Glutamine and Glutamate Exchange between the Fetal Liver and the Placenta

Frederick C. Battaglia

University of Colorado Health Sciences Center, Aurora, CO

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. J. Nutr. 130: 974S–977S, 2000.

KEY WORDS: placental uptake • fetal liver • glutamate • glutamine • parturition

Despite the evidence collected in adults that glutamine (GLN) and glutamate (GLU) play unique roles in nutrition and metabolism, their functions during early development have received scant attention. In fact, only about 20 years ago, while studying the umbilical uptake of nutrients by the ovine fetus, did we make the initial, key observation that the placenta takes up GLU from the fetal circulation, while concurrently releasing GLN into the fetal circulation in very large amounts (Lemons et al. 1976). From this finding, it was clear that all fetal GLU requirements must be met by the fetal production of this amino acid.

Net fluxes of glutamine and glutamate

The early observation that GLU is extracted from the fetal circulation by the placenta (Lemons et al. 1976) was subsequently confirmed in late-gestation ovine fetuses, both in our laboratory and in those of others (Chung et al. 1998, Lemons and Schreiner 1984, Marconi et al. 1989). In addition, studies in rhesus monkeys of the transport of labeled GLU from the maternal into the fetal circulation demonstrated that only GLU transport across the primate placenta (Steigink et al. 1975). Others have shown in humans during cesarean section (when both umbilical arterial and venous blood samples can be obtained) that the fetus demonstrates a negative (umbilical vein – fetal artery) concentration difference for GLU across the placenta (Hayashi et al. 1978). This finding confirms in humans, as in other species, that there is a net uptake of GLU from the umbilical circulation into the placenta. Hence, this phenomenon is not unique to the epitheliochorial placenta, but seems to be a more general characteristic of trophoblasts. Figure 1 presents data from a recent study of 18 pregnant sheep, summarizing the umbilical and uterine uptakes of GLN and GLU (Chung et al. 1998). Note that GLU is taken up by the placenta from both circulations. Additionally, GLN delivery to the fetus (i.e., its umbilical uptake) is significantly greater than uterine uptake, demonstrating net placental GLN production. In the 1980s, fetal surgery progressed to a point that permitted sampling of the venous drainage from the fetal liver. The preparation we utilized is described in Figure 2, with potential infusion sites for tracers in both the maternal and fetal circulations. Thus, for the first time, we were able to look at the fluxes of amino acids.
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) and 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 utilized within the placenta (Loy et al. 1990). The nitrogen derived from the metabolism of BCAA into their respective keto acids contributes to both placental NH₃ production and GLU formation from oxoglutarate (Józwik et al. 1999). Thus, the placental supply of GLU derives from both its uptake from the fetal circulation and its production in the placenta associated with BCAA transamination. Figure 3 summarizes data from several studies (Chung et al. 1998, Józwik et al. 1999, Loy et al. 1991) and indicates the net uptake or release from sheep placenta of the BCAA, GLN and GLU into the uterine and umbilical circulations.

When L-[1-14C] GLU is infused into the fetal circulation,
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 before parturition. The data are derived from a single animal for GLU release from the fetal liver and GLU uptake by the placenta. Figure 4 summarizes the carbohydrate exchange among the fetal liver, placenta and carcass taken from recent data (Timmerman et al., unpublished results) and Wilkening et al. (1994).

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 before parturition. The data are derived from a single animal for GLU release from the fetal liver and GLU uptake by the placenta. (Timmerman et al., unpublished observations).
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