Amino acids have multiple functions in fetoplacental development. The supply of amino acids to the fetus involves active transport across and metabolism within the trophoblast. Transport occurs through various amino acid transport systems located on both the maternal and fetal facing membranes, many of which have now been documented to be present in rat, sheep and human placentas. The capacity of the placenta to supply amino acids to the fetus develops during pregnancy through alterations in such factors as surface area and specific time-dependent transport system expression. In intrauterine growth restriction (IUGR), placental surface area and amino acid uptakes are decreased in human and experimental animal models. In an ovine model of IUGR, produced by hyperthermia-induced placental insufficiency (PI-IUGR), umbilical oxygen and essential amino acid uptake rates are significantly reduced in the most severe cases in concert with decreased fetal growth. These changes indicate that severe IUGR is likely associated with a shift in amino acid transport capacity and metabolic pathways within the fetoplacental unit. After transport across the trophoblast in normal conditions, amino acids are actively incorporated into tissue proteins or oxidized. In the sheep IUGR fetus, however, which is hypoxic, hypoglycemic and hypoinsulinemic, there appear to be net effluxes of amino acids from the liver and skeletal muscle, suggesting changes in amino acid metabolism. Potential changes may be occurring in the insulin/IGF-I signaling pathway that includes decreased production and/or activation of specific signaling proteins leading to a reduced protein synthesis in fetal tissues. Such observations in the placental insufficiency model of IUGR indicate that the combination of decreased fetoplacental amino acid uptake and disrupted insulin/IGF signaling in liver and muscle account for decreased fetal growth in IUGR.

**Keywords:** Amino acid; Placenta; Fetus; IUGR; Oxygen; Insulin; mTOR

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**INTRODUCTION**

Amino acids and glucose constitute the carbon and nitrogen requirements for the placenta and fetus. Recently, a greater understanding of the fetal supply and metabolism of amino acids by the placenta during pregnancy has led to the concept that amino acids act as regulators of placental and fetal development. In addition to being a source of protein building blocks and oxidative fuel sources, amino acids influence metabolic cycling pathways between the placenta and fetus. They also act directly to regulate protein synthesis in various fetal and placental tissues through interactions with the insulin and IGF growth-promoting axis via regulation of the amount and/or activity of a key signal transduction protein, mammalian target of rapamycin (mTOR). This review deals with aspects of human and animal placental amino acid transport, fetal utilization of amino acids, and aspects of the fetal sheep insulin/IGF-I signaling pathway during normal pregnancy. Additionally, we discuss changes in these aspects as they occur in a sheep model of fetal growth restriction, and where possible compare them with human as well as other animal models of IUGR.

**AMINO ACID TRANSPORT ACROSS THE PLACENTA**

In recent years, both in vivo and in vitro studies have highlighted the complex characteristics of placental amino acid transport and metabolism (see reviews, [1–4]). Unlike an organ such as the liver, the placenta must carry out its own metabolic functions while also operating as an organ of transport, delivering amino acids from the maternal circulation into the fetoplacental unit. The concentrations of most amino
acids, particularly some of the essential amino acids, are higher in fetal than maternal plasma (noted in rat, sheep and human pregnancies [5–9]), consistent with active transport of amino acids across the placenta. An increased fetal-to-maternal ratio of plasma amino acid concentrations has been documented for many species, and although the fetal/maternal concentration ratio is greater than 1.0 for most amino acids measured, there are quantitative differences among species, as reviewed [4].

The active in vivo transport of amino acids across the trophoblast involves three fundamental steps: (1) uptake from the maternal circulation across the microvillous membrane; (2) transport through the trophoblast cytoplasm; and (3) transport out of the trophoblast across the basal membrane into the umbilical circulation. This transport is regulated through transporter protein systems on both membranes of the trophoblast. Several mammalian amino acid transport systems have been characterized over the years by such general properties as ion-dependence, transport kinetics, substrate specificity, light chain and heavy chain interactions (monomeric or heterodimeric systems), and regulation of activity, which has allowed the description of multiple transport systems for neutral, anionic, and cationic amino acids [3,10–13]. Specific studies in the human and rat trophoblast have yielded more specific information concerning the location, direction of flux, and functioning of amino acid systems in the placenta (see reviews, [2,4]). Figure 1 represents a summary of selected trophoblast amino acid transport system activity location, for these two species, together with information detailing the related cDNA. In addition to the wide number of systems found to exist on the placental membranes, it is interesting to note that while each system is distinct in its operational requirements, many systems exhibit overlapping substrate specificity. Several of these systems are under investigation in the sheep placenta (GenBank Accession number: LAT-1, AY162432; LAT-2, AY162433; EAAT-1, AY157709; EAAT-2, AY157710; EAAT-3, AY157711) including examination of changes in their expression and transport capacity in IUGR and normal control conditions.

System substrates

Neutral AA
ALA, SER, PRO, GLN, MeAIB, AIB
ALA, SER, CYS, Anionic AA
NEUTRAL AA, BCH
NEUTRAL AA, LYS, ARG, LEU
LEU, ILE, VAL, TRYP, PHE, MET, TYR, GLN, BCH
Cationic AA
Cationic AA
Anionic AA
GLU, ASP
TAU

Heavy (4F2hc or rBAT) and light chain associations

ATA-1, -2 and -3 (SNAT-1, -2 and -4) [21, 116-122]
ASC [56, 118, 119, 123-125]
B₀ [126-129]
₇⁻⁺ rBAT/bo⁺ [23, 130-132]
4F2hc/LAT-1 and 4F2hc/LAT-2 [133-137]
4F2hc/ yLAT-1 and 4F2hc/ yLAT -2 [23, 55, 131, 138-142]
CAT-1, -2B and -4 [22, 23, 138, 139, 143, 144, 145]
EAAT-1, -2 and -3 [146-150]
TAUT [122, 151-153]

Figure 1. Schematic representation of selected sodium-dependent (●) and sodium-independent (○) amino acid transport system activity location for both the apical (maternal) and basal (fetal) facing membranes. Amino acid substrates and the heavy and light chain proteins interactions for each of these placental-specific systems are listed. References for each system’s trophoblast activity location and heavy and light chain interactions are also provided. Notes: substrates in bold represent essential amino acids; MeAIB, methylaminoisobutyric acid; AIB, α-aminoisobutyric acid; BCH, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid.
PLACENTAL AMINO ACID TRANSPORT CAPACITY

An important aspect of placental transport capacity relates to the total placental surface area across which transport can occur. As pregnancy advances, the increasing nutrient demands of the developing conceptus must be met through an appropriate increase in placental nutrient transport capacity. This enhanced performance is facilitated through alterations in placental perfusion and changes in membrane exchange surface area size and function. Fetal weight increases approximately 20-fold between weeks 16 and 40 (term) of gestation in the human, whereas the peripheral villous surface area increases only ninefold [14–17]. Thus, the increased microvillous density on trophoblast cells alone cannot explain the exponential fetal growth occurring over this time period, indicating that fetal growth is supported not only by changes in villous surface area, but rather by the overall change in total exchange capacity. The makeup of this capacity includes the concentration and affinity characteristics of specific amino acid carrier proteins on the cell membrane surface and circulating amino acid concentrations.

Accompanying the maturational changes in trophoblast surface area, the capacities of the amino acid transport systems change with differing expression and transport parameters throughout gestation [18–23]. For example, in the human first-trimester microvillous membrane has increased transport activity compared to term placental vesicles [20], and the protein concentration of the heavy chain, 4F2hc (CD98), which is associated with heterodimeric transport systems, differ between early/mid pregnancy and term placenta [19,23]. Also of interest is that in early gestation, the $K_m$ of the microvillous high affinity System $y^+$L is significantly less than in term preparations [23]. It is also observed that the same amino acid may be transported through different systems, depending upon which membrane is being crossed. In term placenta, t-arginine transport in microvillous membrane preparations is believed to occur through both $y^+$ and $y^+L$ systems, while in the fetal facing basal membrane, transport may be restricted to the $y^+L$ system [23]. Such studies highlight the complex interactions that occur between developing microvillous membrane and basal membrane, within the trophoblast and between the two circulations, to facilitate an increase in nutrient delivery to the growing fetus as gestation advances.

Circulating maternal amino acid concentrations also play a major role in influencing placental amino acid transport capacity and ultimately determining fetal supply of amino acids. In sheep studies, the simultaneous flux from maternal to fetal circulations has been studied for the essential amino acids [24–26]. These recent studies demonstrate striking differences for rates of placental clearance of the essential amino acids where clearance is most rapid for valine, leucine, isoleucine, phenylalanine, and methionine, with differences in their transplacental flux directly attributable to the differences in their concentrations in maternal plasma [25]. This observation among several amino acids studied simultaneously is supported by experiments in which the concentration of individual amino acids is increased in the maternal circulation by infusion, showing that net umbilical uptake of the amino acid increases directly with its maternal plasma concentration. This has been shown for alanine, leucine, lysine, threonine, and glycine [27–31]. However, because of competitive inhibition among multiple amino acids for common transporters, when a large number of amino acids are given to the mother simultaneously, the umbilical uptake of some amino acids increases, but not that of all amino acids [25,26,32]. These observations have direct clinical relevance, as trials of infusions of mixed amino acid solutions into pregnant women to improve amino acid supply to the fetus might produce an imbalance in the actual uptake of amino acids by the fetus, not necessarily a potentially good therapeutic result. Such studies also have shown that placental transport of a given amino acid is a function of its concentration in the maternal plasma and the concentration of inhibitory amino acids, and such relationships are different for each amino acid. Studies in human normal and IUGR pregnancies show similar relationships among maternal plasma concentrations of amino acids and net placental transport to the fetus [33,34].

AMINO ACID TRANSPORT IN ANIMAL MODELS OF PLACENTAL INSUFFICIENCY – IUGR AND HUMAN IUGR

Human placental insufficiency is difficult to study, for ethical and practical reasons, and is frequently limited to studies at term. Thus, the mechanisms responsible for placental insufficiency and IUGR can be best investigated in animal models. Several laboratories have used the pregnant sheep to study early placental growth and development [35,36], and placental—fetal physiological interactions [37–42]. Growth restriction in fetal sheep can be induced by nutritional restriction, placental infarction with microspheres, reduction of placental implantation sites, uterine or umbilical artery clamping or ligation, and exposure of the pregnant ewe to elevated ambient temperatures (hyperthermia model; [35,41,43–45]). The maternal hyperthermia model involves prolonged increases in maternal core body temperature ($\sim 0.6–0.8\, ^\circ\text{C}$ increase; [46]). It is a naturally occurring condition common to sheep that live in warm climates that have a “spring” estrus and carry the pregnancy through the hotter summer months. This model produces placental insufficiency (PI) resulting in IUGR that shares many of the commonly measured characteristics of human IUGR that results from placental insufficiency [47,48], in contrast to mechanical models of placental growth inhibition that usually are imposed late in gestation and involve either surgical reductions in placental size or relatively severe reductions in uterine and/or umbilical blood flow, none of which are characteristic of the common form of human placental growth restriction and nutrient transport insufficiency. Since the early 1980s, our efforts have focused on validating the maternal...
In the hyperthermia-induced IUGR model (PI-IUGR), reduction in fetal oxygenation ranges from mild to severe, with similar variable reductions in placental and fetal weights. In the more severe cases, net umbilical oxygen uptake rate (UO₂, μmol/min/kg fetus) and the ratio between oxygen uptake and the transplacental arterial PaO₂ gradient (UO₂/ΔPO₂, μmol/min/100 g placenta/mmHg) are both significantly reduced (Regnault et al., Unpublished data). The reduced UO₂/ΔPO₂ ratio specifically defines a decreased placental oxygen diffusion capacity. More recent studies examining severe IUGR fetuses have defined a significant relationship between placental weight and the increasing transplacental PaO₂ gradient (Figure 2). In these IUGR fetus the UO₂/ΔPO₂ ratio is reduced by almost 35%. Such observations indicate that the IUGR trophoblast, in this model, has developed reductions in possibly two of the primary factors associated with diffusing capacity, permeability and surface area, and therefore a reduced placental functional capacity. Furthermore, another experimental model of IUGR supports this observation. In transgenic mice with a deletion of the placental-specific transcript (P0) of the Igf2 gene, placental surface area is reduced and placental thickness increased, significantly reducing the theoretical diffusing capacity of these placentae [50,51]. It is interesting to note that in studies specifically concerned with abnormal placental development near term in human IUGR, there is a reduction in inter-microvillous space and absolute value for microvillous and total trophoblastic surface area [52–54], supportive also of a reduced placental functional capacity.

Actual absolute placental amino acid transport is reduced in cases of placental and fetal growth restriction. Reduced uptake of leucine and lysine in vesicles prepared from human IUGR placentae has been described and indicates decreased transporter concentrations and/or activity for neutral and cationic amino acids [55]. Also, in the maternal dietary protein deprivation model of IUGR in the rat, there appears to be a down regulation of placental amino acid transport in systems A, y⁺ and XₐG [56,57]. In the PI-IUGR model there is a reduction of maternal leucine flux into the placenta and into the fetus. In contrast to these changes in placental leucine flux, the uteroplacental oxygen and glucose consumption rates are similar to control animals on a per gram basis, indicating that the decrease in leucine metabolism is not a result of reduced placental metabolic rate [29]. The reduction of leucine flux into the placenta is believed to be the result of a deficiency in the number and/or activity of amino acid transporters in the IUGR placenta. Both fetal leucine concentration and the flux of leucine from the fetus back to the placenta are reduced, and fetal oxidation of leucine is decreased [29]. These findings are similar to those reported to occur in human IUGR [58,59]. Specifically, the fetal/maternal ratio of leucine has been correlated with the severity of growth restriction, and as in sheep IUGR studies, demonstrates a decreased transplacental leucine flux and/or increased protein breakdown within the IUGR fetoplacental compartments [58]. More recent studies in the PI-IUGR sheep model have highlighted other specific defects in the placental neutral and anionic amino acid transport systems [49,60].

Earlier studies in humans showed reduced concentrations of essential amino acids such as leucine and lysine in growth-restricted fetuses [61–63], indicating possible alterations in placental amino acid transporter systems. Recently, however, in situations of well-defined IUGR, but with significantly lower than normal umbilical venous oxygen saturation, oxygen content, and pH, umbilical venous concentrations of leucine and phenylalanine were not significantly different from the AGA pregnancies [59]. Interestingly in the sheep model of placental insufficiency induced IUGR, we also observe that while there are significant reductions in the placental flux of the essential amino acids leucine and threonine [27,29], amino acid concentrations are not necessarily different from normal concentrations. For example in the earlier leucine flux studies, fetal arterial leucine concentration was significantly reduced (~30%) [29], while in later studies, concentrations of threonine were not significantly different between the two study groups [27], yet in both studies, significant reductions in specific amino acid flux per unit placenta were observed. Furthermore, in past and current studies of severely hypoxic and hypoglycemic sheep fetuses in which umbilical uptake of the essential amino acids is significantly reduced, fetal essential amino acid concentrations are unaltered compared to control animals [64–67], similar to observations in humans and guinea pigs [68–70]. It is possible that in the presence of relatively more hypoxic and hypoglycemic conditions, a hypometabolic state within the IUGR fetus contributes to the maintenance of essential amino acid concentrations, despite reduced umbilical uptakes.

![Figure 2](image-url) Relationship between transplacental oxygen gradient (uterine venous PO₂ less umbilical venous PO₂, mmHg) and placental weight (g) in control (●) and IUGR (○) animals near term at 135 days gestational age.
these observations of highly variable differences in fetal amino acid concentrations among conditions and models, both human and animal studies emphasize that placental amino acid transport is reduced in cases of placental growth restriction. This reduction is likely a combination of many factors including changes in trophoblast exchange capacity as well as uteroplacental oxygenation and fetoplacental metabolism.

**FETAL HEPATIC AND SKELETAL MUSCLE UTILIZATION OF AMINO ACIDS**

During normal fetal development there is no appreciable rate of fetal hepatic gluconeogenesis. Fetal hepatic glucose production would be counterproductive since an increased glucose concentration would reduce the transplacental glucose gradient, leading to decreased umbilical glucose uptake from the mother [71,72]. Although gluconeogenesis in the adult liver consumes amino acids, there is no measurable fetal gluconeogenesis, despite the higher concentration of amino acids in the fetal rather than the maternal circulations. However, there is in fact a high rate of hepatic uptake of all of the essential and most of the nonessential amino acids by both lobes of the fetal liver [7,73], including all of the gluconeogenic amino acids. In fetal life, the carbon from these amino acids is released primarily as glutamate and pyruvate with a smaller contribution coming from the hepatic release of serine, ornithine, and aspartate [7,74–76], in contrast to postnatal life, where the carbon from these amino acids is released from the liver solely as glucose. Studies concerned with hepatic function in the model of PI-IUGR are currently being conducted. However, it is interesting to note that in the situation of experimentally elevated fetal dexamethasone levels, analogous to elevated cortisol concentrations as in other models of IUGR, hepatic glutamine and alanine uptakes and hepatic glutamate output are reduced [77]. This might suggest that in the hypoxic, hypoglycemic IUGR fetus, hepatic glutamine and alanine uptakes may also be reduced.

Under normal physiologic conditions, the hind limb conditions of a growing ovine fetus shows net uptake of both essential and nonessential amino acids from the fetal circulation, presumably contributing to the relatively high nitrogen accretion rate of the fetus [78]. The fetal hind limb also has no net release of alanine [73], in contrast to the adult hind limb that displays a large output of alanine and glutamine [79]. The normal ovine fetal hind limb also consumes the two amino acids that are not supplied by the placenta: glutamate and serine, which are produced from the fetal liver in amounts that could account for the combined uptake of glutamate by both placenta and hind limb [75,76,78,80]. With reduced placental supply of glucose to the growth-restricted fetus, there is likely an increased efflux of the gluconeogenic amino acids, glutamine and alanine, and the Branched Chain Amino Acids (BCAA) from the fetal hind limb, possibly from increased rates of protein breakdown, as has been demonstrated to occur in fetal hypoglycemic studies [65,66,81].

**CHANGES IN INSULIN, IGF-I AND AMINO ACID REGULATION OF THE INSULIN/IGF-I SIGNALING PATHWAY IN IUGR**

In the hyperthermia-induced ovine model of placental insufficiency, the fetuses are hypoxic, hypoglycemic [41,42], and hypoinsulinemic and have reduced circulating IGF-I concentrations (Regnault et al., unpublished data). Importantly, with respect to the growth-restricted fetus, insulin and, to a lesser extent, the IGFs activate protein synthesis via the PI 3-kinase/Akt/mTOR/p70S6k/4E-BP-1/eIF4E signaling pathway, as illustrated schematically in Figure 3. Recent, studies have established the initiation phase of mRNA translation as a pivotal site of regulation for global rates of protein synthesis, as well as a site through which the synthesis of specific proteins is controlled [82]. Activation of the insulin and IGF-1 receptor triggers docking of the insulin receptor substrate-1 (muscle),
Mammalian target of rapamycin appears to be a key regulator of cell growth by sensing upstream nutrient and hormonal signals to coordinate gene activation, protein synthesis, and cell growth [83,86]. Mammalian target of rapamycin is a serine/threonine kinase that phosphorylates and thereby coordinates the function of the translational suppressor-eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) and the 70 kDa small ribosomal subunit kinase (p70S6k) [87]. Under conditions of substrate sufficiency (amino acids and glucose) and hormonal stimulation, mTOR phosphorylates the 4E-BP1 repressor on several sites, triggering its dissociation from the inactive 4E-BP-1-eIF4E complex [88,89], thus making eIF4E available for binding to eIF4G. The eIF4E binds to the mRNA cap structure present at the 5'-end of all nuclear transcribed mRNAs to form an eIF4E-methionyl-tRNAi complex. The eIF4E-mRNA complex binds to eIF4G and eIF4A, forming the active eIF4F complex, thereby allowing translation to proceed.

Similar to human IUGR, the ovine model of IUGR also displays decreased fetal insulin and IGF-I circulating concentrations (Regnault et al., unpublished data). In association with this, in the ovine IUGR, there appears to be up regulation of the proximal signals for insulin action involved in control of glucose metabolism (Regnault et al., unpublished data). This up regulation includes an increase of the insulin receptor and a suppression of glycogen synthase kinase-3-β, which normally suppresses glycogen synthesis. Insulin normally inactivates GSK-3b, which thereby dephosphorylates glycogen synthase (GS), leading to the activation of GS [90,91]. Low levels of GSK-3b would therefore tend to favor GS activity and consequently an elevation in glycogen formation. In preliminary studies in our laboratory, fetal hepatic glycogen concentrations in IUGR are indeed elevated, which is similar to what has been previously observed in hyperthermic exposed fetuses [92]. This elevation could be due to a higher GS activity, and/or possibly less glycogen phosphorylase. Interestingly, while there is an up regulation at the proximal end of the insulin signaling pathway, we have observed a concomitant decrease in protein expression more distally in the insulin signaling cascade leading to protein translation. Initiation factor eIF4E is significantly reduced by 63% in IUGR livers, while the translational repressor 4E-BP1 is significantly increased, 2.5-fold (Regnault et al., unpublished data). The significant increase in the downstream translational repressor 4E-BP1, combined with a decrease in the limited amount of eIF4E may be a key mechanism limiting protein translation in IUGR livers.

There also appears to be an increase in proximal insulin signaling in muscle despite reduced insulin/IGF-I concentrations in growth-restricted ovine fetuses. Insulin receptor protein in skeletal muscle is increased 77%, while there is a 36% decrease in the amount of the p85α subunit of PI 3-kinase skeletal muscle from the IUGR fetuses (Regnault et al., unpublished data). It has recently been demonstrated that reduced expression of the murine p85α subunit of PI 3-kinase in heterozygous knockout mice actually improves insulin signaling and ameliorates diabetes, indicating that p85α expression is negatively correlated with insulin sensitivity [93,94]. The mechanism for this effect involves enhanced coupling between the p85α and p110 subunits and increased PI 3-kinase production in mice in vivo. These changes in insulin receptor and p85α may therefore be compensatory responses to low insulin concentrations and/or simultaneous hypoglycemia, and could favor increased responsiveness to insulin to facilitate increased glucose uptake.

In contrast to the liver, the levels of 4E-BP1 and eIF4E examined in fetal skeletal muscle from IUGR animals are unchanged, indicating that fetal growth restriction may have tissue-specific effects on mechanisms for reduced organ growth. However, mTOR was reduced significantly by 38% in hind limb skeletal muscle from IUGR fetuses (Regnault et al., unpublished data). A decrease in mTOR expression potentially has multiple downstream consequences that could lead to a decrease in fetal growth. The mTOR-dependent p70S6K and 4E-BP1/eIF4E pathways are activated independently during muscle growth in vivo [84,95] and these pathways cooperate with each other to promote cell growth and increased cell size. mTOR also coordinates the cellular responses to extracellular nutrient concentrations by modulating nutrient transporter gene expression [85,89,96,97]. The reasons for the reduced mTOR in muscle cells from growth-restricted fetuses are not known. Amino acids, particularly the BCAA, leucine, stimulate mTOR in a number of tissues in the adult [88,98–100], and reduced levels of mTOR may be associated with reduced intracellular amino acid concentrations. As previously mentioned, under hypoxic conditions amino acids leave the cell, including the BCAAs from the fetal muscle [70], which is the only site of BCAA utilization besides the placenta [101,102], and this associated change in mTOR may potentially represent a direct site of protein synthesis control in the growth-restricted fetus. Other factors that impact mTOR signaling include reduced cellular energy (ATP/AMPK levels) [103–105], and DNA damage through changes in the transcription factor p53 [106,107]. The transcription factor p53 is an important regulator of cell cycle progression and apoptosis and has been associated with apoptosis in IUGR fetuses [108–111]. It negatively regulates the expression of Bcl-2 and up regulates Bax expression [112,113], and these two cell transcription factors play major roles in activating the caspase–3 pathway which is necessary for the chromatin condensation and DNA fragmentation that characterize apoptosis [114].

mTOR is also directly regulated by decreased oxygen partial pressure [115]. The reversible inhibition of protein synthesis by hypoxia is thought to be an important aspect of energy...
conservation in an oxygen deficient environment. Arterial PO₂ in growth-restricted fetuses may be as low as 12 mmHg (~2% oxygen), which is similar to the oxygen partial pressures in cell culture conditions in which reduced oxygen levels have been suggested to initiate cellular energy conservation strategies, including the hypophosphorylation of mTOR, independent of other commonly associated hypoxia changes, such as ATP levels, HIF-1 and Akt/protein kinase B and AMP-activated protein kinase phosphorylation [115].

CONCLUSIONS

In severe cases of placental and fetal growth restriction, particularly as shown in a well established ovine model of IUGR with placental insufficiency, the increased transplacental gradients for oxygen is not large enough to overcome the reduced diffusion capacities of the growth-restricted placenta. Both limited oxygen and nutrient substrate supplies, therefore, limit the capacity for fetal protein accretion and may augment mechanisms leading to protein breakdown. Furthermore, hypoxia, reduced nutrient supplies and intracellular concentrations of nutrient substrates may initiate differential cellular energy conservation strategies, some of which may not be fully reversible. The complete mechanisms by which oxygen, nutrient substrates, and related anabolic hormones and growth factors regulate placental amino acid uptake, fetal utilization and metabolism, and cellular growth remain to be a field of active investigation.

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