Placental Transport in Fetal Growth Retardation

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The factors responsible for retarding fetal growth are numerous and not completely understood. Although it is reasonable to assume that altered placental handling and transport of metabolic fuels can affect fetal growth, little is known about the precise relation between these changes and the numerous aspects of fetal growth (1). Indeed, a comprehensive understanding of the role of the various aspects of placental transport in normal fetal growth remains to be developed. In this review, we present information about alterations in placental transport that are associated with fetal (intrauterine) growth retardation (IUGR). Glucose and amino acid transporters are highlighted, and we present information about the effects of nicotine, alcohol, and cocaine on transport and IUGR.

Among the physiologic factors that influence placental transport of metabolic fuels, acid-base status, and exchange of oxygen and carbon dioxide are maternal (uterine) blood flow and the availability of maternally derived metabolic fuels (2,3). The transport of metabolic substances from either maternal to fetal or fetal to maternal circulations is complex, involving different cell sites and various transporters. For example, in the rat glucose is believed to pass from the maternal circulation through pores in the cytotrophoblast. Glucose transporter-1 (GLUT-1) carries glucose into the cytoplasm of the syncytiotrophoblast-1. Glucose passes through gap junctions into the cytoplasm of syncytiotrophoblast-2, where GLUT-1 on the cell membrane transports it to the fetal endothelium. It then passes through pores on the fetal endothelium into the fetal vasculature. Alterations at any of these sites can affect transfer (Fig. 1). Of course, the placenta is more than a conduit for metabolic fuel provision and gas exchange. It actively participates in fetal metabolism, having metabolic relations with different fetal organs—that is, it supplies, takes up, and modifies specific metabolites from the placental circulation.

Species differences and developmental considerations also complicate our understanding of the relation between fetal growth and placental function. Fetal metabolic requirements differ between species. Anatomic differences between species may also be a factor. The expression and function of the various transporters may change.
FIG. 1. Schematic representation of glucose transport in the rat placenta. Glucose passes from maternal capillaries into pores located in the cytrophoblast. GLUT-1 transfers glucose into syncytiotrophoblast-1. Glucose passes through gap junctions from syncytiotrophoblast-1 to syncytiotrophoblast-2. GLUT-1 on the membrane of syncytiotrophoblast-2 transfers glucose into the fetal endothelium.

as gestation progresses. Also, the anatomic and functional relations are complicated in the placenta. For example, the handling of a metabolic substance may differ between the maternal (microvillous) and fetal (basal) facing membranes, cytrophoblast, and endothelial cells.

Glucose transporters—structurally similar proteins encoded by a family of genes and expressed in a tissue-specific manner (4,5)—have been identified on the syncytiotrophoblast, cytrophoblast, and endothelial cells of the human placenta and on syncytiotrophoblast-1 and syncytiotrophoblast-2 of the rat placenta. Our understanding of the mechanistic and regulatory role of glucose transporters in facilitating glucose flux between the maternal and the fetal circulations is limited.

Establishing the role of placental amino acid transporters in normal and fetal growth is even more complex. This is because numerous amino acid transporters have been characterized on a functional basis, and each transports more than one amino acid (6,7). More amino acid transporters have been characterized on a functional than on a molecular basis. Indeed, identification of the molecular characteristics of the known amino acid transporters is limited.

GLUCOSE TRANSPORT

Glucose is an important metabolic fuel for the fetus; alterations in its availability directly affect fetal metabolism and thereby potentially affect fetal growth. This
concept is complicated by the fact that alterations in other metabolic fuels, such as amino acids, and growth-stimulating factors, such as insulin (8), have cumulative effects on fetal growth. Thus, the precise contribution of glucose in modulating fetal growth under normal and IUGR conditions remains to be defined. In this section, we provide the details of in vivo quantitation of glucose flux between mother, placenta, and fetus; of in vitro measures of placental function; and of the activity and expression of placental glucose transporters. These data confirm a role for glucose in fetal growth but also show that factors other than glucose contribute to the development of IUGR.

In considering maternal-fetal glucose flux, three glucose pools—maternal, placental, and fetal—must be considered. There is considerable bidirectional flux between the fetal and maternal pools. In the sheep, the uteroplacental mass interposed between the maternal and fetal glucose pools is considerable; it not only transfers glucose in both directions but also rapidly metabolizes glucose (9,10). Indeed, the fetal glucose pool contributes approximately 40% of the glucose metabolized by the placenta. The dynamic interchange between the three pools highlights the complexity of glucose transport and utilization in the sheep.

Several animal models of IUGR have been developed. Heat stress in the maternal ewe from 39 to 124 days of gestation retards fetal growth (11). Heat stress restricts placental growth and decreases fetal plasma glucose concentrations. It is noteworthy that heat stress does not decrease placental perfusion or increase uteroplacental utilization of glucose; rather, it directly limits the ability of the placenta to transport glucose to the fetus. Carunculectomy, which reduces placental mass by 30%, results in a 52% to 59% decrease in fetal glucose turnover in the sheep (12,13). Such a reduction in placental mass reduces umbilical blood flow. Both umbilical and uterine blood flow and placental mass correlate with fetal mass, confirming that diminished blood flow is a major factor in restricting fetal growth. This relationship has also been reported in the rat (14).

Diminished blood flow with concomitant reduction in glucose provision is believed to retard fetal growth in the human. Asymmetric fetal growth retardation is often attributed to "uteroplacental insufficiency," a term suggesting impaired uterine blood flow, compromised gas exchange, and altered metabolic fuel provision to the fetus. Doppler flow studies in human pregnancies with identified IUGR fetuses confirm that uteroplacental blood flow is diminished (15). Such diminished flow may restrict glucose provision.

Studies in smaller mammals show that decreased uteroplacental perfusion contributes to the development of fetal growth retardation. Ligation of the uterine artery in the pregnant guinea pig between 38 and 53 days of gestation restricts placental and fetal growth and decreases fetal plasma glucose and amino acid concentrations (10). In particular, the transfer of labeled aminoisobutyric acid (AIB) remains reduced over a longer period after ligation than the transfer of labeled glucose. This suggests that the availability of amino acids may be more important than the availability of glucose in the development of fetal growth retardation.

Ligation of the uterine artery in the maternal rat also retards fetal growth. This
method alters numerous physiologic and metabolic variables; for example, it results in metabolic acidosis, hypoglycemia, and diminished total and branched-chain amino acid availability in the fetus (16,17). It is of interest that these and other metabolic variables (such as energy and redox states) return to normal within 24 to 48 hours after uterine artery ligation; nonetheless, subsequent fetal and postnatal growth is retarded (18). As in the guinea pig, the duration of reduction in supply of branched-chain amino acids is greater than that of glucose.

Although it is not possible to perform long-term kinetic studies in the fetal rat, our laboratory did adapt an isotopic glucose technique for acute quantitation of relative glucose uptake by the placenta and various organs of the IUGR rat fetus. Twenty-four hours after ligation, placental glucose uptake is significantly diminished compared with that of controls; corresponding fetal plasma glucose concentrations are also significantly diminished. By 48 hours, placental glucose uptake and fetal plasma glucose concentrations are similar to control levels. As this method measures the accumulation of a phosphorylated glucose analogue in an organ, these findings cannot be used to determine whether increased placental utilization or diminished transfer of glucose, or both, cause fetal hypoglycemia (19). Although the mechanisms for this are not completely understood, the diminished perfusion and transient acido-
sis resulting from ligation may limit placental function.

Little information is available concerning placental glucose transport under conditions of IUGR in the human. In a series of studies, Cetin et al. (20,21) measured glucose and amino acid concentrations in cord blood from IUGR and normal fetuses at time of cesarean section. They found that umbilical venous-arterial differences (UVAD) in glucose were similar in IUGR and normal fetuses; the glucose-to-oxygen quotient also did not differ. On the other hand, IUGR fetuses had lower UVAD amino acid concentrations than normal fetuses. Branched-chain amino acids were significantly diminished. These observations are consistent with studies in laboratory animals suggesting that alterations in amino acids, particularly the branched-chain amino acids, may be a more important factor than glucose availability in the pathogenesis of IUGR.

Limited information is available concerning the expression and regulation of glu-
cose transporters in the placenta under conditions of either IUGR or normal growth. Recently, Takata et al. (22) and Illsley’s group (Jansson et al., ref. 23) reported that GLUT-1 is the dominant isoform in human placenta. Jansson et al. used several techniques and could not detect GLUT-3. GLUT-1 protein density is greater in the microvillous membrane than in the basal membrane of the syncytiotrophoblast. GLUT-1 appears to be developmentally regulated, as its density increases with gestation.

Although in vivo measurement of glucose flux in the human IUGR fetus is not available, studies of membrane vesicles from placentae of IUGR fetuses indicate that D-glucose uptake is probably similar to that of normal fetuses. In addition, GLUT-1 protein densities in the villous and basal membranes of placentae from IUGR fetuses do not differ from those of normal fetuses (23).

Several laboratories have reported the presence of GLUT-1 in the rat placenta
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Takata et al. (25) have pointed out that the proximity of GLUT-1 to gap junctions in microvilli is an important anatomic and functional factor in assuring glucose transport from the syncytiotrophoblast-2 into the fetal vasculature.

Reid et al. (26) and Lane et al. (27) have confirmed that GLUT-1 messenger RNA and protein are present in the rat placenta. In contrast to the human IUGR placenta, the rat IUGR placenta expresses GLUT-1 messenger RNA and protein to a greater extent than normal. Immunohistocytochemistry confirms that GLUT-1 density is increased in the IUGR syncytiotrophoblast (25–27). The up-regulation of GLUT-1 may represent an attempt to compensate for diminished glucose provision to the IUGR rat fetus. Despite the up-regulation of GLUT-1, fetal plasma glucose is diminished in the IUGR fetus. This suggests that GLUT-1 expression is probably not rate-limiting in the transfer of glucose under IUGR conditions in the rat.

Little is known about the control of the expression and function of placental glucose transporters under IUGR conditions. Under normal conditions, insulin up-regulates GLUT-1 in most tissues, including the placenta (28). In vitro studies suggest that insulin and the insulin-like growth factors (IGFs) increase glucose transport in cultured placental vesicles (29). Insulin increases trophoblast cell glucose uptake and up-regulates GLUT-1 expression to a greater extent than glucose (28).

Summary

These observations emphasize the complexity of placental glucose transport under normal and IUGR conditions. Glucose flux across the placenta is bidirectional, and the placenta metabolizes glucose as well. Indeed, little is known about fetal utilization of glucose under either normal or IUGR conditions. In the sheep, guinea pig, and rat, various conditions that cause IUGR result in decreased fetal plasma glucose concentrations. The extent to which altered glucose availability causes IUGR in the human is less clear, as data concerning middle and late gestation are limited. The observations that GLUT-1 function and regulation have been reported to be unchanged in human conditions of IUGR suggest that factors other than glucose transport may be more important in restricting growth in the human fetus.

Amino acid transport

As indicated in the preceding section, the transplacental provision of amino acids is critically important for fetal growth and development. Amino acids are substrates for synthesis and are important fuels for oxidative metabolism. As fetal amino acid concentrations may be altered to a greater extent than glucose under conditions of IUGR, the relative importance of amino acids in influencing fetal growth cannot be underestimated. Unfortunately, understanding of the placental transport of amino acids under conditions of IUGR and normal growth remains rudimentary. This is in part a consequence of the large number of amino acid transporters and their complex biology.
Although amino acid transporters are highly stereospecific, transporting L-amino acids more effectively than D-amino acids, their substrate specificity is low—that is, one transporter may transport a number of different amino acids and different transporters may have overlapping specificities. In addition, microvillous and basal membranes have different populations and densities of the various transporters (30). The regulation of transporter function is not completely understood; the availability of one amino acid may either stimulate or inhibit a transporter's ability to transfer another amino acid. Thus, the biology of amino acid transporter systems is far more complex than that of the glucose transporters.

The microvillus has several transporter systems, including system A, which is sodium-dependent and transports—among other amino acids—alanine, serine, AIB, and proline. System N is also located on the microvillus. It, too, is sodium-dependent and transports histidine and glutamine. The microvillus also has a number of sodium-independent transporters. One system N transporter interacts strongly with leucine, tryptophan, tyrosine, and phenylalanine, and resembles system L. Another sodium-independent transporter transports alanine and serine; it binds weakly with branched-chain and aromatic amino acids (31).

The basal membrane has a sodium-dependent system A, which is similar to the system A transporter found in the microvillus, and it also has a sodium-dependent ASC (alanine-serine-cysteine) system, which can transport alanine, serine, and cysteine, but not AIB. Also on the basal membrane is a sodium-independent L system, which transports leucine and phenylalanine. The basal membrane has a sodium-independent system as well, which transports tyrosine. It is unclear whether the basal membrane has system N (Table 1).

No information is available concerning the coordination of amino acid transporter function between the microvillous and basal membranes. Logically, amino acid transporters on the two membranes must act in concert to achieve a concentrative transfer of amino acids from mother to the fetus. The coordinating mechanisms and signals that coordinate these activities remain to be identified.

<table>
<thead>
<tr>
<th>System</th>
<th>Substrate</th>
<th>Membrane location</th>
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<tbody>
<tr>
<td>A</td>
<td>Neutral AA, AIB</td>
<td>Both</td>
</tr>
<tr>
<td>ASC</td>
<td>Ala, Ser, Cys, anionic AA</td>
<td>Basal</td>
</tr>
<tr>
<td>N</td>
<td>His, Gln</td>
<td>Microvillous</td>
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<tr>
<td>B</td>
<td>Tau</td>
<td>Microvillous</td>
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<tr>
<td>X_{AG}</td>
<td>Asp, Glu</td>
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<tr>
<td>I</td>
<td>Leu, BCH</td>
<td>Both</td>
</tr>
<tr>
<td>Y^-</td>
<td>Lys, Arg</td>
<td>Both</td>
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<td>b^or^-</td>
<td>Lys, Arg</td>
<td>Basal</td>
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<tr>
<td>Y^+L</td>
<td>Lys, Arg</td>
<td>Microvillous</td>
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AA, amino acid; AIB, amino isobutyric acid; BCH, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid.
In vitro and in vivo physiologic studies have been the primary basis for classification of the amino acid transporters. Unlike the glucose transporters, which primarily transfer glucose (GLUT-5 also transports fructose), each amino acid transporter has the capability of transporting more than one amino acid. The molecular characterization of amino acid transporters remains in its infancy. At present, it is extremely difficult to correlate the few cloned amino acid transporter genes with the physiologically characterized transporters. Thus, it is difficult to identify the specific changes in amino acid transporters that are responsible for retarding fetal growth.

The chronically catheterized fetal sheep model has allowed quantitation of maternal-fetal amino acid flux. Studies using this model have shown unique handling of specific amino acids by the placenta under normal circumstances. For example, in late gestation, the fetal liver converts serine to glycine; the placenta has a significant net uptake of fetal serine. The placenta converts at least 15% of serine to glycine, which is released into the umbilical circulation. Glycine is critical for fetal energy metabolism; for example, the fetal hindlimb takes up considerable glycine for oxidation (32,33).

The placenta also modulates placental-fetal metabolism. For example, interorgan cycling of amino acids occurs between fetal liver and placenta. Glutamate is an important amino acid, because it serves as a key intermediate in amino acid metabolism and ammonia homeostasis, and as a neurotransmitter. In the placenta, glutamate is second only to taurine in abundance. Unlike other amino acids, glutamate is not concentrated in fetal blood by the placenta. On the other hand, the placenta does transport glutamine into the fetal circulation. The fetal liver converts glutamine to glutamate. The placenta takes up considerable glutamate from the fetal circulation to allow for protein synthesis and the generation of NADPH (reduced nicotinamide adenine dinucleotide phosphate). This facilitates placental synthesis of cholesterol and steroids. Clearance of glutamate from the fetal circulation is important for the fetus, as excessively raised plasma glutamate concentrations are neurotoxic. As the fetus approaches term, these relations change. Fetal hepatic glutamate release diminishes as glutamate is shifted to fetal hepatic glycogen synthesis (34,35). Several sodium-dependent transporters that can transport glutamate have been cloned and identified. Placental microvilli have both GLT-1 and GLAST-1 (36–38). Their precise location, activity, and expression and involvement in these processes are unclear.

The few data concerning amino acid transport under conditions of IUGR are not consistent, but they do suggest that changes in transporter function or availability contribute to the development of IUGR. In the fetal rat rendered growth-retarded by maternal uterine artery ligation, AIB transport, a marker of sodium-dependent transport, is greatly diminished (39). Similarly, in the guinea pig, maternal uterine artery ligation reduces fetal plasma AIB concentrations by 30% in early gestation and 18% during late gestation. Sodium-dependent transport to the rat fetus rendered growth-retarded by maternal uterine artery ligation is diminished, as labeled AIB is diminished in most fetal organs (16). As maternal uterine artery ligation alters numerous metabolic and physiologic variables, the mechanisms by which this model of uteroplacental insufficiency limits placental amino acid transport is not clear.
A few investigators have used the isolated microvillus method to study this problem. Dicke et al. (40) have reported that the function of a transporter with system A characteristics is significantly diminished in microvilli of placentae from growth-retarded human fetuses. Sibley's group (41) has also observed a similar limitation in the $V_{\text{max}}$ of the system A transporter. Another observation that tends to confirm that system A transporter function may affect fetal growth is that system A amino acid transporters are altered in human diabetic pregnancy, resulting in macrosomic fetuses (42). On the other hand, microvillous system A transporter function has been found to be unaffected in placentae of fetal rats rendered growth-retarded by maternal uterine artery ligation (43).

Quantitation of amino acid flux and fetal plasma concentrations under IUGR and normal conditions is limited. Cetin et al. (20,21,44) have used the cordocentesis method to measure fetal plasma amino acid concentrations during middle and late gestation in the human. Their studies show that total $\alpha$-amino nitrogen and branched-chain amino acids are diminished in the umbilical venous circulation of growth-retarded fetuses. The maternal-fetal ratio of amino acids confirms that transport is reduced under conditions of IUGR. These differences are similar to those reported in the growth-retarded fetal rat (17).

The fact that branched-chain amino acids and particularly leucine are diminished in the circulations during IUGR in both the human and the rat is intriguing and emphasizes the importance of these essential amino acids for normal fetal growth. The branched-chain amino acids are central to protein synthesis and oxidative metabolism. Indeed, under conditions of maternal fuel deprivation, fetal leucine oxidation increases greatly (44,45). Further support for the importance of the branched-chain amino acids comes from studies of normal pregnancy showing that these amino acids are preferentially transported to the fetal circulation. In the sheep, leucine is transported at a rate 95% greater than that of glycine from the maternal to the fetal circulation (46,47). Maternal heat stress in the ewe retards fetal growth. Placental leucine transport, oxidation, and fetal disposal are all significantly reduced (48). Stable isotope studies using cordocentesis in the human also show that the transfer of leucine is significantly greater than that of glycine in normal pregnancies between 20 and 37 weeks of gestation (49).

The precise manner in which the transport of branched-chain amino acids is altered to contribute to the development of IUGR is unclear. Changes in permeability at the syncytiotrophoblast or endothelial interface may be one mechanism. Altered placental and possibly fetal metabolism may also limit branched-chain amino acid availability. In this regard, our laboratory has performed preliminary studies indicating that the expression of a sodium-independent neutral amino acid transporter originally cloned by Tate et al. (50) is diminished in the placenta of the IUGR rat. Lane et al. (51) have found that the messenger RNA for this transporter (307 base pairs) in the IUGR placenta is 85% of normal. This transporter may be one of a family of transporters responsible for branched-chain amino acid transport. Diminished expression of this transporter may be one mechanism responsible for limiting the supply of these critical amino acids to the fetus. The mechanisms by which the
altered physiologic and metabolic relations that cause IUGR actually alter placental amino acid transport are unclear. Oxidative metabolism per se may not be a critical factor, as perfused human placenta will transport amino acids and carry out protein synthesis even when gassed in 100% nitrogen (52).

Summary

At present, a comprehensive understanding of the role of amino acid transporters in the growth of the normal and the IUGR fetus is not available. This is in part a consequence of the fact that amino acid transporters are located at numerous placental sites and can carry multiple amino acids. In addition, the placenta has a complex metabolic relation with the fetus, in that it processes various amino acids and exchanges them with fetal organs. Fetal utilization of amino acids also complicates understanding of amino acid availability. The in vivo data indicating that the availability of amino acids, particularly the branched-chain amino acids, is more profoundly altered than glucose in IUGR pregnancies suggest an important role for amino acids in fetal growth. At this point, limited observations are available concerning the alterations of amino acid transporters at the molecular level.

MATERNAL SUBSTANCE ABUSE AND PLACENTAL TRANSPORT

Maternal use of illicit drugs and excessive consumption of alcohol are associated with IUGR and fetal anomalies. It is likely that multiple factors are responsible for these complications. A few studies have attempted to address the potential effects of these substances on placental transport. For example, limited data suggest that alcohol may not alter placental glucose transport but to some extent does reduce transport of AIB, leucine, and valine (52–54). Alcohol, particularly with prolonged maternal use, reduces the transport of specific amino acids. Several models using isolated villi from primates and rats chronically exposed to ethanol have shown diminished AIB and valine uptake (55). These changes appear to be a direct effect of ethanol rather than of acetoaldehyde (56).

Cocaine abuse and excessive maternal tobacco use are also associated with IUGR. Both nicotine and cocaine reduce AIB and valine uptake in human placental villous slices. Of note, when placental slices are exposed to both ethanol and nicotine, transport is reduced even more; the effects of nicotine and cocaine in reducing AIB transport appear to be additive rather than synergistic (57).

These observations offer only glimpses into a variety of potential mechanisms responsible for IUGR associated with maternal ethanol, cocaine, and nicotine use.

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DISCUSSION

Dr. Talamantes: Why do you measure IGF-BP-1 in pregnancy in the rat? Is that the main binding protein?

Dr. Ogata: I did not show BP-3, I didn’t want to go off on a tangent on the fetus, but we found that both BP-1 and BP-3 are up in the fetal rat; the whole issue of which is the more important binding protein is, I think, still up in the air.

Dr. Talamantes: I think just as important would be the protease, much more than the binding protein. Do you get an increase or an alteration of the BP protease?

Dr. Ogata: We have no data.

Dr. Talamantes: When you measure protein for glucose transporter and say it is up or down, how do you know that the structure of the receptor itself isn’t altered, and how do you account for alterations in the structure of the transporter?

Dr. Ogata: In the placenta we have not done actual glucose transport studies. In our other fetal organs we have done both in vivo and in vitro studies to look at deoxyglucose uptake. So I think we feel reasonably comfortable that function correlates with what we see with respect to protein and NMR. But I should caution that we have not done any isolated vesicle work in the placenta.

Dr. Rennie: Was that NAT transporter actually the Tates clone?

Dr. Ogata: Yes.

Dr. Rennie: So are you aware that there is a lot of controversy about whether that is indeed a transporter?

Dr. Ogata: In Tates’ article, he says it is the system L transporter. I realize it has gone back and forth as to what it is, and I think there was also a suggestion that it may be a cotransporter rather than a system L.

Dr. Rennie: I think there is a lot of evidence that it is an amino acid transport activator, which of course would be very interesting, because it appears that if you inject it into oocytes it causes such a widespread increase in amino acid transport that it is almost inconceivable that a single transporter of protein is responsible for the phenomena observed. Therefore, that is the evidence that it is actually some kind of activator. The other thing is that it has only three membrane-spanning domains, so it doesn’t look like a conventional transporter, but it would be very interesting if a single protein regulated a whole lot of other proteins in a coordinated fashion.

Dr. Ogata: This is the whole issue of trying to get at the molecular biology of amino acid transporters. There has been such a tremendous amount of work done to characterize these on a physiologic level, but again this particular transporter was received from complementary DNA from kidney injected into oocytes, and so we are going in the other direction here.

Dr. Rennie: I think that we have to address an important theoretical issue that often seems
to get much behind, which is that for amino acid transport in terms of metabolism what is important is the relation between the first-order rate constant for transport—in other words, the ratio between $V_{\text{max}}$ and $K_m$, and the necessary rate of disposal for appropriate growth. I think there is a good possibility that for the branched-chain amino acids and possibly a couple of others, including maybe methionine for other reasons, there is the strong likelihood that a decrease in transporter activity would be important in limiting protein accretion. But I find it very hard to believe that transporters that transport nonessential amino acids, with the possible exception of glycine or serine if collagen synthesis is important, really matter very much at all. I think this is something that people often don’t think about—whether there is just such a large capacity there that it doesn’t really matter if you halve it or reduce it by 75%, and so far we have not really attempted to match up the numbers here. I think that is something we should be constrained to do—to really see to what extent a fall of 75% would make any difference whatsoever in the capacity of the placenta to deliver sufficient amino acids. It is something we should keep in mind.

Dr. Sibley: We found a decrease in system A activity, and the human data suggest that there is a decreased fetal plasma concentration of amino acids that would be transported by that transporter, so the two do go together, although I accept what you say, that you have to do the calculations. Nevertheless, the data suggest that the two go together. But we must not forget a whole raft of things we don’t know about: we know only about the microvillous membrane—we don’t know if that’s rate-limiting; the basal plasma membrane might be rate-limiting for transports; and we don’t know anything about the basal membrane in IUGR. We know that amino acid transporters, particularly system A, are affected by a number of variables, such as the intracellular concentration of amino acids—system A shows $\text{trans}$ inhibition—and we don’t know what the concentrations of amino acids in the syncytiotrophoblast are in IUGR. We also know that system A is affected by pH and we don’t know what the pH of the trophoblast is in IUGR; we do know that the IUGR fetus is acidemic. So I absolutely agree with you, we are at a very basic level in understanding this problem, and we should not forget all the complications involved.

Dr. Battaglia: There is another point, though, that maybe got lost. It is not just a matter of how much you need for protein synthesis, because you are oxidizing essential amino acids and you are losing them from the fetal circulation into the placenta. For the only one for which we have really good data, leucine (in the heat stress model), the fetus makes an interesting adjustment. It lowers the concentration, and because oxidation rate is driven by concentration, this leads to a lower oxidation rate. The back flux is also concentration-dependent, so you reduce the loss of leucine to the placenta. So with one simple step, you have adjusted the outflow of leucine and redirected it to protein synthesis. The real question is: what are the endocrine regulators that led to resetting leucine concentration lower? The lowering of leucine concentration should not be interpreted as implying that the placenta is not working. This is a resetting, which has very significant survival value to the fetus, because it is redirecting output towards accretion and away from oxidation and loss into the placenta. So far, we have studied only one amino acid in detail, but there the situation is clear.

Dr. Rennie: I think that one of the fascinating links here might be transport of methionine, because if serine is making mainly glycine, then you have to have some methyl groups to get that reaction to go, so the one-carbon pool is going to be important there.

Dr. Battaglia: You don’t need the methyl group for glycine production, you need it for resynthesizing serine, and that goes on in the liver.

Dr. Rennie: But nevertheless there is going to be a requirement for that if that is to happen. Methionine is something we haven’t really looked at, and the cysteine-methionine metabolism is likely to be very important.

Dr. Battaglia: I agree with you.