72 Placental transport and metabolism

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As a fetal organ, the placenta not only is obligated to the fetus but also answers to the mother. More than merely a conduit for the provision of oxygen and nutrients to the fetus, the placenta actively regulates the passage of substrates necessary for fetal growth and development. The importance of placental function and dysfunction is manifest in a variety of adult chronic illnesses that are now felt to be a consequence of in utero insults. This phenomenon is known as fetal origins of adult disease and includes cardiovascular disease and features of the metabolic syndrome, including dyslipidemia, type 2 diabetes, insulin resistance, and obesity. The finding that the placenta is capable of influencing an individual's general health years following its relatively brief service is a testament to its critical effect on intra- as well as extrauterine survival. Preventative care and overall health begin in utero and require a healthy placenta. This realization has implications not only for an individual's quality of life but also for societal approaches to public health.

Placental nutrient transport potential involves multiple variables including placental size, architecture, blood flow, nutrient production and consumption, and transporters for glucose, lipids, and amino acids.

The placenta grows continuously throughout gestation. This benefits the fetus in a number of ways and is one determinate of fetal growth. The larger the placenta, the larger the surface area available for nutrient exchange. There is also a decrease in trophoblast thickness, decreasing the diffusion distance between maternal and fetal circulations. These changes support the observations that placental growth in the midtrimester is associated with fetal weight in the third trimester and that overall there is a positive correlation of placental size with fetal size (1–3).

Environmental insults, which reduce placental weight, such as nutritional conditions and glucocorticoid administration, can also have an effect on placental morphology. Changes in barrier thickness, surface area available for exchange, vascularity, and rates of proliferation and demise of certain cell types are ways in which placental efficiency may be diminished or enhanced (4,5). For example, hypoxia has been associated with a reduction in barrier thickness between maternal and fetal capillaries in the human placenta, presumably encouraging diffusional change (6). Maternal food restriction in guinea pigs, whose hemomonochorionic placenta is more like the human placenta than other non-primates, alters placental size and structure. Undernutrition is associated with reduced placental weight, decreased surface area available for exchange, and increase in membrane thickness. The placenta under these circumstances not only is small but also has diminished substrate transport capacity (4).

Placental growth and function also depend upon adequate blood flow. This requires normal trophoblast invasion and

remodeling of the spiral arteries, achieved by vasculogenesis, new blood vessel formation from endothelial precursor cells, and angiogenesis, new vessel formation from those already present. Deficient conversion of the spiral arteries leads to impaired villous perfusion and hypoxia, which itself can have a pejorative effect on vascular remodeling by limiting proliferation and growth of fetal vessels (7,8). This results in increased resistance to blood flow in the umbilical arteries, which is reflected in abnormal flow velocity waveforms using Doppler ultrasound. Growth of the placenta, its blood vessels, and its blood supply are intertwined such that, under normal circumstances, fetoplacental growth correlates with the ability to provide oxygen and nutrients to the placenta for subsequent transfer to the fetus.

The consumption and production of nutrients by placental tissues impact the availability of nutrients for transport to the fetus. In humans, 40% to 70% of the glucose and oxygen taken up by the uterus is utilized by uteroplacental tissues, which also produce lactate and metabolize amino acids for fetal use (9,10). Just as placental growth, morphology, and blood supply are subject to exogenous factors, uteroplacental management of carbohydrates and amino acids is influenced by a host of variables including placental size, nutrient availability, and concentrations of hormones such as glucocorticoids, growth hormone, and insulin growth factors in maternal and fetal blood (11–13). In sheep, hypoglycemia is associated with decreased placental glucose consumption (14) while preterm exposure to cortisol has the opposite effect (15). Similarly, placental disposition of essential amino acids is influenced by undernutrition, heat stress, and treatment with IGF-1 (14,15), which enhances fetal and placental amino acid uptake (16). These are ways in which placental utilization of nutrients is influenced by environmental factors with subsequent effects on nutrient availability to the fetus.

Hormones are produced by the placenta and released to the mother and fetus. These include peptides, steroids, glycoproteins, and cytokines. Progesterone and placental lactogen have effects on the mother, which promote glucose delivery to the fetus (2). The placental variant of growth hormone (GHv) and IGF-1 and IGF-2 may influence nutrient provision by endocrine effects on maternal metabolism and/or paracrine effects on placental potential for simple and facilitated diffusion (16,17). Binding of these hormones to placental receptors can change placental clearance of analogs of glucose and amino acids in vivo and in vitro (18). Maternal levels and placental expression of GHv are decreased in pregnancies with growth-restricted fetuses, implicating changes in placental endocrine function as a cause rather than a result of abnormal fetal growth (19).

Placental prostaglandins (PG) PGE₂ and PGF₂α affect fetal nutrient and oxygen provision indirectly by their effects on

regional blood flow, uterine contractility, and fetal endocrine function (20,21). In vitro studies using murine placenta subjected to oxidative stress through a process of hypoxia/reoxygenation have demonstrated significant increases in the concentrations of cyclooxygenase, enzymes that stimulates PG production (22). In nonhuman primates, undernutrition increases activity of placental PGH synthase and levels of PGE₂ and PGF₂α. These increases correlate with reduced uteroplacental glucose consumption and are reversible by restoration of normoglycemia (20). PG dehydrogenase (PGDH), an enzyme that converts active prostaglandins into their inactive metabolites, has also been demonstrated in placental tissue (23). Changes in PG synthesis and metabolism have been associated with cortisol concentrations as glucocorticoids enhance PGH synthase activity and reduce PGDH activity, which increases intrauterine production of PGE₂ and PGF₂α (21,23). These changes increase with advancing gestation, a time of rising fetal cortisol concentrations and myometrial contractility.

11-β-hydroxysteroid dehydrogenase type-2 (11-β-HSD-2) is a placental enzyme that inactivates glucocorticoids, compounds produced by the trophoblast that regulate organ growth and maturation. Fetal exposure to glucocorticoids is associated with growth restriction in both animals and humans. By converting cortisol to cortisone, 11-β-HSD-2 forms a placental barrier by limiting transfer of free cortisol from mother to fetus. Decreased 11-β-HSD-2 activity and increased levels of cortisol in the fetus have been associated with fetal growth restriction (24). It is presumed that the placenta mitigates the effects of steroids on fetal growth as experimental studies have shown that repeated doses of corticosteroids given to pregnant ewes resulted in reduced birth weight while direct administration to the fetus did not interfere with fetal growth (25,26). In humans, placental activity of 11-β-HSD-2 correlates with birth weight (27). Additionally, gene expression of 11-β-HSD-2 is sensitive to environmental and nutritional stressors. Hypoxia (in vitro) and infection decrease activity, which may lead to increased cortisol levels and suboptimal growth (28). While in vitro data derived using a variety of cell models are inconclusive, evidence to date suggests that glucocorticoids may decrease glucose transfer and increase amino acid transport (29). Glucocorticoids also influence fetal growth via their effects on placental production and activity of other hormones, including prostaglandins, progesterone, and estrogens (28). This is another way in which the placenta adapts to conditions in utero in an attempt to maintain optimal fetal growth.

Insulin-like growth factors, especially IGF-1, are presumptive regulators of placental transport based on the observations that IGF receptors are expressed in the syncytiotrophoblast, which in vitro studies have demonstrated increased glucose uptake and system A activity following treatment with IGF-1 (30) and that reduced fetal levels of IGF-1 (31) and expression of the IGF receptor were associated with intrauterine growth restriction (IUGR) (32). Based on the above, it has been proposed that reduced levels of IGF-1 in the maternal circulation could result in diminished transplacental transport of glucose and amino acids while increased levels of IGF-1, as occurs in diabetes, would have the opposite effect.

A relatively recent addition to the armamentarium regulating placental transport activity (maternal nutritional status, placental blood flow, maternal/placental hormone production, hypoxia) is mammalian target of rapamycin (mTOR). A serine/threonine kinase, mTOR protein is expressed in the cytosol of the syncytiotrophoblast and is thought to regulate cell growth by its influence on translation and transcription through a mechanism of “nutrient sensing” (33). This refers to a proposed process whereby mTOR regulates production of proteins related to cell growth in response to the placental environment, including nutrient availability, oxygenation, and growth factors. These proteins regulate nutrient transporters and thereby affect fetal growth. In vitro data supporting the proposed role of mTOR in fetal growth include the finding that the activity of the mTOR signaling pathway is down-regulated in IUGR and that inhibition of mTOR resulted in nearly complete inhibition of leucine uptake by the system L amino acid transporter (34).

In addition to the aforementioned influences on placental transport and fetal growth, the organization of the placental plasma membrane interface between the maternal and fetal circulations is considered to be a critical component of placental function. This interface is the syncytiotrophoblast that consists of a microvillous membrane (MVM), exposed to maternal venous blood and a basal membrane (BM), which is in contact with the fetal circulation. Available and accumulating evidence indicate that the placenta employs multiple nutrient transporters to provide the sustenance necessary for fetal growth. The MVM and BM contain specific receptors and proteins that regulate the supply of glucose, lipids, and amino acids available to the fetus. Following is a review of the cellular mechanisms responsible for fetal nutrition.

GLUCOSE

Glucose transport is facilitated by a family of isoforms with the prefix GLUT. In human placenta, six GLUT isoforms have been identified at the mRNA level (35,36). The major placental GLUTs are GLUT1 and GLUT3 (37–39), whose abundance and activity differ in response to a variety of environmental factors, including diabetes, maternal nutritional status, hypoxia, and reduced uterine blood flow (28). These GLUTs have different kinetic activity and are differentially expressed within the placental membranes. GLUT3 occurs in the MVM at the maternal-fetal interface and is presumed to be responsible for the rate of glucose delivery to the fetus. GLUT1 tends to be located in the plasma BM and may modulate placental glucose consumption as well as being the rate-limiting step in transplacental glucose transport (39,40).

FATTY ACIDS

Long-chain polyunsaturated fatty acids (LC-PUFA) are important not only for maternal health but also for fetal growth and central nervous system development. The LC-PUFA arachidonic acid (AA) and docosahexaenoic acid (DHA) are present in high concentrations in the fetal brain and regulate the structure and function of neural membranes (41). Diminished DHA in brain lipids is associated with learning impairment in various species. Eicosanoids, which are derived from AA, are integral to cell division and other important physiological processes (41).

The observation that LC-PUFA are higher in plasma lipids of the cord than in maternal plasma lipids at birth supports the notion of active maternal–fetal transfer, which is a complex, incompletely understood process. Human placental receptors to very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein facilitate uptake of maternal plasma lipoproteins (42).

In addition, placental lipoprotein lipase, which is localized in the MVM, hydrolyzes lipoproteins (43). The free fatty acids (FFA) released diffuse across the plasma membrane. Fatty acid transport proteins, fatty acid translocase, and plasma membrane fatty acid-binding proteins (FABPpm) facilitate unesterified fatty acid uptake into the placental cells (44). An isoform of FABPpm unique to the placenta occurs only in the MVM of the syncytiotrophoblast, suggesting that it may be important in placental FFA uptake (45). While they are thought to encourage transmembrane passage of FFA, the manner in which this is accomplished by FABP is uncertain. Once transported into the syncytial cytoplasm, FFA bind to FABP and are presented to the BM through which they are presumed to be transported to the fetus via either diffusion or facilitation by FABPs (46).

AMINO ACIDS

While glucose is the primary fuel for the fetus, amino acids are critical as they are precursors for protein synthesis as well as nonprotein compounds, such as nitric oxide, neurotransmitters, and polyamines. The types and balance of essential and nonessential amino acids supplied to the fetus are important determinates of fetal growth. Amino acid concentrations in the fetal plasma exceed those in the mother (47). The uptake and transport of amino acids across the trophoblast membrane is an active process regulated by at least 15 different transport proteins with different structures, overlapping substrate specificity, expression, and activity. Sodium-dependent transport systems and their substrates include systems A (alanine, serine, proline, glycine), ASC (alanine, serine, cystine), N (histidine, asparagine, glutamine), β (taurine), X_{AG}^- (glutamate and aspartate), and GLY (glycine, sarcosine). Cationic amino acids are transported via system y^+ . Small neutral amino acids are handled by system ASC. System L transports neutral and branched-chain amino acids while aromatic amino acids are the substrate for system T (48).

There are two main types of amino acid transporters, both of which are present in the placenta: accumulative transporters and amino acid exchangers (49). The former regulate influx of amino acids and lead to increased concentrations within the cell. Amino acid exchangers swap amino acids from outside the cell with those inside the cell. This allows the composition of amino acids within the cell to be altered to meet fetal metabolic requirements, with no change in total concentration. Exchangers are one potential means by which nonessential amino acids in the fetal circulation can be exchanged for less readily available essential amino acids within the placenta. Such a process is one way in which the placenta meets the unique growth and energy demands of the fetus.

Net amino acid transfer across the placenta is necessary to sustain fetal growth. There is active transport of amino acids across the MVM into the syncytiotrophoblast via accumulative

transporters (47). These include subtypes of system A, a sodium-dependent transporter, which transports small neutral amino acids (SNAT1, SNAT2, and SNAT4), such as alanine, serine, glycine, and proline and system X_{AG}^- , which regulate uptake of glutamate and aspartate. System A transporters are notable among MVM accumulative transporters in that their substrate amino acids are also subject to exchange transport (50).

Although the mechanisms of amino acid uptake by the maternal-facing MVM have been delineated, the means by which amino acids traverse the BM to the fetus are less well understood. In studies of isolated perfused placenta, exchange and nonexchange transport systems have been demonstrated. The activity of the exchange systems was suggestive of system ASC and isoforms of system L (LAT1, LAT2). Possible nonexchange transporters include system N, system T (TAT1), and the system L isoform LAT4 (51).

In summary, the appropriate quantity and balance of amino acids are essential for fetal and placental health. Provision of amino acids from the maternal circulation into and through the placenta to the fetus requires the coordinated activity of multiple transport proteins, which function differentially in the MVM and BM to provide and maintain the appropriate levels of specific amino acids required for protein synthesis and energy metabolism.

CHANGES ASSOCIATED WITH ABNORMAL FETAL GROWTH

Fetal growth restriction connotes changes in the demonstrated and proposed mechanisms of nutrient transport sufficient to preclude normal fetal growth.

Using vesicles prepared from the MVM and BM of the syncytiotrophoblast from placentas of IUGR pregnancies, changes in amino acid transport systems have been demonstrated including both decreased volume and transport capacity for amino acids. Downregulation of systems A, L, and TAU in the MVM results in reduced provision of taurine, lysine, and leucine (52,53). Additionally, reduced activity of lipoprotein lipase, necessary for placental transport of FFA, has been reported in MVM from IUGR pregnancies (54). Diminished transport of leucine and lysine has been detected in BM vesicles (55). The expression and activity of glucose transport proteins is unaltered in IUGR (56).

In vitro studies demonstrating alterations in amino acid transport have served as a prelude to a variety of in vivo investigations attempting to extend in vitro findings. While the numbers of patients in these studies is small, the results to date support the notion of the placenta as an arbiter of amino acid availability.

Fetal blood sampling of 4 AGA and 14 IUGR human pregnancies coincident with a constant infusion of a leucine isotope revealed that the change in steady-state fetal/maternal leucine enrichment was significantly lower for IUGR pregnancies than appropriate-size-for-gestational-age (AGA) pregnancies. Additionally, the magnitude of the decrease in IUGR pregnancies correlated with the clinical severity of IUGR. The conclusion from this work was that the decrease in the fetal/maternal leucine ratio may be due to reduced placental leucine flux and/or increased protein catabolism in the fetal and placental tissues (57).

In a different study of seven AGA and seven IUGR human pregnancies, fetal blood sampling was performed shortly following maternal intravenous bolus administration of a solution containing isotopes of leucine, phenylalanine, glycine, and proline. Leucine and phenylalanine use exchange transporters and are transferred transplacentally more rapidly than amino acids that do not use exchange transporters, such as glycine and proline. Following maternal administration, the fetal/maternal enrichment ratio for the essential amino acids leucine and phenylalanine was significantly reduced in IUGR versus AGA pregnancies, consistent with inhibited transplacental flux. The fetal/maternal enrichment ratio of the nonessential amino acids glycine and proline was not significantly different (58).

Intravenous infusion of a solution of amino acids in 10 patients with uncomplicated pregnancies prior to cesarean section revealed a significant increase in the maternal concentration of all amino acids versus 16 control patients. Umbilical venoarterial differences were measured as an index of placental amino acid provision to the fetus. For most amino acids, the fetal concentration and the venoarterial concentration difference per micromole of oxygen increased, indicating amino acids cross the placenta rapidly. However, the umbilical uptakes of three essential amino acids, threonine, histidine, and lysine, did not change significantly despite increases in the maternal concentration. Thus, increasing maternal concentrations led to an increase in the delivery of most, but not all, amino acids to the fetus (59).

A similar protocol was used to study whether maternal infusion of amino acids could increase umbilical uptake and fetal amino acid concentrations in 18 pregnancies complicated by IUGR. Eight patients received a pre-cesarean section intravenous infusion of a solution of multiple amino acids. The remaining 10 patients were controls. Similar to what was described in uncomplicated pregnancies, the maternal concentration of all amino acids was significantly increased in the infusion group versus the controls. The umbilical uptake in the infusion group was significantly higher for leucine, isoleucine, methionine, arginine, serine, proline, and glycine. By contrast, there was no increase in the uptake of three essential amino acids, lysine, histidine, and threonine, in these IUGR pregnancies (60).

In contradistinction to the attention afforded placental changes in IUGR pregnancies, alterations associated with accelerated fetal growth have been less extensively studied. Evidence to date suggests that surplus substrate alone incompletely explains the pathology of large-for-gestational-age (LGA) fetal growth patterns. Strict glucose control does not necessarily prevent LGA newborns in diabetic pregnancies (61), implicating altered placental transport capacity as another mechanism of abnormal growth. Increased expression and activity of glucose transporters in the BM of pregnancies complicated by type 1 diabetes have been demonstrated (62). Given the fact that glucose delivery to the fetus is mediated by the BM, this is one potential means by which excess glucose is made available to the fetus in spite of maternal normoglycemia. Similar changes have not been reported in LGA pregnancies with gestational diabetes mellitus (GDM) (63). This implicates insulin as a factor in increased glucose transport. BM amino acid transport systems are reportedly unaltered in LGA diabetic pregnancies (64). There are conflicting reports on system A and

system L activity in the MVM of these pregnancies (65). However, these studies involved different populations in one of which the placental weight was increased in proportion to the fetal weight (64), which was not the case in the other study (65). In vivo studies have revealed increased umbilical levels of amino acids in GDM pregnancies with good control (66) and increased umbilical vein and artery glucose levels in fetuses of GDM mothers with normal glucose levels (67).

In summary, as the purveyor of nutrient provision to the fetus, the placenta is a vital organ, not only in the sense of its necessity for fetal survival but also as an entity capable of regulating its own response to maternal and fetal conditions. In considering the maternal-placental-fetal trinity, evidence continues to accumulate delineating the active role of the placenta in adjusting nutrient provision based on a host of ever-changing influences that are normally balanced to sustain equilibrium between maternal supply and fetal demand. Under normal circumstances, the placenta provides the appropriate balance and quantity of glucose, amino acids, and lipids to support optimum or at least adequate fetal growth. Disturbances on either side of the placenta are known to stimulate changes within the MVM and BM of the syncytiotrophoblast intended to compensate so as to protect its charge, the fetus. The response of the placenta to an unfriendly environment is typically to autoregulate as much as possible to best promote fetal survival. This is accomplished via multiple transporters, hormones, and growth factors that coordinate fetal nutrient demands with maternal supply. In so doing, changes may be initiated which, while necessary to maintain fetal viability, result in signaling and long-term changes in nutrient metabolism sufficient to increase the postnatal risks for cardiovascular and metabolic disorders.

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