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MINIREVIEW ARTICLE

Glutamate–glutamine cycle and exchange in the placenta–fetus unit during late pregnancy

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Abstract The present review focuses on the physiological functions of glutamate–glutamine exchange involving placental amino acid transport and umbilical amino acid uptake in mammals (particularly in sows), with special emphasis on the associated regulating mechanisms. Glutamate plus glutamine are among the most abundant and the most utilized amino acids in fetus during late gestation. During pregnancy, amino acids, notably as precursors of macromolecules including proteins and nucleotides are involved in fetal development and growth. Amino acid concentrations in fetus are generally higher than in the mother. Among amino acids, the transport and metabolism of glutamate and glutamine during fetal development exhibit characteristics that clearly emphasize the importance of the interaction between the placenta and the fetal liver. Glutamate is quite remarkable among amino acids, which originate from the placenta, and is cleared from fetal plasma. In addition, the flux of glutamate through the placenta from the fetal plasma is highly correlated with the umbilical glutamate delivery rate. Glutamine plays a central role in fetal carbon and nitrogen metabolism and exhibits one of the highest fetal/maternal plasma ratio among all amino acids in human and other mammals. Glutamate is taken up by placenta from the fetal circulation and then converted to glutamine before being released back into the fetal circulation. Works are required on the glutamate–glutamine metabolism during late pregnancy in physiological and pathophysiological situations since such works may help to improve fetal growth and development both in humans and other mammals. Indeed, glutamine supplementation appears to ameliorate fetal growth retardation in sows and reduces preweaning mortality of piglets.

Keywords Glutamate · Glutamine · Placenta–fetus unit · *N*-carbamoylglutamate

Abbreviations

BCAA	Branched-chain amino acids
CoA	Coenzyme A
CPS1	Carbamyl phosphate synthetase 1
GDM	Gestational diabetes
GS	Glutamine synthetase
IUGR	Intrauterine growth restriction
MSG	Monosodium glutamate
NADPH	Nicotinamide adenine dinucleotide phosphate
NAG	*N*-acetylglutamate
NAGS	NAG synthase
NCG	*N*-carbamoylglutamate
GDH	Glutamate dehydrogenase

Introduction

Fetal growth and development are dependent upon the adequate provision of oxygen and substrates from the

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maternal circulation. Understanding the link between placental functions and fetal growth is critical to comprehend the mechanisms underlying altered fetal growth, not only for humans in a clinical perspective; but also for animals like pigs in an agronomic perspective. The placenta is the organ responsible for the exchange of nutrients, gases, metabolic waste and biologically active substances between the maternal and the fetal system. Thus, placenta by supporting the required blood flow plays a central role in the growth and development of the fetus (Campos et al. 2012). The fetus exerts an acquisitive demand for nutrients, which is satisfied through morphological and functional adaptations of the placenta (Larque et al. 2013). This is particularly crucial when the genetically determined drive for fetal growth is compromised by adverse intrauterine conditions. These adaptations change the efficiency by which the placenta supports fetal growth, resulting in optimal growth for the conditions prevailing in utero (Fowden et al. 2009). Fetal growth is primarily determined by nutrient availability, which is intimately related to placental nutrient transport (Jones et al. 2007). In mammals, intrauterine growth depends on the size, morphology, blood supply and transport capacity of the placenta, as well as on synthesis and metabolism of nutrients by the uteroplacental tissues (Cetin and Alvino 2009; Fowden et al. 2006).

During pregnancy, amino acids are important precursors for fetal development and growth, in relationship notably with the biosynthesis of macromolecules including proteins and nucleotides, signaling functions of amino acids (by themselves or through the production of metabolites); and ATP production (Wu et al. 2013a). Amino acid concentrations are generally higher in fetus than in mother. Fetal growth is dependent on both the quantity and relative composition of amino acids delivered to the fetal circulation, and impaired placental amino acid supply is associated with restricted fetal growth (Cleal et al. 2007). The relevance of these differences to fetal growth is strongly suggested by a number of studies demonstrating differences in amino acid placental transfer and metabolism occurring in human pregnancies associated with intra uterine growth restriction (IUGR) when compared with the normal situation (Cetin 2001; Lin et al. 2014). The role of placental blood flow for the supply of amino acids (including glutamate and glutamine) from mother to fetus in pregnancies must be emphasized particularly in situation of IUGR. All amino acids, except tryptophan, are present in the intervillous space at concentrations nearly twofold higher than in the maternal venous blood in humans (Camelo et al. 2004). Thus placental amino acid transfer to fetus through transporters in placenta plays key roles (Avagliano et al. 2012; Lewis et al. 2013). Among amino acids, the transport and metabolism of glutamine and glutamate during fetal development exhibit unique characteristics that clearly emphasize the importance of the interaction between the placenta and the fetal liver, with important physiological consequences (Regnault et al. 2002; Wu 2013).

Glutamate–glutamine cycle and exchange in the placenta–fetus unit

Glutamate–glutamine cycle

The nonessential amino acid L-glutamate is extensively metabolized by enterocytes in various pathways, including those involved in enterocyte protein synthesis, in the production of other amino acids and intracellular compounds like glutathione, and in ATP production through its oxidation (Fig. 1) (Blachier et al. 2009). However, it is worth to note that, as indicated in recent articles, the dietary requirements must be determined not only for essential amino acids but also for semi-essential and nonessential amino acids (Wu et al. 2013c, 2014). Glutamate is widely represented in proteins among other amino acids (Brosnan and Brosnan 2013). Indeed, glutamate is a major amino acid in alimentary and endogenous proteins. Glutamate is also present in its free form in cells of animal and plant tissues. In contrast, glutamate is present only at low concentrations in blood plasma mainly because of large utilization by the intestinal epithelium during the process of transfer from the luminal content to the bloodstream. Glutamate is implicated in numerous physiological and metabolic functions in

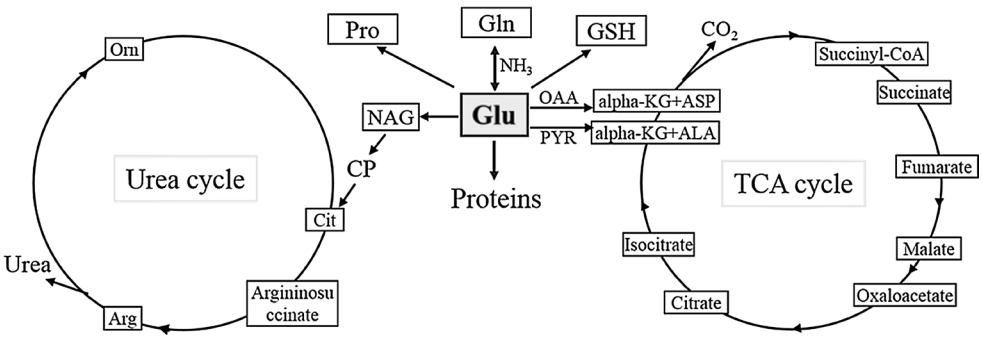

Fig. 1 Schematic view of the general glutamate metabolism in mammals. alpha-KG, alpha-ketoglutaric acid; *ALA* alanine; *Arg* arginine; *ASP* Aspartic; *Cit* citrulline; *CP* carbamyl phosphate; *Gln* glutamine; *GSH* glutathione; *Glu* glutamate; *NAG N*-acetylglutamate; *OAA* oxaloacetate; *PYR* pyruvate; *Orn* ornithine; *Pro* proline; *TCA cycle* tricarboxylic acid cycle

the body. Glutamate is the precursor of the metabolic regulator *N*-acetylglutamate (NAG) which is an allosteric activator of carbamoylsynthetase 1, the first enzyme of the urea cycle. In addition, glutamate is an excitatory neurotransmitter, and free glutamate in the food, also known as the umami taste, represents one of the five basic tastes (Nakamura et al. 2008).

Many of the glutamine functions are connected to the formation of glutamate from glutamine. Glutamine can be converted into glutamate and ammonia through the catalytic activity of glutaminase. Interestingly, it has been shown in pig enterocytes that exogenous glutamate can decrease glutamine utilization by inhibiting the glutaminase activity (Blachier et al. 1999). However, glutaminase is virtually absent from the placenta of several species (e.g. the pig). Glutamine also serves as an essential precursor for the synthesis of proteins, purine and pyrimidine nucleotides, and amino sugars (Wu 2009). Glutamine is important not only for energy supply and as a precursor for nucleotide synthesis; but also as a signal for cell proliferation (Yamauchi et al. 2002) and protein biosynthesis (Blachier et al. 2009). Such disparate glutamine levels between mother and fetus suggest that glutamine is actively synthesized and released into the fetal circulation by the porcine placenta (Self et al. 2004).

There are two major enzymes in glutamine metabolism in cells: glutaminase and glutamine synthetase (GS). The former enzyme will degrade glutamine into glutamate and ammonia, while the latter will catalyze glutamine synthesis from glutamate and ammonia. In neurochemistry, to make a long story short, the glutamate–glutamine cycle is a sequence of events by which an adequate supply of the neurotransmitter glutamate is maintained in the central nervous system.

In fact, the glutamate–glutamine cycle is operative in several cell types including colonocytes (Andriamihaja et al. 2010) where it acts as a way to control ammonia intracellular concentration. As presented below, glutamate–glutamine cycle and exchange in the placenta–fetus unit are related to important physiological functions in gestation, especially during fetal development.

Glutamate–glutamine exchange in the placenta–fetus unit

Dietary requirement of amino acids for the placenta–fetus unit has to be considered not only regarding essential amino acids (which cannot be synthesized by the fetus or the placenta) but also regarding "nutritionally nonessential amino acids" (Wu et al. 2013c, 2014). The amino acid dietary requirement depends partly on the umbilical uptake characteristics for these different amino acids. Glutamate–glutamine is among the most abundant and the most accreted amino acids in fetal pigs in late gestation. In vivo, the umbilical uptake allows the nutritional supply of amino acids to the fetus. During gestation, the most abundant amino acid in placental tissue of sow is glutamate/glutamine closely followed by glycine, and proline (Wu et al. 2013b). In the pig placenta, the concentrations of glutamine increased progressively between days 20 and day 40 of gestation, and glutamine levels are highest between days 40 and 60 of gestation and declined thereafter; while concentrations of glutamate and alanine in placenta remain relatively constant throughout gestation in porcine placenta (Self et al. 2004). From days 60 to 114 of gestation, fetal accretion rate for glutamate/glutamine is the highest, followed by glycine, proline plus hydroxyproline, aspartate/asparagine, leucine, arginine, alanine and lysine in decreasing order (Fig. 2) (Wu et al. 1999).

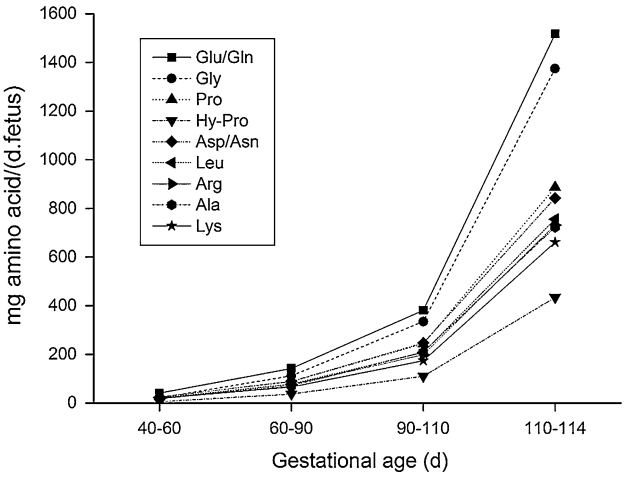

Fig. 2 Rates of amino acid accretion in fetal pigs. Data are compiled from Wu et al. (1999)

Glutamate is quite remarkable among amino acids which originate from the placenta is cleared from fetal plasma. Furthermore, in mammals the flux of glutamate into the placenta is highly correlated to the umbilical glutamate delivery rate. The placental clearance for fetal plasma is highest for glutamate followed by leucine, serine, alanine, glycine and tyrosine, while plasma clearance for maternal plasma is highest for methionine followed by phenylalanine, isoleucine, leucine, valine, tryptophan, threonine, histidine and lysine (Fig. 3) (Regnault et al. 2002). Glutamate is taken up from the fetal circulation and then converted to glutamine before being released back into the fetal circulation. The concentration of glutamate in the umbilical venous blood is approximately 10 % of the fetal arterial concentration, with umbilical venous glutamate concentrations representing approximately 20 % of fetal arterial concentration (Timmerman et al. 2000). A large net efflux of glutamate from the fetal liver sustains the fetal glutamate concentration. If hepatic release is reduced, as observed

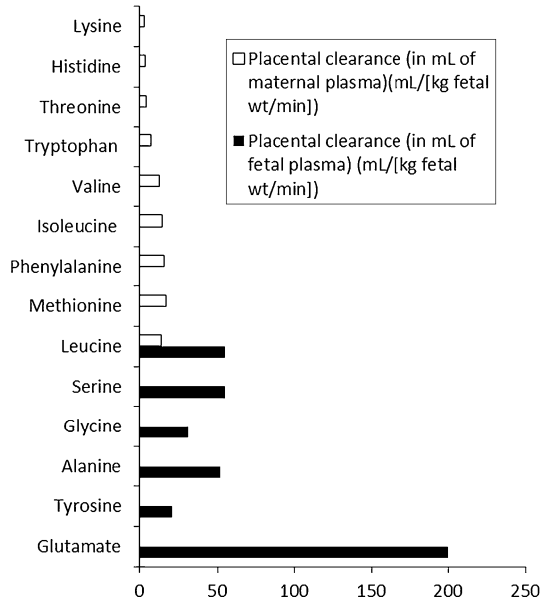

Fig. 3 Schematic view of the placental blood flow to and from the fetus. Data are compiled from Regnault et al. (2002)

during dexamethasone-induced parturition, glutamine plays a central role in fetal carbon and nitrogen metabolism and exhibits the highest fetal/maternal plasma ratio among all amino acids in pigs (Wu et al. 2011).

Throughout most of the gestation, there is an interorgan exchange of glutamine and glutamate between the placenta and fetal liver. The hypothesis of glutamate–glutamine cycle and exchange has been proposed to be functional also between the mother and the fetus (Battaglia 2000; Vaughn et al. 1995). The fetal glutamate concentration thus falls dramatically and the glutamate placental uptake is proportionally reduced. The fetal liver, through its production of glutamate, controls the supply of an important oxidative fuel for the placenta in most mammals including human, pig and sheep (Fig. 4). This is demonstrated by the observation that when L-(1-^{13}C) glutamate is infused into the fetal circulation, approximately 70 % of the glutamate is oxidized, including the fraction taken up by the placenta. Placental glutamate uptake from fetal circulation is also used for glutamine production and contributes to 5 % of the umbilical glutamine uptake (Moores et al. 1994; Vaughn et al. 1995).

The results obtained with the sheep model showed that glutamine is taken up by the fetal liver, and 45 ± 8 % of the glutamine taken up is released as glutamate. The fetal liver released large quantities of glutamate, as evidenced by a sixfold increase in plasma glutamate concentration in the blood flowing through the left hepatic lobe; and by a hepatic glutamate output-to-O_2 uptake molar ratio of 0.15 ± 0.01. In conjunction with a previous study in the sheep model on the fetal glutamate metabolism, data demonstrate that glutamine entering the fetal circulation is converted to glutamate by the fetal liver at a rate of approximately 3–4 μmol min^{-1} kg $fetus^{-1}$ (Moores et al. 1994; Vaughn et al. 1995). Results show that for the human placenta, there is no net transfer of glutamic acid from the mother to the fetus; and a very efficient placental system for glutamate uptake across the fetal surface is functional (Fig. 3).

Physiological functions of glutamate–glutamine cycle and exchange in gestation

Physiological functions of glutamate–glutamine cycle and exchange

Firstly, glutamate is the major precursor of glutamine, which reinforces the importance of the direct link between placenta and fetal liver. The functions of glutamine are numerous and include the role of this amino acid as a

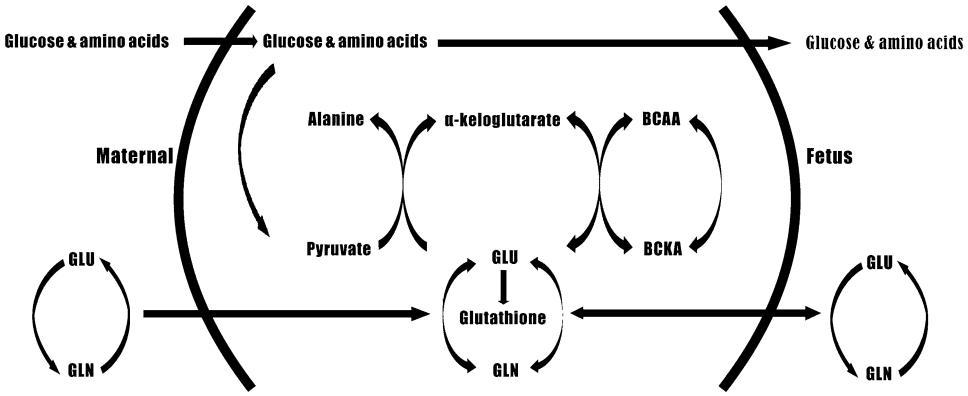

Fig. 4 Schematic diagram of Glutamate–Glutamine exchange in the placenta–fetus unit. *BCAA* branched-chain amino acids; *BCKA* branched-chain keto acid; *GLU* glutamate; *GLN* glutamine. Please note that the relative flux of substrates in the different metabolic pathways is not indicated in the figure

substrate for protein synthesis and as an anabolic precursor for muscle growth. Glutamine may also be involved in numerous physiological and metabolic functions including the acid–base balance in the kidney, the role as a substrate for ureogenesis in the liver and as a substrate for hepatic and renal gluconeogenesis, the role as an oxidative fuel for intestine and cells of the immune system and as an interorgan nitrogen transport, the role as a precursor for neurotransmitter synthesis and as a precursor for nucleotide and nucleic acid synthesis and finally the role as a precursor for glutathione production (Newsholme et al. 2003a, b). Many of these functions are connected to the formation of glutamate from glutamine. Secondly, glutamate and glutamine are the main metabolic fuel source for rapidly dividing cells in placenta and fetal liver (Marc Rhoads and Wu 2009). Thirdly, placental glutamate oxidation is linked to placental nicotinamide adenine dinucleotide phosphate (NADPH) production (Kovacevic and McGivan 1983).

Glutamate–glutamine cycle and intrauterine growth restriction

Malnutrition is well known to be a major cause of pregnancy complications, such as intrauterine growth restriction (IUGR), or even worse, like embryonic loss and fetal death during gestation (Lin et al. 2014). Metabolites (including amino acids, glucose, ammonia, urea, and lipids) in umbilical vein plasma exhibited a cluster of differences between IUGR and NBW fetuses on d 90 and 110 of gestation (Lin et al. 2012). Impaired placental amino acid supply is associated with IUGR (Cleal et al. 2007). In IUGR pregnancy, placental expression of glutamate dehydrogenase (GDH) mRNA is reduced compared to normal pregnancies, and GDH protein expression is also slightly but significantly reduced in IUGR placenta compared to normal placenta; whereas GS and GA mRNA and protein expression are not different between the two types of pregnancy (Jozwik et al. 2009). Low birth weight newborns had lower levels of glutamine, proline, and alanine than did the control newborns (Ivorra et al. 2012). These results indicate that for IUGR, glutamate-to-alpha-ketoglutarate transformation in the placenta is limited, yet glutamine synthesis followed by reconversion to glutamate seems to be preserved. This may reflect down-regulation of GDH in response to decreased fetal liver output and reduced umbilical artery glutamate concentrations in human IUGR pregnancies. In a recent report, it has been shown that intrauterine growth restriction alters the hepatic proteome in fetal pigs. Notably and of particular interest, the IUGR fetus had a higher activity of glutamate oxaloacetate transaminase than the normal-weight counterpart at Day 110 of gestation (Liu et al. 2013).

Maternal testosterone (an intermediate in the biosynthetic pathway for estrogen synthesis) concentration affects amino acid delivery to the fetus by down-regulating specific amino acid transporter activity, which may play a role in IUGR (Sathishkumar et al. 2011). Some drugs also affect glutamate–glutamine cycle and exchange. Intravenous infusion of dexamethasone in the fetal lamb causes a two- to threefold increase in plasma glutamine and other glucogenic amino acids and a decrease of plasma glutamate to approximately one-third of the normal value (Timmerman et al. 2000).

Glutamate–glutamine cycle and exchange in fetuses

In a recent study using the sheep model, twin fetuses were 16 % lighter than singletons and had a smaller placenta, with 28 % decreased placentome weight and 35 % fewer placentomes (van der Linden et al. 2013). In twins, umbilical artery plasma is characterized by lower glutamate concentration and greater glutamine concentration than concentrations measured in fetal plasma or umbilical vein plasma. However, no difference in amino acid concentrations was observed between these pools in singletons (van der Linden et al. 2013). It has been demonstrated that in the hypoxic IUGR fetus, the reduction in amino acid uptake is not due to a disproportionally small placental amino acid transport capacity. It rather appears as the consequence of decreased fetal oxidative metabolism and growth rate combined to reduced fetal amino acid demand (Regnault et al. 2013).

Placental glutamine synthesis may help to ensure the placenta's ability to supply this amino acid to the fetus thus avoiding that this becomes limiting for fetal growth. Glutamine synthesis may also influence placental transport of other amino acids, metabolism, nitrogen flux and cellular regulation. In umbilical vein and artery of pregnant females with gestational diabetes (GDM), significant increases of amino acid concentrations are observed for valine, methionine, phenylalanine, isoleucine, leucine, ornithine, glutamate, proline, and alanine; whereas glutamine concentration is significantly decreased. This is related to the fact that placental amino acid exchange is altered in GDM pregnancies (Cetin et al. 2005). Moreover, the changes observed for glutamine and glutamate in the umbilical samples suggest that in GDM, the fetal hepatic production of glutamate is increased, likely as a consequence of the endocrine changes in the fetal compartment (Cetin et al. 2005).

Glutamate/glutamine and reproduction

In humans, the infants are dependent on endogenous synthesis and on exogenous supply of glutamine to meet the challenges of the external environment and a tripling of

body weight in the first 3–4 months of life (Neu 2001). Supplementation with some functional amino acids (e.g. arginine and glutamine) may be useful for preventing fetal growth restriction and improving health and growth of IUGR neonate (Wu 2013). Indeed, supplementing 1 % glutamine to the swine diet during late gestation enhances fetal growth, ameliorates fetal growth retardation in gilts and reduces preweaning mortality of piglets (Wu et al. 2011). Recently, it has been reported that administration of alcohol to pregnant ewes led to a 21–30 % reduction in the plasma concentrations of glutamine and related amino acids, Furthermore, acute administration of glutamine to ewes, together with alcohol administration, was able to improve the profile of most amino acids (including citrulline and arginine) in both maternal and fetal plasma (Washburn et al. 2013). L-Glutamine supplementation is able to mitigate the alcohol-induced acid–base imbalances and the alterations of the fetal regional brain blood flow (Sawant et al. 2014).

Studies have shown that dietary glutamate metabolism in newborn piglets relates to the synthesis and requirements of arginine and proline (Wu 1998). It has been proposed that proline, but not glutamate, would be the major contributor to arginine synthesis in human preterm infants (Tomlinson et al. 2011). Glutamine is also a possible precursor for L-arginine in enterocytes, this latter amino acid being a precursor for nitric oxide synthesis in murine macrophages (Murphy and Newsholme 1997), although the conversion of arginine into nitric oxide and citrulline is quantitatively relatively minor when compared with the other L-arginine catabolic pathway that is through arginase catalytic activity. L-Arginine concentrations are likely to be higher in the syncytiotrophoblast cytosol than in the maternal or fetal plasma in pigs (Cetin et al. 1996). L-Arginine may stimulate placental growth and the transfer of nutrients from mother to embryo or fetus promoting conceptus survival, growth, and development (Wu et al. 2010). It has been reported that the number of piglets born dead per litter was significantly decreased in arginine-supplemented group suggesting that this amino acid may help to meet fetal growth requirements during late gestation in pigs. In recent studies, the use of L-arginine supplementation was proved to enhance the reproductive performance of pigs (Gao et al. 2012; Mateo et al. 2007). It is worth to note that placenta can synthesize glutamine from branched-chain amino acids (BCAA) and release glutamine into the fetal circulation; a process which may affect the Gln–Glu cycle (Self et al. 2004).

With the major recent changes introduced in the pig production, notably in China; reproductive efficiency of sows has been improved. However, to obtain more fetuses and higher fetal growth rates require an increased provision of nutrients for supporting the metabolic needs of both the sow and her fetuses. High embryonic loss and fetal deaths during gestation obviously limit the number of piglets born alive (Town et al. 2005). Supplementation with glutamate may represent a way to increase the efficiency of pig production. Indeed, a recent publication has clearly shown that dietary supplementation with MSG in post-weaned pigs is safe and improves growth performance as well as plasma concentrations of several amino acids including glutamate, glutamine, lysine, methionine, phenylalanine and leucine (Rezaei et al. 2013). Although the effects of MSG given to the mother on the fetus have not, to the best of our knowledge, been tested; it has been shown that maternal glutamate supplementation results in a sharp increase in maternal plasma glutamate levels but had no effect upon fetal glutamate levels in the primate (Stegink et al. 1975). In addition, glutamate may play a beneficial role for the control of lipid peroxidation in pregnancy, as well as in the prevention of free radical-linked deleterious effects that can affect the health of both mother and fetus (Salvolini et al. 2012). However, some key functions of Glutamine (synthesis of Gln-tRNA, aminosugars, carbamoylphosphate, NAD(P), as well as purines and pyrimidines; renal ammoniagenesis; and regulation of ODC expression) cannot be met by glutamate (Wu 2009). Glutamate–glutamine cycle and exchange may thus play important beneficial roles in sows' reproduction; but obviously, more experimental works are required to test this important working hypothesis. Incidentally, sows represent a good animal model for the research in the field of reproduction, and a large set of data have been obtained with this animal. This is notably due to its large agronomical utilization for meat production, and as an experimental model with analogy with human physiology including nutrition.

Placental glutamine synthesis has been demonstrated in animals and is thought to increase the availability of this metabolically important amino acid to the fetus (Day et al. 2013). In studies with pigs, Self et al. (2004) first reported glutamine synthesis from branched-chain amino acids in the mammalian placenta. Recently, glutamate metabolism was investigated in the isolated dually perfused human placental cotyledon. L-(U-^{13}C)glutamate was used to investigate the fate of carbon atom and L-(^{15}N)leucine to study the fate of amino-nitrogen atom. Labeled amino acids were perfused via maternal or fetal arteries at defined flow rates, and the enrichment and concentration of amino acids in the maternal and fetal veins were measured following 5 h of perfusion. The results showed that glutamate taken up from the maternal and fetal circulations was primarily converted into glutamine; the majority of which was released into the maternal circulation. Enrichment of ^{13}C or ^{15}N glutamate in placental tissue was lower than in either the maternal or fetal circulation, suggesting metabolic compartmentalization within the syncytiotrophoblast (Day et al. 2013).

Potential neurotoxicity of glutamate in pathological conditions

Glutamate, one of the most common amino acids found in plants and animals, is present at a high level in many proteins and peptides and in most tissues when compared with other amino acids (Brosnan and Brosnan 2013). Under physiological conditions, glutamate in the plasma is not toxic to either mother or fetus. However, when glutamate levels increase in the maternal or fetal plasma under pathological conditions or intentional overconsumption of glutamate, and/or when the blood–brain barrier is affected, toxicity may occur. As said above, glutamate is a major excitatory neurotransmitter in the mammalian central nervous system (Gottlieb et al. 2003). Although glutamate plasma level can be controlled in part by high catabolism in the enterocytes during transfer from the lumen to the bloodstream (Blachier et al. 2009), high circulating levels may be neurotoxic for the foetus, and thus, the glutamate level in the fetal circulation must be tightly controlled. With rat as a model, it was found that maternal oral administration of MSG (2.5 or 4.0 mg/g body weight/day) given at a late stage of pregnancy decreases the threshold of convulsion in the litters at 10 days of age postnatal age. Furthermore, the results of the Y-maze discrimination learning test were found to be significantly impaired after MSG supplementation in the 60-day-old filial mice (Yu et al. 1997).

Fetal nutrition is obviously not simply related to the amount of nutrients reaching the fetus, but also to the balance of nutrients. The relative availability of specific amino acids may determine the pace and the nature of fetal growth and development. For example, inherited systemic deficiency of glutamine based on a defect of glutamine synthetase was recently described in two newborn patients with an early fatal course of disease (Haberle et al. 2005).

Thus, the mechanisms involved in the regulation of the glutamate–glutamine cycle and exchange may help to improve the reproduction of animals especially in pigs. This may have important implications for pig production around the world, and asks for new experimental works.

Metabolic regulation of glutamate utilization

As briefly presented in the introduction, NAG is an obligatory allosteric enzyme activator, involved in liver ureagenesis in mammals. NAG activates the first and rate-limiting enzyme of ureagenesis, carbamyl phosphate synthetase 1 (CPS1) (Fig. 1) (Heibel et al. 2012). The enzyme that produces NAG from glutamate and Coenzyme A (CoA), NAG synthase (NAGS), is allosterically inhibited by arginine in microorganisms and plants but activated in mammals (Caldovic et al. 2010). NAC concentration in the liver is closely correlated with the concentration of glutamate, with the NAGS activity in the liver, and with the excretion of urea (Tujioka et al. 2005). In previous studies, supplementation with *N*-carbamoylglutamate (NCG), a safe and metabolically stable analog of NAG, increases the endogenous synthesis of arginine, not only in piglets as initially demonstrated (Wu et al. 2004), but also in sows during late gestation and improves the reproductive performance of sows (Liu et al. 2012). In addition, supplementation with NCG decreased plasma concentration of glutamate and proline while increasing plasma arginine concentration in sows (Liu et al. 2011). These results suggest that NCG improves the reproduction performance of sows (Liu et al. 2012; Wu et al. 2012). From these results, it can be hypothesized that NCG may affect the reproductive performance of animals by regulating the glutamate–glutamine cycle and exchange in the placenta–fetus unit.

Conclusion and perspectives

Glutamate–glutamine cycle and exchange in placenta–fetus unit most likely play important roles in fetal growth and development. When considering the placental amino acid transport and umbilical amino acid uptake, the sparing effect of supplemental glutamate on glutamate–glutamine exchange in placenta is worth to be studied more deeply. Indeed, this may provide a theoretical basis for the nutritional supplementation with amino acids such as glutamine and/or glutamate for improving nutrition of pregnant sows, notably in case of altered fetal growth. Progress in that scientific area will depend on a constant flow of novel experimental data with relevant animal models. Among these latter, the pig model appears to be of particular interest as a model relevant to prudent extrapolation to humans, and as a model for agronomic research.

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Conflict of interest None of the authors have any conflict of interest to declare.

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