% of uteroplacental oxygen consumption, depending on maternal glycaemia.

Table 3. Effect of glucose supply on uteroplacental glucose metabolism in ewes during late pregnancy

Variable	Glucose supply	
	Low	High
Plasma glucose concentration (mmol l^{-1})	2.23 ± 0.13	4.93 ± 0.29
Uteroplacental metabolic rates (mmol min^{-1})		
Glucose consumption	164 ± 22	313 ± 39
Lactate production	109 ± 12	182 ± 21
Fructose production	3.9 ± 1.1	7.0 ± 2.5
Glucose oxidation	26.7 ± 3.5	42.7 ± 7.5

Values are means ± SEM (n = 8).
Data from Aldoretta *et al.* (1994)

Oxidizable substrates that might contribute to the remaining 66–77% of uteroplacental respiration include ketones (Carver and Hay, 1995) and acetate, at least in caruncular tissues (Bell, 1993), certain amino acids, and carbon derived from the turnover of carbohydrate and lipid stores in placental tissues. The significance of placental synthesis of lactate and fructose for fetal metabolism is reviewed elsewhere (Battaglia and Meschia, 1988; Bell, 1993; Hay, 1995). In short, umbilical uptake and fetal oxidation of these glucose-derived substrates are estimated to contribute up to 20% of fetal energy requirements, additional to the 40–50% contributed by the direct oxidation of glucose.

Amino acid metabolism

Placental metabolism substantially affects both the quantity and composition of amino acids delivered to umbilical venous blood. The turnover rate of placental constitutive proteins is very rapid but net deposition of protein is negligible during the latter half of ovine pregnancy when placental dry weight is essentially static (Ehrhardt and Bell, 1995). Nevertheless, net consumption by uteroplacental tissues of glutamate, serine, and the branched chain amino acids is appreciable (Liechty *et al.*, 1991; Chung *et al.*, 1998), implying significant catabolism or transamination of these acids. An additional, small fraction of this net loss of amino acids will be in the form of secreted peptides. Placental net catabolism was estimated recently to account for 24% of uterine uptake of amino acid nitrogen in well-fed, late-pregnant ewes (Chung *et al.*, 1998).

The ovine placenta has very little enzymatic capacity for urea synthesis but produces considerable amounts of ammonia, much of which is released into maternal and, to a lesser extent, fetal circulations (see Hay, 1998). This is consistent with reports of extensive placental deamination of branched chain amino acids to their respective keto acids, which are released into fetal and maternal bloodstreams (Smeaton *et al.*, 1989; Loy *et al.*, 1990), and with rapid rates of glutamate oxidation in the placenta (Moores *et al.*, 1994). Transamination of branched chain amino acids accounts for some of the net glutamate acquisition by the placenta, the remainder of which is taken up from the umbilical circulation (Moores *et al.*, 1994). That which is not quickly oxidized combines with ammonia to synthesize glutamine, which is then released back into the umbilical bloodstream (Chung *et al.*, 1998). Some of this glutamine is converted back to glutamate by the fetal liver, which produces most of the glutamate consumed by the placenta (Vaughn *et al.*, 1995). This establishes a glutamate–glutamine shuttle which promotes placental oxidation of glutamate and fetal hepatic utilization of the amide group of glutamine.

Another example of the influence of placental metabolism on the pattern of amino acids delivered to the fetus is the almost quantitative conversion of serine, mostly taken up from maternal blood, to glycine by the placenta (Chung *et al.*, 1998). This reconciles earlier observations of major discrepancies between negligible net uptake of glycine by the uterus and substantial net release of

Table 4. Maternal weight change, fetal weight, and indices of placental glucose transport at day 135 of pregnancy in ditocous ewes fed 100% (Fed) or 60% (Underfed) of predicted energy requirements for the preceding 14 days

Variable	Fed	Underfed	PSE	Significance of difference (*P*)
Δ maternal weight (kg)	5.3	−2.7	1.0	< 0.001
Fetal weight (kg)	3.58	3.46	0.16	ns
Plasma glucose (mmol l^{-1})				
Maternal	3.72	2.84	0.09	< 0.001
Fetal	0.57	0.49	0.03	< 0.05
Maternal–fetal gradient	3.15	2.33	0.03	< 0.001
Placental 3MG clearance (ml min^{-1} kg^{-1} placental weight)	117	176	7	< 0.001
CB sites (pmol mg^{-1} protein)	105	126	3	< 0.01
GLUT protein (arbitrary units)[a]				
GLUT 1	1.00	0.83	0.06	ns
GLUT 3	1.00	1.19	0.04	< 0.05

Values are means ($n = 5$).
PSE: pooled standard error; ns: not significant; 3MG: 3–*O*-methyl glucose; CB: cytochalasin B binding sites.
[a]Expresssed relative to Fed group.
Adapted from Ehrhardt (1997)

this amino acid into the umbilical circulation (see Hay, 1998). In addition to ensuring a supply of the most abundant amino acid in fetal blood, this process is important for placental purine synthesis via the donation of the side-chain β-carbon atom of serine to form methylenetetrahydrofolate.

Placental Adaptations to Altered Supplies of Energy and Nitrogen

Maternal nutrition is often uncertain and variable, especially in extensively managed ruminant herds and flocks, with potential effects on fetal nutrient supply, growth and well-being, particularly during late pregnancy. Domestic ruminants, like other mammals, have developed various adaptive mechanisms to ameliorate the direct impact on fetal growth and development of all but the most serious nutritional vagaries. Some of these involve altered responses of maternal tissues such as liver, adipose tissue, and muscle to insulin and, possibly, other regulatory hormones. The net result is substitution of NEFA for glucose as energy sources in maternal insulin-responsive tissues, and increased availability of glucose for insulin-independent uptake by the placenta (Bell, 1993; Bell and Bauman, 1997). Fetal metabolic adaptations become necessary when maternal and placental responses fail to maintain a fully adequate fetal glucose supply (Bell, 1993; Hay, 1996). These include induction of hepatic gluconeogenesis, increased reliance on amino acids as a primary energy source, and, inevitably, reduced rates of protein synthesis and growth.

Glucose transport and metabolism

We recently tested the idea that the placenta is more than a passive beneficiary of maternal metabolic adaptations designed to support fetal glucose uptake in the face of a fluctuating maternal energy supply. Various indices of placental glucose transport capacity were compared in well-fed and moderately undernourished, ditocous ewes during late pregnancy (Ehrhardt, 1997). Results are summarized in Table 4. Restriction of maternal energy intake to 60% of predicted requirements for 2 weeks caused moderate maternal and fetal hypoglycaemia and a 26% decrease in maternal–fetal

glucose concentration gradient. In these ewes, placental glucose transport capacity, assessed *in vivo* by measurement of clearance of the nonmetabolizable analogue, 3-O-methyl glucose, was increased 50% over values in well-fed ewes. Estimation of placental glucose transporter abundance *in vitro* by binding of cytochalasin B, and by the concentration of the GLUT3 transport protein as measured by Western blotting, were each increased by about 20%; concentration of the other major placental glucose transporter isoform, GLUT1, was unchanged. The effectiveness of these adaptations was indicated by unimpaired fetal growth in the underfed ewes (Table 4).

During more severe maternal undernutrition or starvation for several days, the ability to repartition maternal glucose in favour of the conceptus becomes limited and uterine and umbilical net uptake of glucose dwindle directly with the decline in maternal glucose supply (Bell, 1993; Hay, 1995). Under these conditions, the development of profound fetal hypoglycaemia helps to sustain the maternal–fetal gradient in glucose concentration by restricting the reverse transfer of glucose to the placenta, and reducing placental glucose consumption (Hay, 1995). More specific manipulation of maternal and fetal glycaemia by prolonged maternal infusion with insulin has shown that the decline in fetal glucose concentration is not proportional to that of the mother. This tends to decrease the maternal–fetal glucose concentration gradient, protecting placental glucose consumption at the expense of the fetus. In response, fetal glucose needs are diminished by a reduction in fetal growth rate (Carver and Hay, 1995).

Amino acid transport and metabolism

Fasting ewes for 5 days during late pregnancy had relatively little effect on placental delivery of amino acids to the fetus despite significant reductions in maternal plasma concentrations of many amino acids (Lemons and Schreiner, 1983). This suggests that during short term energy or protein deprivation, placental mechanisms for active transport of amino acids are unimpaired and may even be upregulated. Under similar fasting conditions, the uteroplacental deamination of branched chain amino acids appeared to be increased, as judged from a threefold increase of the efflux of α-ketoisocaproate into uterine and umbilical circulations (Liechty *et al.*, 1991). This finding suggests that increased protein catabolism and amino acid oxidation may partly substitute for the likely reduction in placental glucose oxidation under these conditions.

Placental responses to more prolonged restriction of energy or protein have not been investigated. However, in ewes fed adequate energy but insufficient protein during the last month of pregnancy, fetal growth and protein deposition over this period were reduced by 18% (McNeill *et al.*, 1997). This finding implies that neither maternal mobilization of labile protein stores nor putative adaptations in placental capacity for amino acid transport were sufficient to offset a 50% reduction in maternal supply of absorbed amino acids.

Conclusions

In healthy, well-managed ruminants, the placenta exerts an appropriate constraint on fetal growth during late gestation. When environmental factors, including maternal nutrition, retard placental development, associated reductions in nutrient transport capacity can lead to fetal growth retardation. Normal regulation and environmental modulation of early placental growth appear to be critically important in this regard, but are poorly understood. Recent observations of placental stunting in overfed adolescent ewes (Wallace *et al.*, 1996) offer an intriguing model for further study. The specific aspect(s) of placental nutrient transport that are normally most limiting have not been conclusively defined. However, it is revealing that even in very well-fed, monotocous ewes, direct fetal infusion with glucose during the last month of gestation caused an 18% increase in birth weight of lambs (Stevens *et al.*, 1990). Identification of the specific proteins responsible for placental glucose transport, together with early evidence for their molecular regulation, offer possibilities for more fundamental studies of gene expression. The complexity of placental transport systems for amino

acids has so far defied detailed investigation in ruminants. The unique importance of amino acids as substrates for both fetal growth and oxidative metabolism demands serious study of the means by which their placental transfer is regulated.

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