**Glutamate and Glutamine in Metabolism**

### Glutamine and Glutamate Exchange between the Fetal Liver and the Placenta

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**ABSTRACT** The transport and metabolism of glutamine (GLN) and glutamate (GLU) during fetal development exhibit unique characteristics that clearly emphasize the importance of the interaction between the placenta and the fetal liver. GLN is delivered into the fetal circulation at a rate that is the highest of all the amino acids. In contrast, ~90% of fetal plasma GLU is extracted by the placenta. Conversely, the fetal liver has a large net output of GLU and a net uptake of GLN. We have studied the fluxes of GLU and GLN into and out of the placenta and fetal liver, as well as their interconversion in these organs, during late gestation in sheep. In the fetus, 45% of GLN carbon taken up by the liver exits as GLU; indeed, the production of GLU from GLN is large, ~3.7 μmol/min-kg fetus), and accounts for virtually all of the GLU produced in the fetus. In contrast, only 6% of GLU carbon is converted to GLN in the placenta; most of the fetal plasma GLU taken up by this organ is converted to CO₂. Remarkably, placental GLU uptake accounts for >60% of the fetal plasma GLU disposal rate. In some respects, the net output of GLU from the liver in fetuses replaces the net hepatic glucose output that is characteristic of postnatal life. We also examined GLN and GLU fluxes in pregnant sheep during either dexamethasone-induced or spontaneous parturition. At parturition, a striking reduction in GLU output from the fetal liver occurred, leading to a fall in fetal arterial GLU concentrations and a marked decrease in placental GLU uptake. These changes were progressive as parturition advanced and correlated with a marked decrease in progesterone output from the pregnant uterus.


**KEY WORDS:** placental uptake • fetal liver • glutamate • glutamine • parturition
acids into and out of the fetal liver and placenta simultaneously. Subsequent studies using this procedure revealed the existence of important interorgan cycles for amino acids between fetal liver and placenta. Specifically, we observed the opposite arrangement for GLU and GLN across the fetal liver than that across the placenta. That is, the fetal liver experiences a large uptake of GLN from the fetal circulation, and a large net hepatic release of GLU, a phenomenon that is not found in normal postnatal hepatic metabolism. In essence, we found the following:

1. The placenta delivers GLN into the fetal circulation;
2. GLN is extracted by the fetal liver and used for the net hepatic release of GLU; and
3. The GLU circulating in fetal blood is taken up by the placenta.

Placental glutamate supply

Because there is little uterine uptake of GLU, placental GLU supply is determined by measuring placental GLU production and GLU delivery to the placenta from the fetal circulation. The coefficient of extraction of GLU from fetal plasma as it perfuses the placenta is 90%, a very high value that is unique to GLU (Moores et al. 1994). Thus, the GLU supply to the placenta is determined primarily by the umbilical delivery rate (represented by the umbilical plasma flow) to the fetal arterial GLU concentration. The latter is a function of fetal hepatic GLU release. Tracer GLU and GLN studies of the fetal lamb have shown that the hepatic production rate of glutamate from glutamine is virtually identical to the total fetal glutamate production rate from glutamine (Vaughn et al. 1995). Thus, the fetal liver is the primary site for glutamate production and, as such, also determines the glutamate supply to the placenta.

Recent data from our laboratory suggest that the placental production of GLU from oxoglutarate may be driven by the high rate of transamination of the branched-chain amino acids (BCAA) to their respective keto acids. The ovine placenta has a high level of activity of the branched-chain transaminases, which is consistent with other data on tracer leucine fluxes across the placenta and in the fetal circulation. These studies have shown that 20–25% of leucine uptake from the maternal circulation is used for the net hepatic release of GLU; and 3) the GLU circulating in fetal blood is taken up by the placenta.

![FIGURE 1](image1.png)

**FIGURE 1** The uterine and umbilical uptakes of glutamate (Glu) and glutamine (Gln) are presented as well as their fetal and maternal arterial concentrations. The uptakes for each circulation were calculated as the (flow × arteriovenous concentration difference). *P < 0.05, ***P < 0.001 (paired t test). From Chung et al. (1998).

**FIGURE 2** Schematic of the infusion and sampling sites utilized for tracer studies in late gestational lambs (see text). Abbreviations: A, maternal artery sample; V, uterine vein sample; a, umbilical artery sample; g, umbilical vein sample; h, left fetal hepatic vein; i, fetal venous infusion; II, maternal venous infusion.

**FIGURE 3** The net fluxes, measured in vivo, of the branched-chain amino acids, glutamine, glutamate and ammonia, into and out of the ovine placenta. The values are expressed in μmol/kg fetus/min. Note the contribution of the branched-chain amino acids to both glutamate and NH₃ production within the placenta. Abbreviations: gln, glutamine; glu, glutamate; akg, α-ketoglutarate; TCA, tricarboxylic acid cycle; bcaa, branched-chain amino acids; aka, branched-chain α-keto acids; NH₃, ammonia. From Chung et al. (1998), Loy et al. (1990), and Józwik et al. (1999).
uptake from the fetal plasma (arteriovenous differences across the umbilical circulation fell from control values of 18 ± 3 to 2 ± 3 μmol/mmol O₂). At the same time, progesterone output from the pregnant uterus also decreased significantly. Thus, the events leading up to parturition are associated with profound changes in fetal hepatic and placental GLU and GLN metabolism. However, with the use of this paradigm, we could not distinguish whether these changes were due to the many endocrine changes associated with parturition or simply to the dexamethasone used to induce parturition.

Our ongoing studies are attempting to clarify this latter issue, but at present are very preliminary. One study examined fetal hepatic and placental GLU and GLN metabolism during spontaneous parturition (Timmerman et al., unpublished observations). The experimental design enables us to sample the fetal circulation, including the hepatic venous circulation and the maternal uterine circulation, beginning 7–10 d before expected parturition. The results to date have revealed both similarities to and differences from dexamethasone-induced parturition. The similarities relate to changes in GLU and progesterone metabolism. During spontaneous parturition, there is a marked decrease in net fetal hepatic GLU output, leading to a decrease in placental GLU uptake from the fetal circulation (see Fig. 5, which presents data for a single animal). Coincident with these changes, progesterone output from the maternal uterus decreases.

A second preliminary study examined whether GLN carbon flux within the fetal liver is altered during parturition (Timmerman et al., unpublished observations). We utilized the model of dexamethasone-induced parturition to study the fluxes of L-[1-13C] GLN and L-[3H4,5] GLU in the fetal circulation. These fluxes were measured in each animal before and after a 25-h fetal infusion of dexamethasone. The most significant finding was that the ratio of 13CO₂ to GLUm was 2.5–4.0 times higher during the dexamethasone infusion compared with a control period. Thus, GLN carbon is redirected into oxoglutarate and the tricarboxylic acid cycle and away from GLU release.

Changes in glutamine-glutamate metabolism during parturition

During parturition, endocrine changes occur in the fetal circulation that signal a shift from the fetal to the postnatal pattern of net hepatic glucose or GLU release. For this reason, we thought it would be instructive to study net hepatic and placental uptake and/or release of GLN and GLU around the time of parturition. To facilitate these studies, we used a fetal infusion of dexamethasone to induce labor in late-gestational fetal lambs (Barbera et al. 1997). The arteriovenous concentration differences for GLN and GLU were measured in a control period that preceded dexamethasone infusion, and then at 25 h and at 40–48 h after dexamethasone infusion began. At 25 h, GLU release from the fetal liver had fallen dramatically from 180 ± 65 to 45 ± 18 μmol/mmol O₂. This change produced a significant fall in fetal plasma GLU concentrations and led to a significant decline in placental GLU uptake around the time of parturition. The similarities relate to changes in GLU and progesterone metabolism. During spontaneous parturition, there is a marked decrease in net fetal hepatic GLU output, leading to a decrease in placental GLU uptake from the fetal circulation (see Fig. 5, which presents data for a single animal). Coincident with these changes, progesterone output from the maternal uterus decreases.

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SUMMARY

Glutamine and GLU metabolism play important and unique roles during fetal development. Their interorgan exchange (between fetal liver and placenta) and particularly, the fetal liver’s central role in maintaining GLU supply to the placenta, illustrate that these two organs form an integrated organ system in early development.

LITERATURE CITED


