Partition of maternal nutrients to the placenta and fetus in the sheep

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Utilizing the Fick Principle, the fluxes of oxygen and glucose leaving the uterine circulation and entering the fetal umbilical circulation were measured simultaneously in 35 chronically catheterized sheep. Additionally, the distribution of placental lactate into the uterine and umbilical circulations was measured by the same techniques. Under unstressed conditions, placental oxygen consumption accounted for approximately half the oxygen exiting the uterine circulation. Placental glucose consumption averaged 75% of the glucose exiting the uterine circulation, and this proportion increased with decreasing glucose concentration in the maternal artery. Lactate was produced at a high rate by all placentae, and distributed disproportionately to the fetus, in spite of higher fetal lactate concentration.

Fetal metabolism was aerobic, as demonstrated by a high rate of net oxygen consumption and a high rate of net lactate consumption. Fetal oxygen metabolism correlated well with fetal weight and with the sum of net fetal lactate and glucose consumption.

lactate; glucose; oxygen; fetal metabolism; placental metabolism

Introduction

Fetal growth and metabolism require a continued supply of oxygen and nutrients from the mother. The placenta imposes additional demands upon the mother for a supply of oxygen and calories to maintain pregnancy (Meschia et al., 1980). The placental portion of the nutritional requirement of the conceptus has received comparatively little attention; however, it has been demonstrated that this component represents a major contribution to the nutritional support of pregnancy in the ovine pregnancy (Meschia et al., 1980).

If the individual substances nourishing the fetus are considered, the interrelationships of the fetus and placenta become even more interesting. A large proportion of the oxygen supplied by the mother is consumed by the sheep placenta, and only...
about half the oxygen leaving the placenta enters the fetal circulation. Similarly, glucose is consumed in large amounts by the placenta, with concomitant placental production of lactate, and both lactate and glucose enter the fetal circulation (Burd et al., 1975; Char et al., 1976; Battaglia et al., 1978; Hay et al., 1981; Sparks et al., 1981). Together, glucose and lactate can account for 65 to 75% of the total rate of oxidative metabolism in the fetal sheep. A similarly high rate of placental consumption of glucose and production of lactate has been demonstrated in vivo (Comline et al., 1976) and in vitro in several species, including the human (Murphy et al., 1925; Villlee, 1953; Holzman et al., 1979).

Over the last 5 yr, studies from this laboratory have addressed individually the metabolism of glucose, lactate, and oxygen in placenta and fetus. It is the intent of this paper to review this cumulative experience with the aim of defining interrelationships of fetal and placental metabolism of these nutrients.

Materials and methods

The interrelationships of fetal and placental metabolism were studied in 35 normal sheep with a gestational age of between 130 and 145 days. The sheep were prepared with chronic indwelling catheters as previously described (Burd et al., 1975; Meschia et al., 1980; Hay et al., 1981a; Sparks et al., 1981). Under pentobarbital sedation (5 mg/kg) and pontocaine spinal anesthesia (6 mg in 10% glucose), polyvinyl catheters were placed in the maternal femoral artery and uterine vein and in the fetal umbilical vein and pedal artery. The fetal pedal arterial catheter was advanced such that the catheter tip sampled the descending aortic blood supplying the umbilical artery. In addition, an infusion catheter was placed in the fetal pedal vein and advanced to the level of the fetal femoral vein. Animals were allowed to recover from surgery for at least 5 days before study, with free access to water and food (oats, alfalfa pellets and hay). In some animals, maternal hypoglycemia was induced by restriction of maternal food intake.

Samples of whole blood were withdrawn simultaneously from maternal artery, maternal uterine vein, fetal artery and fetal umbilical vein. Whole blood was collected in capillary tubes coated with sodium fluoride (NaF) and kept on ice until measurement of oxygen content using a Lex-O₂-Con (Lexington Instruments, Lexington, MA). Whole blood for measurement of lactate concentration was collected into ice-coated syringes and precipitated immediately with cold perchloric acid. Lactate concentration was measured with a lactate dehydrogenase enzymatic method (Burd et al., 1975; Olsen et al., 1971). Whole blood for measurement of glucose was collected in syringes coated internally with dried EDTA and NaF, and precipitated immediately with barium hydroxide and zinc sulfate. Glucose was measured using a glucose oxidase method (Saifer et al., 1958).

Umbilical and uterine blood flows were measured simultaneously using the transplacental diffusion technique (Meschia et al., 1967; Meschia et al., 1980). Following a bolus priming injection, antipyrine was continuously infused via the fetal pedal venous catheter, and the concentration of antipyrine was measured in whole blood from the fetal umbilical vein, fetal artery, maternal artery and maternal uterine vein by an autoanalyzer technique. Umbilical and uterine blood flows were
then calculated from these concentrations by an application of the Fick Principle.

Similarly, the net fluxes of glucose, oxygen and lactate from the uterine circulation to the conceptus were calculated as the product of uterine blood flow times the maternal arterial-uterine venous concentration difference. The net flux of glucose, oxygen and lactate from the placenta to the fetus was calculated as the product of the fetal umbilical blood flow times the fetal umbilical venous-fetal arterial concentration difference in whole blood. The net uteroplacental uptake or production of glucose, lactate and oxygen were calculated as the difference between the net flux exiting the maternal uterine circulation to the placenta, and the net flux exiting the placenta to the fetal umbilical circulation. Since the myometrial contribution to uteroplacental metabolism is small (Meschia et al., 1980), the uteroplacental metabolism will be referred to as ‘placental’ throughout the remainder of the paper.

The paired or unpaired Student’s t-test was used as appropriate to compare differences in means. Regression analysis utilized standard linear regression techniques. Regression coefficients were compared using analysis of covariance.

Results

Oxygen metabolism

There was a high rate of oxygen uptake by the placentae of all fetuses. Mean placental oxygen utilization was $1.05 \pm 0.11$ mmol/min. Oxygen uptake by the placenta was independent of maternal arterial oxygen content over the narrow range of maternal oxygen content which occurred spontaneously (4.9–6.8 mM), and the correlation between arterial oxygen content and placental oxygen consumption was not statistically significant ($r = 0.16$, $P > 0.1$).

There was also a high rate of fetal oxygen consumption, averaging $1.15 \pm 0.05$ mmol/min in 21 fetuses. Fetal oxygen consumption was not related to maternal arterial oxygen content or to fetal umbilical venous oxygen content over the range of

![Fig. 1. Fetal oxygen consumption as a function of fetal weight.](image-url)
oxygen contents observed spontaneously. Net fetal oxygen consumption was positively related to fetal weight (Fig. 1).

The pregnant uterus required a total of $2.18 \pm 0.11 \text{ mmol/min}$ of oxygen. Net uterine uptake of oxygen was significantly related to both net placental oxygen consumption ($r = 0.91, P < 0.001$), and to net fetal oxygen consumption ($r = 0.62, P < 0.001$) (Fig. 2). The oxygen flux to the conceptus was partitioned approximately equally to fetus and placenta over the ranges of oxygen consumption spontaneously observed.

**Glucose metabolism by the conceptus**

There was a high rate of glucose uptake from the uterine circulation, averaging $45.6 \pm 5.5 \text{ mg/min}$. Unlike oxygen, the net uptake of glucose from the uterine circulation was significantly related to the concentration of glucose in the uterine artery ($r = 0.63, P < 0.001$). The placenta consumed a large amount of this glucose, averaging $33.1 \pm 4.7 \text{ mg/min}$, while the fetal glucose consumption was much smaller, averaging $12.0 \pm 1.4 \text{ mg/min} (P < 0.001)$. The net consumption of glucose by both placenta and fetus was significantly related to maternal arterial glucose concentration ($r = 0.55, P < 0.001$ and $r = 0.72, P < 0.001$, respectively).

The partition of the glucose flux entering the conceptus from the uterine circulation is presented in Fig. 3. This figure demonstrates that over the large range in uterine glucose uptake observed spontaneously, placental glucose consumption always represented the major component of glucose utilization, accounting for 70 to 85% of the total uterine glucose flux.

**Lactate metabolism by the conceptus**

During the unstressed experimental conditions of the present data, the placenta consistently produced a large amount of lactate, averaging $13.8 \pm 1.2 \text{ mg/min}$,
equivalent in weight to about one-third of the net placental glucose uptake. This occurred in spite of the measured high rate of placental oxygen consumption noted above. There was no significant relationship between placental oxygen consumption and placental lactate production over the ranges observed ($r = 0.08$).

The partition of placental lactate production is presented in Fig. 4. Over the wide range in placental lactate production spontaneously observed, lactate is preferen-

![Graph showing the relationship between placental and fetal lactate production](image)

**Fig. 3.** Net fetal and placental glucose consumption as a function of uterine glucose uptake.

**Fig. 4.** Partition of placental lactate production into the mother (Δ--Δ) and into the fetus (○--○).
Fig. 5. Fetal arterial lactate concentration (panel A) and fetal umbilical venous-arterial lactate concentration difference (panel B), as a function of fetal arterial oxygen concentration.

tially partitioned into the fetal circulation. Despite a higher concentration of lactate in the fetal umbilical artery (1.68 ± 0.09 mM) than in the maternal artery (0.66 ± 0.05 mM, \( P < 0.001 \)), approximately 60% of the placental lactate production is discharged into the fetal umbilical circulation.

Relationship of fetal lactate and fetal arterial oxygen content

As noted in Fig. 5A, the concentration of oxygen in the fetal umbilical artery showed a significant negative correlation with the concentration of lactate in the umbilical artery (\( r = -0.56, P < 0.001 \)). Figure 5B demonstrates that as fetal blood oxygen content decreases, the umbilical venous-fetal arterial lactate concentration difference widens, consistent with increased net fetal uptake of lactate. Umbilical blood flow was not significantly related to either maternal or fetal arterial blood oxygen content and we observed an inverse relationship between fetal arterial blood oxygen content and fetal umbilical lactate uptake (\( r = 0.62, P < 0.001 \)), analogous to that presented in Fig. 5B. Restated, increased fetal umbilical lactate uptake and widened fetal umbilical venous–fetal arterial lactate concentration difference were each associated with decreased fetal arterial oxygen content.

Interrelationship between fetal oxygen, lactate and glucose metabolism

Lactate and glucose can account for 65 to 75% of the oxygen consumption in the
fetal lamb (Meschia et al., 1980). Figure 6 demonstrates a significant relationship between net fetal oxygen consumption and the sum of net fetal glucose and net fetal lactate consumptions.

Discussion

Clinicians and investigators alike have paid relatively little attention to the nutrition and in vivo metabolism of the placenta, as well as to metabolic interactions of the placenta with the developing fetus. To some extent this may result from a perception of the placenta as a simple organ with minimal metabolic needs, across which nutrients flow by diffusion to meet the more important needs of the fetus. The placenta has also been regarded as an 'aging' organ, whose function deteriorates towards term. Models of placental transport of oxygen and other nutrients have been proposed which have excluded or overlooked placental metabolic requirements. More recently, studies with radioactive tracers have utilized models of nutrient flux from mother to the fetus which are based on the assumption of zero placental metabolism (Hodgson et al., 1977; Anand et al., 1979).

The present data in the unstressed pregnant sheep support quite different views of the placenta and its interaction with the fetus. For example, the sheep placenta metabolizes glucose extremely rapidly. Of the typical 40 mg glucose per minute exiting the uterine circulation, net placental glucose consumption averaged approximately 30 mg/min. Considering a typical term sheep uteroplacental mass of ~ 1 kg, this rate of net glucose consumption approximates that of brain tissue.

Placental glucose consumption in the fed state represents approximately 75% of the glucose exiting the uterine circulation. As maternal glucose concentration falls, the net glucose consumption of both placenta and fetus decrease. However, the placental reduction is relatively less severe than the fetal. For example, from the regression lines shown in Fig. 3, one can calculate that a 50% reduction in net
glucose uptake by the conceptus from 40 to 20 mg/min reduces placental glucose consumption by 45% and reduces fetal glucose consumption by 70%. The significance of the rapid placental glucose consumption, and its relative preservation during maternal hypoglycemia, remains unclear.

The oxidative metabolism of the placenta is also rapid, with net placental oxygen consumption averaging 1 mmol/min, or about 50% of the oxygen exiting the uterine circulation. For a typical term sheep uteroplacenta weighing ~ 1 kg, this rate of oxygen consumption approaches the range seen in metabolically active organs such as brain (~ 1.5 mmol per kg per min). In contrast to placental glucose metabolism, placental oxidative metabolism correlates poorly with arterial oxygen concentration over the range observed spontaneously.

In each of the sheep pregnancies studied, the placenta represented a site of substantial net lactate production. Placental lactate production averaged approximately one-third the rate of net placental glucose consumption. If the net placental lactate production is subtracted from the net placental glucose consumption, the resulting net glucose consumption is sufficient to account for approximately 87% of the placental oxygen consumption in the fed state.

From the viewpoint of fetal metabolism, the placenta provides the fetus with a substantial net supply of lactate. Quantitatively, the fetal sheep has a net lactate consumption of ~ 2 mg per kg per min, exceeding the net consumption of any other exogenous carbon source except glucose (~ 4.5 mg per kg per min). There is little conversion of lactate to glucose in the fetus, and ongoing studies in our laboratory suggest that approximately 75% of the lactate entering the umbilical circulation is metabolized oxidatively to carbon dioxide (Hay et al., 1981).

These observations contrast sharply with the older view that a large part of fetal metabolism is anaerobic (Hendricks et al., 1957). This view was based in part upon observations in many species that the concentration of lactate is higher in fetal than maternal blood (Loeser et al., 1932; Hendricks et al., 1957; Comline et al., 1976; Sparks et al., 1982). The present study reconfirms these concentration relationships, and makes the additional observation of an inverse relationship between fetal arterial lactate concentration and fetal arterial oxygen concentration (Fig. 5A). While it would be tempting to ascribe this to net fetal anaerobic metabolism at lower oxygen tensions, Fig. 5B shows instead that the increased lactate concentration was associated with increased umbilical venous–fetal arterial differences in lactate concentration difference; i.e., lower oxygen concentration correlates with an increase rather than a decrease of net lactate utilization by the fetus.

In interpreting the present data, two important points need to be emphasized. First, the present data reach conclusions that are valid only over the physiologic ranges in concentration measured. Thus, while net fetal lactate consumption appears to increase as fetal arterial oxygen concentration decreases, it is unlikely that this trend will continue as fetal oxygenation approaches zero. Similarly, it seems reasonable that placental lactate production will eventually rise substantially at very low placental oxygenation. The present experiments have not dealt with these extremes of pathophysiology, and it is not certain that such conditions would be compatible with fetal survival. However, these experiments have described normally occurring variations in fetal environment, and the relationships derived obtained over ranges
compatible with long-term fetal growth, oxidative metabolism and survival.

The second point is that the uptakes measured by application of the Fick Principle represent the overall uptake or release of a substrate in net. These net uptakes do not imply homogeneity within each anatomical compartment sampled. Thus, that the fetus is a net consumer of lactate in all fetuses studied does not exclude that individual organs within the fetus may locally produce lactate. Such local production of lactate by fetal organs has been observed by brain and hindlimb in the fetal lamb. Similarly, that a relationship was not observed for an anatomical compartment in net does not imply that such a relationship may not obtain for localized regions within that compartment. Thus, the lack of a strong relationship between maternal or fetal oxygen content and net lactate production by the whole placenta, does not imply the absence of the relation for local areas within the placenta. For example, if there were areas of the placenta whose local oxygenation were dependent primarily on fetal arterial blood and which distributed their lactate production primarily into the fetus, then the data presented in Figs. 5 and 6 would be compatible with such areas increasing their local lactate production in response to lowered local oxygen availability.

Our data directly demonstrate that fetal metabolism is largely aerobic. Figure 1 documents a rapid rate of oxygen consumption, linearly related to fetal weight. Interestingly, the regression line does not pass through the origin, so that the expression of oxygen consumption as proportional to fetal weight (e.g. mmol per kg per min) would be misleading. As noted previously, recent radioactive tracer studies in our laboratory have demonstrated that as much as 75% of the lactate and 60% of the glucose in the fetal circulation are metabolized oxidatively to carbon dioxide (Hay et al., in prep.) Figure 6 demonstrates a positive relationship between net fetal oxygen consumption and the sum of net lactate and glucose umbilical uptakes consistent with the tracer observations.

The present study underscores the importance of quantitative measurement of the nutrient fluxes leaving the uterine circulation and entering the fetus. Measurement of nutrient concentrations in a single uterine and a single fetal vessel would not have revealed the high rate of placental metabolism, or correctly characterized the rapid net fetal consumption of lactate. For the term newborn, the net flux of nutrients can be calculated from measurement of the intake and net retention of the nutrients supplied by milk; similar characterization of the placental fluxes supporting the fetus in late gestation may provide important clues for optimal nutrition of the preterm infant during the transition from prenatal to postnatal life.

References


