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REVIEW ARTICLE

Transport of amino acids through the placenta and their role

M. A. Grillo · A. Lanza · S. Colombatto

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Abstract Amino acids are transported across the human placenta mediated by transporter proteins that differ in structure, mechanism and substrate specificity. Some of them are Na^+-dependent systems, whereas others are Na^+-independent. Among these there are transporters composed of a heavy chain, a glycoprotein, and a light chain. Moreover, they can be differently distributed in the two membranes forming the syncytiotrophoblast. The transport mechanisms involved and their regulation are only partially known. In the placenta itself, part of the amino acids is metabolized to form other compounds important for the fetus. This occurs for instance for arginine, which gives rise to polyamines and to NO. Interconversion occurs among few other amino acids Transport is altered in pregnancy complications, such as restricted fetal growth.

Keywords Transport systems · Glycoprotein associated transporters · Indoleamino 2,3-dioxygenase · Polyamines

Introduction

Glucose is the fetus's main fuel and lipids are also important. Amino acids are vital for its development as they are the components of proteins and are essential precursors for the synthesis of non-protein substances, such as nitric oxide, polyamines, neurotrasmitters, purine and pirimidine nucleotides, etc.

M. A. Grillo (✉) · A. Lanza · S. Colombatto
Dipartimento di Medicina e Oncologia Sperimentale,
Sezione di Biochimica, Università di Torino,
Via Michelangelo 27, 10126 Torino, Italy
e-mail: mariaangelica.grillo@unito.it

Maternal plasma amino acid levels are 20–25% below normal as early as the first trimester. All amino acids, except tryptophan, are present in the intervillous space at concentrations 186% higher than in the maternal venous blood. This is in agreement with an active transport mechanism (Camelo et al. 2004).

Placental amino acid uptake is mediated by transporters on the microvillous membrane of the syncytiotrophoblast, while the efflux to the fetus is mediated by transporters on its basal membrane. The placental barrier between the maternal and the fetal circulation is the singular epithelium called the syncytiotrophoblast, whose apical microvillous membrane is in direct contact with the maternal venous blood of the intervillous space, whereas the basal membrane is in front of the fetal circulation through the umbilical circle into the placental villi. The placenta continues to grow and differentiate during pregnancy and its efficiency is enhanced by a tenfold increase in the volume of its villi and an increase from 0.08 to 12.5 m^2 in the area of their enveloping trophoblast accompanied by a reduction of its thickness from 18.9 to 4.1 μm and in the distance btween the maternal and foetal circulation from 55.9 to 4.8 μm (Myatt 2006).

The two membranes contain different types of amino acid transporters.

Table 1 illustrates the transport systems of the placenta divided according to their structure and function, and the amino acids involved. Several transporters are monomeric and usually polytopic proteins. The Na^+-independent transporters comprise heterodimeric transporters composed of a heavy chain, a glycoprotein (the best known are rBAT and 4F2hc), and a light chain linked by a disulfide bond. The heavy chains are thought to have only one transmembrane helix, whereas the light chains are believed to have 12 transmembrane domains.

Table 1 Amino acid transport systems in the placenta

Transport systems	Protein	Substrates
Na^+-dependent systems		
A	SNAT(1, 2, 4)	Alanine, Serine, Proline, Glycine
ASC	ASCT(1, 2)	Alanine, Serine, Cystine
N	SN1	Histidine, Asparagine, Glutamine
X^-_{GA}	EAAT(1–3)	Glutamate, Aspartate
β	TAUT	Taurine
B $^{o,+}$	ATB $^{o,+}$	Cationic and neutral amino acids
GLY	GLYT1	Glycine and Sarcosine
Cationic amino acid transport systems		
y^+	CAT 1–4	Cationic amino acids
Glycoprotein associated transport systems		
asc	asc1/4F2hc	Small neutral amino acids and D-serine
$b^{o,+}$	$b^{o,+}$/rBAT	Cationic and neutral amino acids
L	LAT1,LAT2/4F2hc	Neutral amino acids, branched-chain amino acids and tryptophan
y^+L	y^+LAT1/4F2hc	Cationic amino acids
x_c^-	xCT/4F2hc	Glutamate/cystine exchange
T	TAT1	Aromatic amino acids

Na^+-dependent amino acid transport systems

System A is encoded by three genes that give rise to three subtypes of neutral amino acid transporters (SNAT): SNAT1, SNAT2 and SNAT4. The three isoforms are highly homologous. Gene expression varies from one tissue to another. SNAT2 alone is ubiquitous in mammalian tissues. SNAT1 is expressed in heart, brain and placenta. SNAT4, initially found in the liver only, has now been demonstrated in the placenta also (Desforges et al. 2006). SNAT4 mRNA expression is higher in the first trimester, whereas its protein expression is higher at term. Its location in the two syncytiotrophoblast membranes points to its involvement in amino acid transport across the placenta.

These transporters are involved in the transport of serine and glycine: serine is predominantly transported by system A (SNAT1 and SNAT2) and system L, glycine by system A and system Gly (Dicke et al. 1993). However, uptake of serine is much higher than that of glycine, despite the greater demand for glycine as opposed to serine for protein synthesis (Lewis et al. 2007).

The ASC system mediates transport of the short-chain neutral amino acids, such as alanine, serine, cysteine. Two isoforms are known, ASCT1 and ASCT2. Both are expressed in the human placenta and located in the basal membrane only.

System N is restricted to glutamine, asparagine and histidine. Two isoforms are known in human tissues, but their presence in the human placenta is contested. (Karl et al. 1990; Novak et al. 1997).

The anionic amino acids glutamate and aspartate are not conveyed across the placenta (Hoeltzli et al. 1990), though X^-_{AG}, a Na^+ and K^+ dependent transport system for these amino acids is present in both syncytiotrophoblast membranes (Carriapa et al. 2003). Its five isoforms are called Excitatory Amino Acid Transporters (EAAT 1–5). EAAT 1, 2 and 3 are found in the placenta: isoform 3 predominates in the apical membrane; isoforms 1 and 2 are predominant in the basal membranes. However, since glutamate and aspartate concentrations are much higher in the placenta than in the fetal or in the maternal circulation, glutamine is evidently taken up by the fetal liver and metabolized to glutamate, which is then taken up by the placenta (Jansson 2001).

System β transports β-amino acids. Of these, taurine is essential during fetal life and vital for fetal growth. It is not involved in protein synthesis, but utilized for other processes. Its concentration in the placenta is much higher than in the maternal blood due to the presence of an active Na^+ and Cl^--dependent transport system in the microvillous membrane, with a 2:1:1 Na^+/Cl^-/taurine stoichiometry (Ramamoorthy et al. 1994). Transport in the basal membrane is much less active. However these transporters act in conjunction with an Na^+-independent system. The lower plasma taurine concentration noted in intrauterine growth restriction (IUGR) fetuses is apparently due to reduced transporter activity (Norberg et al. 1998), perhaps as the result of dysregulation, since experiments in YAR cells have shown that the taurine transporter is inhibited by activation of protein kinase C (Kulanthaivel et al. 1991).

Another cationic and neutral amino acid transport system is $B^{o,+}$ (B for broad specificity) (Van Winkle et al. 1990). Leucine transported by this system (Van Winkle et al. 2006) triggers signalling by the "mammalian target of rapamycin" (mTOR), a serine/threonine kinase needed for differentiation of motile trophoblasts. Moreover it is suggested that this system regulates the penetration stage of blastocyst implantation with possible long-term consequences. The importance of mTOR is illustrated by the demonstration by Roos et al. (2007) that mTOR protein is expressed in the transporting epithelium of the human placenta and regulates amino acid transport, though not that by system A.

System G1y is specific for glycine and its methylated derivative, sarcosine.

Cationic amino acid transport systems

Cationic amino acids are transported by four groups of transporter. The first is the y^+ family composed of five confirmed members CAT1, CAT2A, CAT2B, CAT3 and CAT4 (Closs et al. 2006). The CAT1 system is considered to be the major cationic transport system in the placenta (Ayuk et al. 2000). It is a sodium-independent, low affinity and high capacity system. An other system, y^+L is present in the basal membrane and in lower amount also in the microvillous. This system is less sensitive to membrane potential differences (Eleno et al. 1994). The electrical potential gradient across the plasma membrane of the trophoblast provides a strong driving force for the accumulation of the cationic amino acids inside the cell (White 1985). On hyperpolarization the permeability of cationic amino acids of the apical membrane increases more for system y^+ than for system y^+L. This will allow rapid entry of amino acids down the prevailing electrical potential into the cell. Then amino acids will leave the cell through the y^+L system relatively insensitive to membrane potential. This is possible as this sytem can perform an exchange with neutral amino acids in the presence of Na^+.

The other systems are $b^{o,+}$, Na^+-independent, and $\beta^{o,+}$, Na^+-dependent. CAT2A is mainly expressed in liver, while CAT2B, which has a much higher affinity, is induced in many types of cells. By contrast with CAT1, CAT2A is insensitive to transstimulation. Human CAT3 is specific for cationic amino acids.

Glycoprotein-associated transport systems

System asc transports small neutral amino acids and is inhibited by 2-aminoisobutyric acid. It also transports D-serine, which acts as a co-agonist of the NMDA receptors in the central nervous system (Mothet et al. 2000). Asc-1 (the only one found in humans, Palacin et al. 2005), combined with 4F2hc, preferentially operates in an exchange mode (Fukasawa et al. 2000), although not exclusively.

Another heterodimeric system is $b^{o,+}$, formed by a light chain combined with the glycoprotein rBAT. This transporter mediates the Na^+-independent uptake of cationic amino acids and cystine. Its function in the placenta is still under discussion (Jansson 2001).

System L (L for leucine preferring) is expressed in the microvillous and the basal membrane and regarded as the main route for the transport of branched-chain and aromatic amino acids. Two isoforms, LAT1 and LAT2, with different affinities for the substrates, most neutral amino acids, branched as well as aromatic, have long been known. Recent additions are LAT3 identified in human hepatocarcinoma cells (Babu et al. 2003), and LAT4 in the human placenta also (Bodoy et al. 2005).

Other heterodimeric transporters are those of the y^+L family. Its two isoforms y^+LAT1 and y^+LAT2 exchange cationic amino acids against neutral amino acids plus Na^+ (Verrey et al. 2000). y^+LAT1 is present in the placenta.

System x_c^- transports cystine and glutamate. It provides cysteine for glutathione synthesis and has other functions (Christensen 1990). This system is almost ubiquitous in cultured mammalian cell lines. Its physiological role appears to be the entry of cystine and the exit of glutamate. As cysteine is the rate-limiting precursor for glutathione synthesis, the intracellular level of glutathione is regulated by x_c^- activity. This system is formed of two proteins, 4F2hc and a novel protein of 502 amino acids with 12 putative transmembrane domain (Sato et al. 1999), the so-called xCT light chain.

L-tyrosine transport in the human placenta is different in isolated brush borders and basal membrane vesicles: in the first case, system L is thought to be responsible, in the second, system T (Kudo and Boyd 1990). TAT1 (T-type amino acid transporter 1) has since been shown to display Na^+-independent and low affinity transport of aromatic amino acids (tryptofan, tyrosine, phenylalanine). As TAT1 mRNA is strongly expressed in the placenta, TAT1 may be responsible for its system T activity (Kim et al. 2001).

For other tissues, it has been suggested that TAT1 controls the amino acid efflux via LAT2-4F2hc. This would suggests that by allowing aromatic amino acids to efflux, TAT1 provides the obligatory exchanger LAT2-4F2hc with influx substrates and therefore controls the net efflux of other neutral amino acids (Ramadan et al. 2007).

Metabolism of amino acids in the placenta

The fate of the serine taken up is not known. Serine hydroxymethyl-transferase, which transforms serine into glycine, is very low in the placenta (Lewis et al. 2005). Moreover, the source of glycine, which is required by the fetus in large amounts, remains to be established. It may be derived from serine that has crossed the placenta, or from the serine synthesised in the fetus from glucose via 3-phosphoglycerate. The second mechanism would increase the amount of methylenetetrahydrofolate needed for the synthesis of purine nucleotides. According to Cetin (2001), the fetal liver is also able to transform glycine into serine by the combined action of serine hydroxymethyltransferase and glycine dehydrogenase.

Arginine has several functions. It is used for protein synthesis, the synthesis of nitric oxide (NO) by nitric oxide synthases (NOS) and the synthesis of polyamines through the formation of ornithine: this can also be a precursor of proline.

Nitric oxide is an important endogenous regulator of vascular tone, in health and disease. This occurs in the placental regulation also. NOS isoforms are actively expressed in the syncytiotrophoblast. Activity appears to be mainly Ca^{++}-dependent, due therefore to eNOS. However iNOS is the predominant isoform in the human pregnant uterus (Ali et al. 1997) and iNOS mRNA is detected early in the syncytiotrophoblast and placental artery smooth muscle (Baylis et al. 1999).

A functional link has been suggested between CAT1 and eNOS, and CAT2B and iNOS, ensuring appropriate delivery of L-arginine to these NOS isoforms (Casanello et al. 2007). Higher expression of the human transporter hCAT1 mRNA and eNOS has been observed in gestational diabetes. It is suggested that this results from an increase of extracellular adenosine level. Activation of protein kinases would then activate arginine transport (San Martin and Sobrevia 2006; Vasquez et al. 2004).

When arginine is metabolized by arginase, ornithine and urea are formed. Two forms of arginase are known: arginase I, located in cytotrophoblasts only, and arginase II is also located in syncytiotrophoblasts where eNOS is equally present, which means that the two enzymes compete for the substrate, arginine. The ornithine thus formed can be used for polyamine synthesis. It has been shown that polyamines play essential roles in the maintenance of early pregnancy. And in ovine placenta it has been shown that in these conditions ornithine decarboxylase (ODC), the regulatory enzyme of polyamine synthesis, and arginase activities and polyamine concentration were highest (Kwon et al. 2003). Moreover, experiments performed by administering difluoromethylornithine (DFMO), an ODC inhibitor, to rats have shown that placental weight, ODC activity and DNA are significantly decreased. Depression of ODC activity has been postulated as the major cause of IUGR induced in rats by DFMO (Ishida et al. 2002).

Polyamines are also taken up, although the identity of the transporter(s) is still unknown (Phanstiel et al. 2007). In the intestinal epithelial cells only polyamines have been suggested to be taken up by a y^+ unknown transporter utilized by lysine also (Sharpe and Seidel 2005). Experiments performed in JAR human placental choriocarcinoma cells have shown that they are taken up and released by an independent mechanism. Ornithine decarboxylase and spermidine/spermine acetyltransferase (SSAT) activities and the intake and output transport rates are much higher than in e.g. L1210 cells. As a result, a much higher concentration of polyamines is observed. The uptake appears to be regulated by an inhibitory protein, possibly ODC-AZ. Moreover, protein kinase C (PKC) appears to be involved (Fontana et al. 1996). In other cells, too, such as astrocytes, some isoforms of the glutamate transporter would seem to be regulated by PKC (Susarla et al. 2004). It is now clear that systems y^+ and y^+L are downregulated by PKC in different cell lines (Rotmann et al. 2007).

In the human placenta, arginase activity is highest in the first trimester and then decreases. It is suggested that this early elevation may be responsible for proliferation of human trophoblasts by increasing polyamine production (Ishikawa et al. 2007).

Surprisingly, placental polyamine synthesis is different in an other mammal: in the porcine placenta it occurs mainly from proline through the action of proline oxidase and ornithine aminotransferase, whereas arginase is not detectable (Wu et al. 2005).

Tryptophan transport across the syncytiotropboblast is an important function of system L, whereas part of the tryptophan taken up is transported across the basal membrane by means of system LAT-2 and system y^+L (Kudo and Boyd 2001a). System y^+L is a high affinity route whose importance increases when the tryptophan concentration is low. Both systems display "trans" effects with other extracellular amino acids (Kudo and Boyd 2001b). Yet another part of the tryptophan taken up is metabolized by indoleamine 2,3-dioxygenase (IDO), an enzyme thought to suppress the maternal immune response to the allogenic murine fetus and hence required to prevent rejection of the fetus by maternal T cells. As blockers of the activity of tryptophan inhibit its transport by system L and vice versa, its uptake by system L is thought to be rate-limiting and of importance in the maintenance of pregnancy (Wagner et al. 2001). Cytokines, such as interferon γ, induce IDO and tryptophanyl-tRNA synthesis is increased at the same time with the result that the ability of the placenta to synthesise protein is not impaired (Mellor and Munn 1999).

However, the idea that IDO prevents rejection of the fetus and that this is due to a decrease in tryptophan concentration has been followed by another suggestion, namely that the tryptophan metabolites 3-hydroxy-kynurenine, 3-hydroxy anthranilic acid and to a lesser extent kynurenine and picolinic acid, which were shown to inhibit T-cell proliferation (Frumento et al. 2002; Terness et al. 2002) are responsible. It has also been suggested that NO can have a role,either affecting the immune system directly or the IDO pathway (Gonzalez et al. 2004). At low NO production, therefore, IDO activity would be increased, whereas in the event of inflammation iNOS would be induced and high NO production would inactivate IDO and favour the immune response (Lopez et al. 2006). However, it has not yet been shown that IDO has an immunoregulatory role in vivo (Terness et al. 2006).

Interconversion also occurs between glutamine and glutamate. Glutamine is taken up by the fetal liver (Marconi et al. 1989). About 45% is converted to glutamate (Battaglia 2000) and utilized within the uterus and placenta, where it gives rise to NADPH useful for other syntheses, and to ammonia, wich will be excreted (Cetin 2001). However in the sheep fetal liver at parturition a striking reduction in glutamate output was observed, leading to a marked decrease in placental glutamate uptake (Battaglia 2000).

Part of the glutamate is also used with cysteine and glycine to form glutathione. This synthesis is possible in the placenta since it contains both the enzymes required, namely glutamyl-cysteine synthetase and glutathione synthetase (Wellner et al. 1974). The observation has been confirmed in mouse embryo, where the mRNA for both the subunits necessary for glutamate-cysteine synthetase have been detected, and also the protein subunit possessing catalytic activity (Diaz et al. 2002). However, the protein expression is strictly regulated (Diaz et al. 2004). This synthesis is important, as GSH is necessary for many functions, such as detoxification of xenobiotics, removal of hydrogen peroxide and free radicals, maintainance of free protein sulphydryl groups, glutathionylation of several proteins, etc. All the enzymes involved, i.e. glutathione peroxidase, GSSG reductase, GSH S-transferase (GSTP1-1) and gamma glutamyltranspepetidase are present in the human placenta.

GSTP1-1 has other functions. It inhibits c-Jun N-terminal kinase signalling through interaction with the C terminus (Wang et al. 2001) and may thus be supposed to participate in regulation of the cell cycle, DNA repair and apoptosis (Adler et al. 1999). However GSH used by peroxidase and reductase is regenerated, whereas that used by the transferase is consumed and must be replaced by resynthesis from its amino acids. Moreover, it has been suggested that glutathionylated proteins can also be formed by other mechanisms, that is in response to oxidative and nitrosative stress (Klatt and Lamas 2000). Here, too, however, GSH is consumed.

Since GSTP1-1, like the other human GST classes, has bene shown to bind NO, they have been proposed as intracellular NO carriers or scavengers (Cesareo et al. 2005).

Branched-chain amino acids are transaminated in the placenta and give rise to glutamate. Leucine can also be deaminated and give rise to its ketoacid. Then ammonia is released to the maternal circulation, whereas the ketoacid and leucine itself are transferred to the fetus. However states of protein accretion and positive nitrogen balance are associated with downregulation of the rate of transamination of leucine (Kahlan and Parimi 2006).

Conclusion

These findings show that the transport of amino acids through the placenta is essential for the fetus. However, the relationship between placental function and the fetal growth rate deserves further study. The plasma amino acid concentration of IUGR delivering babies at birth is higher than in the case of appropriately grown for gestational age babies (Malandro et al. 1996; Cetin et al. 1996). Jansson et al. (2006), however, have shown that IUGR in human pregnancy is associated with down-regulation of transporter system A and that this reduction precedes IUGR. According to Shibata et al. (2006) an enhanced placental renin-angiotensin system is a potential contributor to the reduced system A amino acid transport in IUGR. It must not be forgotten, however, that the transport of any amino acid from placenta to fetus depends on the presence of inhibitory amino acids (Jozwik et al. 2004). Therefore administration of amino acids would be useful, provided due considerations were given to the right composition of their mixture.

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