Human Placental Transport in Altered Fetal Growth: Does the Placenta Function as a Nutrient Sensor? – A Review

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Intrauterine growth restriction is associated with a range of alterations in placental transport functions: the activity of a number of transporters is reduced (Systems A, L and Tau, transporters for cationic amino acids, the sodium-proton exchanger and the sodium pump), placental glucose transporter activity and expression are unchanged whereas the activity of the calcium pump is increased. In contrast, accelerated fetal growth in association to diabetes is characterized by increased activity of placental Systems A and L and glucose transporters. Evidence suggests that these placental transport alterations are the result of specific regulation and that they, at least in part, contribute to the development of pathological fetal growth rather than representing a consequence to altered fetal growth. One interpretation of this data is that the placenta functions as a nutrient sensor, altering placental transport functions according to the ability of the maternal supply line to provide nutrients. Placental transporters are subjected to regulation by hormones. Insulin up-regulates several key placental transporters and maternal insulin may represent a “good nutrition” signal to increase placental nutrient transfer and the growth of the fetus. Preliminary evidence suggests that placental mammalian target of rapamycin, a protein kinase regulating protein translation and transcription in response to nutrient stimuli, may be involved in placental nutrient sensing.

INTRODUCTION

Intrauterine growth restriction (IUGR) constitutes an important clinical problem associated with increased perinatal morbidity [1], higher incidence of neuro-developmental impairment [2] and increased risk of adult disease, such as diabetes and cardiovascular disease [3,4]. Similarly fetal overgrowth, resulting in the delivery of a large-for-gestational age baby (LGA), represents a risk factor for operative delivery, traumatic birth injury [5] and developing diabetes and obesity later in life [6,7]. Thus, the adverse consequences of altered fetal growth are not limited to the perinatal period and the concept of an important developmental origin of adult disease may have a profound impact on public health strategies for the prevention of major illnesses. Currently, no specific strategies for treatment and intervention are available in cases of altered fetal growth, and in order to make significant progress in this area a better understanding of the underlying pathophysiological mechanisms is needed.

The growth restricted human fetus has reduced plasma concentrations of certain key amino acids [8] and some are hypoglycemic and hypoxic in utero [9]. Although generally accepted that IUGR is associated with limitations in nutrient and oxygen supply, the mechanisms involved remain to be fully established. Similarly, the fetal overgrowth often observed in pregnancies complicated by diabetes has been attributed to an excess glucose delivery to the fetus due to maternal hyperglycemia [10]. However, in modern clinical management of the pregnant woman with diabetes, maternal glucose levels are rigorously controlled throughout second and third trimesters suggesting that there are mechanisms other than maternal hyperglycemia that contributes to fetal overgrowth in these pregnancies. In this paper we will briefly review recent advances in the study of human placental transport functions...
in association to altered fetal growth. These findings suggest that alterations in the expression and activity of placental nutrient and ion transporters may play a key role in regulating fetal growth in normal and complicated pregnancies.

**PLACENTAL BLOOD FLOW IS REDUCED IN IUGR**

Measurements of maternal placental blood flow and volume blood flow in the umbilical circulation clearly suggest that blood flows are reduced on both sides of the placental exchange barrier in association with IUGR. However, it is unlikely that the blood flow reduction is a sufficient explanation for the reduced levels of various nutrients in the fetal circulation. In general, the transfer of a molecule across a barrier may be limited by the actual diffusion (diffusion-limitation) or by the rate by which the molecule is supplied to and removed from the barrier by blood flow (blood flow-limitation). An example of a molecule subjected to blood flow-limited transport is oxygen, which is a highly lipophilic and a relatively small molecule that diffuses across the placental barrier without difficulty. Thus, it is likely that the reduction in placental blood flows contribute to fetal hypoxia in IUGR. In contrast, transplacental transport of nutrients such as glucose and amino acids will be less affected by changes in blood flow since the transport across the barrier is the primary limiting factor for the transfer of these molecules.

**ARE PLACENTAL TRANSPORT FUNCTIONS ALTERED IN IUGR?**

Given the diffusion-limitation of nutrient transport across the human placenta it was hypothesized that IUGR is associated with alterations in the activity of placental transporters which may contribute to the growth restriction. This hypothesis has been tested in experimental systems from the human placenta, primarily isolated syncytiotrophoblast plasma membranes. In the human placenta there are two cell layers between the maternal blood in the intervillous space and in the fetal circulation: the syncytiotrophoblast transporting epithelium and the fetal capillary endothelium (Figure 1). Human placental capillaries closely resemble other non-brain continuous capillaries, having wide paracellular clefts [11] which allow relatively unrestricted transfer of molecules like glucose and amino acids across the capillary wall. Instead, it is the two polarized plasma membranes of the syncytiotrophoblast that represent the primary barrier for transplacental transfer of nutrients and most ions. The plasma membrane directed towards the maternal blood is the microvillus membrane (MVM) whereas the basal plasma membrane (BM) faces the fetal capillaries (Figure 1). Thus, studies of the transport characteristics of isolated syncytiotrophoblast plasma membranes may provide important information on transplacental transport in normal and complicated pregnancies.

**REDUCED ACTIVITY OF PLACENTAL AMINO ACID TRANSPORTERS IN IUGR**

Glucose transporter isoform 1 (GLUT 1) is the primary transporter mediating facilitated glucose transfer across the human placental barrier in the second half of pregnancy and glucose movement across BM appears to be the rate-limiting step [12,13]. Fetal hypoglycemia in IUGR is unlikely to be due to changes in placental glucose transporters since both GLUT 1 protein expression and glucose transport activity in syncytiotrophoblast plasma membranes have been reported to be unaltered in IUGR [12,13].

Transport of amino acids across the human placenta is an active process resulting in amino acid concentrations in the fetal circulation that are substantially higher than those in maternal plasma. In IUGR, the activity of System A, a Na⁺-dependent transporter mediating the uptake of non-essential neutral amino acids, is markedly reduced in MVM [14,15], especially in IUGR babies who are delivered prematurely [13]. In addition, the activity of a number of placental transport systems for essential amino acids, such as lysine, leucine [16] and taurine [17], is reduced in MVM and/or BM isolated from IUGR placentas. These in vitro findings are compatible with a recent study in pregnant women in which Paolini et al. demonstrated, using stable isotope techniques, that placental transfer of the essential amino acids leucine and phenylalanine is reduced in IUGR [18]. The down-regulation of placental amino acid transporters in IUGR results in a decreased delivery of amino acids to the fetus and is likely to be an important factor causing the low fetal plasma concentrations of...
certain amino acids in this pregnancy complication. Amino acids are, together with glucose, the primary stimulus for secretion of fetal insulin, probably the most important growth-promoting hormone in utero. Therefore, it appears that there is a direct link between down-regulation of placental amino acid transporters and restricted fetal growth in IUGR.

The IUGR fetus is typically characterized by having markedly decreased subcutaneous fat depots, contributing to the thin appearance of the IUGR newborn. This may be due to decreased fetal fat synthesis and/or restricted placental transfer of free fatty acids. Indeed, a recent report demonstrates that the activity of MVM lipoprotein lipase, the first critical step in transplacental transfer of free fatty acids, is reduced in IUGR [19]. These data are in line with clinical studies showing lower fetal/maternal ratios for long-chain polyunsaturated fatty acids in IUGR [20]. However, the cellular mechanisms mediating free fatty acid movement across the placenta remain to be fully established and placental fatty acid transport has not been studied in IUGR.

| Table 1. Summary of reported alterations in the activity of nutrient and ion transporters in the human placental barrier in association with IUGR |
|------------------|----------|----------|-----------|
| Transport system | MVM      | BM       | References |
| Taurine         | ↓        | ↔        | [17,47]   |
| Lysine          | ↔        | ↓        | [16,57]   |
| Leucine         | ↓        | ↓        | [16]      |
| Glucose         | ↔        | ↔        | [12,13]   |
| Ca\(^{2+}\) ATPase | ↓        | ↑        | [26]      |
| Na\(^{+}/H\(^{+}\) exchanger | ↓ | ↓ | [14,22] |
| Na\(^{+}/K\(^{+}\) ATPase | ↓ | ↔ | [23] |
| Lipoprotein lipase | ↓ | — | [19] |

Increase (↑), unaltered (↔) or reduced (↓) transporter activity in isolated microvillous plasma membrane (MVM) and basal plasma membrane (BM) vesicles.

ALTERATIONS IN PLACENTAL ION TRANSPORT IN IUGR

A subgroup of IUGR fetuses displays signs of chronic acidosis in utero [21]. The activity and expression of the sodium-proton exchanger, the primary pH-regulating transporter in the syncytiotrophoblast, are reduced in association with IUGR [14,22] and we speculate that these alterations contribute to the development of acidosis in these fetuses. Furthermore, MVM Na\(^{+}/K\(^{+}\) ATPase activity is decreased in IUGR, which may result in an impaired driving force for a range of Na\(^{+}\) dependent transport processes in the placenta [23]. Postnatally IUGR is associated with reduced bone mineralization both in childhood [24] and in adult age [25] and there is a possible link between restricted fetal growth and osteoporosis later in life. In the third trimester there is a rapid mineralization of fetal bone, a process crucially dependent on an efficient transport of calcium across the placenta. Interestingly, the activity of BM Ca\(^{2+}\) ATPase is markedly increased in IUGR possibly due to elevated fetal levels of an active fragment of parathyroid hormone related peptide (PTHrp 38–94) [26]. The up-regulation of a key component of the placental Ca\(^{2+}\) transport system may represent a response to an increased Ca\(^{2+}\) demand in relation to placental size in IUGR due to the asymmetric growth in this condition. In IUGR, fetal and placental weights are often reduced to a similar degree whereas fetal length, related to bone mass, is relatively preserved. Thus, a smaller placenta has to supply Ca\(^{2+}\) for a near-normal bone mass, requiring up-regulation of placental Ca\(^{2+}\) transport [26]. If this interpretation of data is correct, compensatory changes in placental Ca\(^{2+}\) transfer remain insufficient considering the link between IUGR and reduced bone mineralization. Reported alterations in the activity of nutrient and ion transporters in the human placental barrier in association with IUGR are summarized in Table 1.

PLACENTAL NUTRIENT TRANSFER IS INCREASED IN FETAL OVERGROWTH

Transplacental transport of glucose is a facilitated process and net transfer is therefore strongly dependent on the concentration gradient of glucose between maternal and fetal blood. Pedersen proposed some 50 years ago that fetal overgrowth (“macrosomia”) in association with diabetes is caused by maternal hyperglycemia that increases net transfer of glucose to the fetus, resulting in increased fetal insulin secretion and growth [10]. However, despite marked improvements in the clinical management of these patients with strict maternal blood glucose control the incidence of LGA babies in pregnancies complicated by diabetes remains surprisingly high. In fact, the correlation between various indices of maternal glucose control and fetal growth is poor, suggesting that other factors than maternal hyperglycemia may contribute to accelerated fetal growth. One possibility is that diabetes affects placental transport functions. Indeed, placental glucose transport capacity [27,28] and the activity of placental LPL [19] have been reported to be increased in insulin-dependent diabetes (IDD) associated with accelerated fetal growth, but not in gestational diabetes (GD) [19,29]. Thus, up-regulation of placental glucose transporters in IDD may contribute to increased placental glucose transfer and stimulate fetal growth even if the mother is normoglycemic. The activity of the placental amino acid transporter System A is increased in diabetes, independent of accelerated fetal growth and placental transport of leucine is increased in GD pregnancies [30]. In contrast to these findings, a previous study indicated that System A activity is reduced and the activity of System L is unaltered in microvillous plasma membrane vesicles isolated from IDDM pregnancies with LGA babies [31]. These two studies were carried out in different populations and, notably, placental weight was increased in parallel to fetal weight in one study [30] whereas placental weight was largely unaffected in the other [31]. Thus, the placental response to
metabolic disease may differ between study populations although outcome with regard to fetal weight is the same.

Reported alterations in the activity of nutrient and ion transporters in the human placental barrier in association with fetal overgrowth in diabetes are summarized in Table 2. Collectively, these findings suggest that diabetes in pregnancy is associated with enhanced placental capacity for nutrient transfer.

ARE THE ALTERATIONS IN PLACENTAL TRANSPORT SPECIFIC?

One possible explanation to the observed changes in placental transporter expression and/or activity is that they are the result of a generalized pathological effect on, e.g., the properties of the plasma membranes in which the transporters are embedded. However, no marked differences in cholesterol content, FFA composition, membrane fluidity, or passive permeability in IUGR as compared to AGA syncytiotrophoblast plasma membranes have been reported [32]. In addition, the findings that various transporter activities may be either decreased, unchanged or increased in the one and same pregnancy complication (IUGR) strongly argues against this possibility. Furthermore, alterations in transporter function are commonly observed in only one of the two polarized plasma membranes of the syncytiotrophoblast. Thus, we argue that reported changes in transport activities in syncytiotrophoblast plasma membranes in IUGR and fetal overgrowth in association with diabetes are the result of specific regulation.

REGULATION OF PLACENTAL NUTRIENT AND ION TRANSPORTERS

The findings of altered activity and expression of placental transporters in pregnancies complicated by abnormal fetal growth have stimulated interest in regulation studies. Although our understanding of the regulation of placental transporters remains incomplete and warrants further studies, some pieces of information are available. Glucocorticoids decrease the expression of placental glucose transporters [33]. Most of the previous studies [34], but not all [35], show that insulin does not affect placental glucose transporters at term. In a first trimester trophoblast cell line glucose transport activity was increased after 1 h of incubation with insulin, IGF-I or IGF-II [36,37]. We recently demonstrated that human placental glucose transporter activity was not affected by hormones such as leptin, GH, IGF-I, insulin and cortisol, at term [38]. However, in first trimester, insulin stimulated mediated glucose uptake at 6–8 weeks of gestation [39]. We have shown the presence of the insulin-sensitive glucose transporter GLUT 4 in the cytosol and microvillus plasma membranes of the syncytiotrophoblast in first trimester [39]. This is the first report of localization of GLUT 4 to the transporting epithelium of the human placenta.

IGF-I has been shown to stimulate System A uptake in cultured trophoblast cells [37,40,41]. Similarly, insulin increases transport of neutral amino acids in the perfused human lobule [42] and in cultured trophoblast cells [37,43]. In addition, System A transporter activity and expression are down-regulated by hypoxia [44]. We reported that a 1-h incubation with leptin and insulin stimulated System A activity uptake by 50–60% in primary villous fragments at term [45]. Furthermore, nitric oxide and oxygen radicals have been shown to reduce the activity of several placental amino acid transporters [46,47]. The mechanisms of regulation of placental ion transporters are largely unknown, however, the basal plasma membrane Ca\(^{2+}\) ATPase is stimulated by the fetal hormone PTHrp 38–94 [48].

DOES THE PLACENTA FUNCTION AS A NUTRIENT SENSOR?

In a situation, such as IUGR, where fetal plasma concentrations of amino acids are decreased it might be expected that placental transporters will be up-regulated in an attempt to increase transport. Similarly, in situations with maternal (and fetal) hyperglycemia (diabetes) a down-regulation of placental glucose transporters may seem appropriate. However, the data reviewed in this paper (Tables 1 and 2) indicate the opposite. We have recently developed a working hypothesis that we believe takes into account the data that we, and others, have obtained and provides a testable model for further study. We have suggested that the placenta may act as a nutrient sensor, coordinating nutrient transport functions with maternal nutrient availability [49]. According to this hypothesis the ability of the maternal supply line to deliver nutrients (i.e., placental blood flow, maternal nutrition, substrate and oxygen levels in maternal blood etc.) regulates key placental nutrient transporters (Figure 2). With this perspective placental transport alterations represent a mechanism to match fetal growth rate to a level which is compatible with the amount of nutrients that can be

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Table 2. Summary of reported alterations in the activity of nutrient and ion transporters in the human placental barrier in association with fetal overgrowth in diabetes

<table>
<thead>
<tr>
<th>Fetal overgrowth</th>
<th>MVM</th>
<th>BM</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>System A</td>
<td>↑</td>
<td>←</td>
<td>[30]*</td>
</tr>
<tr>
<td>Taurine</td>
<td>↔</td>
<td>↔</td>
<td>[30]</td>
</tr>
<tr>
<td>Lysine</td>
<td>↔</td>
<td>←</td>
<td>[30]</td>
</tr>
<tr>
<td>Leucine</td>
<td>↑*</td>
<td>←</td>
<td>[30]*</td>
</tr>
<tr>
<td>Glucose</td>
<td>↔</td>
<td>↑ b</td>
<td>[27–29]</td>
</tr>
<tr>
<td>Ca(^{2+}) ATPase</td>
<td>←</td>
<td>↑</td>
<td>[26]</td>
</tr>
<tr>
<td>Na(^{+})/H(^{+}) exchanger</td>
<td>↔</td>
<td>↑</td>
<td>[31]</td>
</tr>
<tr>
<td>Na(^{+})K(^{+}) ATPase</td>
<td>↔</td>
<td>←</td>
<td>[58]</td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>↑</td>
<td>←</td>
<td>[19]</td>
</tr>
</tbody>
</table>

Increased (↑), unchanged (↔) or reduced (↓) transporter activity in isolated microvillus plasma membrane (MVM) and basal plasma membrane (BM) vesicles.

* Only GD.
* Only IDDM.
* Different results have been reported by others [31], see text.
provided by the maternal supply line. In the case of IUGR the placenta may register a lack of normal increase in placental blood flow or maternal malnutrition and as a consequence some key placental transporters are down-regulated in order to decrease fetal growth. Similarly, hyperglycemia early in pregnancy (which is common even in the well-regulated IDDM patient) may convey a “good nutrition” signal to the placenta resulting in up-regulation of glucose and amino acid transporters.

The placental nutrient sensor hypothesis discussed in this review concerns interactions between the ability of the maternal supply line to deliver nutrients to the placenta and placental supply capacity. Fetal demand may also modify placental nutrient transport capacity, interactions that may be mediated by imprinted genes, such as the Igf2 gene, as recently proposed by Reik et al. [50].

POSSIBLE MECHANISMS INVOLVED IN PLACENTAL NUTRIENT SENSING

The mechanisms conveying information about the ability of the maternal supply line to deliver nutrients and regulating placental nutrient transporters remain speculative. However, it is likely that the activity of key placental nutrient transporters in a particular situation represents an integrated response dependent on information from a number of signalling pathways. For example, we propose that maternal nutrition influences placental transporters and fetal growth by altering the levels of metabolic hormones such as insulin, IGF-1 and leptin, which all have been shown to regulate placental nutrient transporters [37,39–41,43,45]. In IUGR, a pregnancy complication associated with reduced placental blood flow, hypoxia may also down-regulate placental amino acid transporters [44]. In addition, we have recently pursued the possibility that the mammalian target of rapamycin (mTOR) signalling system represents an “intrinsic” placental nutrient sensing mechanism. mTOR is a serine/threonine kinase and represents an important nutrient sensing pathway in mammalian cells by controlling cell growth through regulation of translation and transcription in response to nutrient availability, in particular branched chain amino acids [51], hypoxia [52] and cellular energy status [53]. The down-stream effects of mTOR are mediated by phosphorylation of 4E-BP1 (eukaryotic initiation factor 4E binding protein 1) and S6K (p70 S6 kinase) [54]. Our preliminary data indicate that mTOR protein is highly expressed in the cytosol of the syncytiotrophoblast, that mTOR regulates placental transport of the essential amino acid leucine, and that placental mTOR expression is related to fetal growth in pregnancy complications [55]. Thus, these initial observations are compatible with the hypothesis that placental mTOR is involved in nutrient sensing, regulating placental transport according to resources available in the maternal supply line. Future research will prove or reject this hypothesis.

POSSIBLE CLINICAL IMPLICATIONS

Recently it was proposed that the placental transporter alterations in IUGR, summarized in Table 1, represent a placental transport “phenotype” characteristic for intrauterine under-nutrition [56]. This phenotype could, for example, be used to differentiate between an IUGR baby (pathological

Figure 2. Does the placenta function as a nutrient sensor? The figure illustrates the hypothesis that placental nutrient and ion transporters are regulated in response to a primary event, such as a lack of increase in placental blood flow, maternal malnutrition or hyperglycemia. Alterations in placental transport activity result in changes in nutrient delivery to the fetus which, in turn, affects fetal growth. Hormones produced by the placenta or the mother, hypoxia and nutrient sensing mechanisms “intrinsic” to the placenta (such as mammalian target of rapamycin-mTOR) may be involved.
transport phenotype) and a constitutionally small baby (normal transport phenotype), thereby providing a diagnostic tool to identify small-for-gestational age babies that have been subjected to restricted growth in utero. Fetal under-nutrition is a risk factor for adult disease such as diabetes and cardiovascular disease. However, birth weight is a very crude proxy for nutrition in fetal life and it is possible that the placentental transport phenotype may provide better information with regard to postnatal prognosis and long-term consequences.

REFERENCES


