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GLUCOSE, LACTATE AND OXYGEN METABOLISM IN THE FETAL PIG DURING LATE GESTATION

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SUMMARY

Using [U-14C]glucose tracer, rates of umbilical uptake, utilization and production of glucose, and of CO2 production from glucose carbon, were measured in seven chronically catheterized fetal pigs, when the sow was in the fed state, between 100 and 113 days of gestation (term, 114 ± 2 days). At the same time, rates of umbilical O2 and lactate uptake were determined in all seven fetuses by the Fick principle. The mean fetal rates of umbilical glucose uptake, glucose utilization and CO2 production from glucose carbon were 38.4 ± 4.2, 41.3 ± 5.2 and 126.9 ± 12.6 mmol min⁻¹ (kg fetal body weight)⁻¹, respectively (n = 7). No glucose production was therefore detected in the fetuses. Production of CO2 from glucose carbon accounted for 37.3 ± 3.4% (n = 7) of the umbilical O2 uptake, which averaged 340 ± 13 mmol min⁻¹ kg⁻¹ (n = 7). There was also significant umbilical lactate uptake in the fetal piglets when the sow was in the fed state (32.6 ± 10.4 mmol min⁻¹ kg⁻¹, n = 7, P < 0.05). No significant changes in fetal glucose, O2 or lactate metabolism were observed with increasing age towards term. The fetal rates of glucose metabolism and of umbilical uptake of O2 and lactate were not correlated with the fetal blood glucose level. Hence, glucose is used for both oxidative and non-oxidative metabolism in utero and is an important, although not the sole, source of carbon for metabolic processes in the fetal pig during late gestation.

INTRODUCTION

Carbohydrate has an important role in fetal metabolic balance in a wide variety of species (Hay, 1994; Fowden, 1995). It is supplied to the fetus primarily in the form of glucose and lactate, and is used for both oxidative metabolism and the accretion of new fetal tissue (Battaglia & Meschia, 1988; Fowden, 1995). In the foal and lamb, the net fetal supply of lactate is produced by the uteroplacental tissues, while the fetal glucose requirement is met almost entirely by the transplacental transport of glucose from the mother with little, if any, de novo glucose production by the fetal tissues, at least during normal intra-uterine conditions (Battaglia & Meschia, 1988; Hay, 1994; Fowden, 1995). In both species, more carbon is provided as glucose than as lactate and glucose levels are higher than those of lactate in the fetus during late gestation (Hay, 1994; Fowden & Silver, 1995a, b). However, the actual rates of uptake, utilization and oxidation of glucose carbon differ in the fetal foal and lamb during late gestation, which may relate to the differences in placental morphology and maternal nutrition observed between ruminant and non-ruminant species (Silver, Steven & Comline, 1973; Fowden & Silver, 1995a, b).

The pig is a non-ruminant which, like the horse, obtains some glucose directly from the gut and has a diffuse placenta (Cunha, 1966; Leiser & Dantzer, 1988). However, levels of lactate are higher than those of glucose in the fetal pig and fetal glucose production has been detected in individual piglets within a normal litter (Aherne, Hays, Ewan & Speer, 1969; Randall,
1977; Comline, Fowden & Silver, 1979). In part, this may be due to the increased competition for nutrients between littermates in a polytocous species but, since much of the metabolic data on the fetal pig has been derived from acute experiments (see Silver, 1980), it may also reflect the adverse effects of anaesthesia and surgery. Hence, in the present study, the specific rates of glucose and lactate uptake, and of the utilization, production and oxidation of glucose carbon, have been measured in chronically catheterized fetal piglets during late gestation and the values compared with those observed in the fetal lamb and foal at equivalent stages of gestation.

METHODS

Animals

Five Large White sows of known gestational age were used in these experiments. They were housed separately and fed commercial sow feed (10 kg day\(^{-1}\) Sowcare Gold 16; BOMC Silcock, Bury St Edmunds, UK) throughout the experimental period. Half the daily ration was fed at 08.00–09.00 h and the remainder was given between 16.00 and 17.00 h. Food, but not water, was withdrawn 12 h before surgery and normal feeding patterns were generally restored within 24 h of operation.

Operative procedures

Between 99 and 104 days (term, 114 ± 2 days), the sows were anaesthetized with sodium pentobarbitone (20–30 mg kg\(^{-1}\)) administered via a superficial ear vein and one or two fetuses in each litter were catheterized under aseptic conditions (Table 1). Using the surgical procedures described previously (Silver, 1980), catheters were inserted into the fetal dorsal aorta and caudal vena cava via the femoral vessels and into a uterine vein draining the uterine horn containing the catheterized fetus(es). In addition, a catheter was inserted directly into the common umbilical vein at the level of the umbilicus and secured in position with a fine ligature (5/0 Merocryl 1 metric; Ethicon, Edinburgh, UK) and tissue glue (cyanoacrylate adhesive, C-2 PermaBond; Eastleigh, UK).

The fetal and maternal catheters were sutured to the fetal skin and uterine wall, respectively, and exteriorized through the flank of the sow (Silver, 1980). Each fetus was given antibiotic at surgery and again at the end of the metabolic study (50 mg ampicillin i.v., Penbritin; Beecham Ltd, UK). The sows received antibiotic (10 ml Streptopen i.m.; Glaxo Ltd, UK) on the day of surgery and for the 3 days thereafter. Fetal arterial and umbilical venous catheters were generally patent throughout the experimental period, but in one animal the umbilical venous catheter did not flow until 14 days after surgery. Metabolic measurements were therefore made on the fetuses 2–14 days after catheterization at a mean gestational age of 104.4 ± 1.8 days (n = 7, Table 1). All catheterized piglets were alive at delivery, which occurred spontaneously at a mean gestational age of 112.4 ± 0.8 days (n = 5). Fetal body weight was measured at birth (Table 1).

Experimental procedures

Tritiated water (\(^{3}\)H\(_{2}\)O, 10 μCi ml\(^{-1}\); Amersham International) and universally labelled \([^{14}\text{C}]\)glucose (7.5–10 μCi ml\(^{-1}\) in 0.9% NaCl (w/v); ICN Biochemicals, High Wycombe, UK) were infused together into the fetal caudal vena cava for 2–3 h at known rates of between 0.04 and 0.05 ml min\(^{-1}\) after an initial priming dose (5 ml) given between 09.00 and 10.00 h. Blood samples were taken simultaneously from the umbilical vein, fetal artery and uterine vein before infusion (0 min, 1.5 ml samples) and when a steady state had been established (Fig. 1) at known times approximately 120, 140 and 160 min after beginning the infusion (2.5 ml samples).

The blood samples were analysed immediately for blood pH, gas tensions, packed cell volume (PVC) and oxygen (O\(_2\)) content (0.4 ml), and for \([^{14}\text{C}]\)carbon dioxide (\(^{14}\text{CO}_2\)) where appropriate (0.9 ml). The remainder (1.7 ml) was added to a chilled tube containing EDTA for subsequent analyses. An aliquot (0.5 ml) of EDTA-treated blood was deproteinized with zinc sulphate (0.3 m) and barium hydroxide (0.3 m) and, after centrifugation, the supernatant used for the determination of blood lactate, \(^{14}\text{C}\)-labelled
Table 1. Details of the fetal body weight, litter size and gestational ages at the time of surgery, metabolic study and delivery of the animals used in this study

<table>
<thead>
<tr>
<th>Sow no.</th>
<th>Fetus no.</th>
<th>Gestational age (days)</th>
<th>Fetal body weight at delivery (kg)</th>
<th>No. of fetuses in litter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At surgery</td>
<td>At study</td>
<td>At delivery</td>
</tr>
<tr>
<td>1</td>
<td>F1</td>
<td>98</td>
<td>100</td>
<td>111</td>
</tr>
<tr>
<td>1</td>
<td>F2</td>
<td>99</td>
<td>101</td>
<td>115</td>
</tr>
<tr>
<td>2</td>
<td>F1</td>
<td>99</td>
<td>113</td>
<td>115</td>
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<tr>
<td>2</td>
<td>F2</td>
<td>102</td>
<td>105</td>
<td>112</td>
</tr>
<tr>
<td>3</td>
<td>F1</td>
<td>103</td>
<td>106</td>
<td>111</td>
</tr>
<tr>
<td>4</td>
<td>F1</td>
<td>104</td>
<td>106</td>
<td>113</td>
</tr>
<tr>
<td>5</td>
<td>F1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Mean (± S.E.M.) values of total glucose (A), $^{14}$C-labelled blood glucose (B), glucose specific activity (C) and $[^{14}$C]carbon dioxide (D) in arterial (●) and umbilical venous blood (○) of chronically catheterized fetal piglets ($n = 7$) with respect to time after beginning the infusion of tracer glucose (0 min).
and total blood glucose concentrations. The remaining EDTA sample was centrifuged at 4 °C and the plasma stored at −20 °C until required for ^3H_2O measurements.

**Biochemical analyses**

The blood gas status, PCV, O_2 content and whole blood concentrations of glucose, lactate, [^14C]glucose, ^3H_2O and ^14CO_2 were measured in all three sets of simultaneous blood samples. Blood O_2 saturation and haemoglobin concentration were determined using a haemoximeter (OSM2; Radiometer, Copenhagen, Denmark). Blood pH and partial pressures of O_2 (P_{O_2}) and CO_2 (P_{CO_2}) were measured using ALB330 Radiometer equipment and corrected for a fetal body temperature of 38 °C.

The concentrations of whole blood glucose and lactate were determined enzymatically using glucose oxidase and lactate dehydrogenase, respectively (Fowden, Thian, Silver, Ralph & Harding, 1992). Plasma ^3H_2O concentrations were measured using a scintillation counter and, after correcting for quenching, converted to blood concentrations as described by Bell, Battaglia & Meschia (1988). Labelled glucose and CO_2 were determined using chemical methods described previously (Hay, Sparks, Quissell, Battaglia & Meschia, 1981; Hay, Myers, Sparks, Wilkening, Meschia & Battaglia, 1983; Fowden & Hay, 1988). The mean recovery of [^14C]glucose from the anion exchange columns was 97.4 ± 1.4% (n = 7). No correction for glucose recovery was therefore made. The mean recovery of ^14CO_2 from blood was 86.9 ± 0.9% (n = 7); hence, all blood ^14CO_2 values have been corrected for recovery.

**Calculations**

All calculations were made using equations derived for steady-state kinetics. Umbilical blood flow was measured using the ^3H_2O steady-state diffusion technique (Meschia, Battaglia & Burns, 1980). Net umbilical uptake rates of glucose, lactate and oxygen, and net umbilical excretion rates of [^14C]glucose and ^14CO_2, were calculated by the Fick principle as the product of umbilical blood flow and the venous–arterial (uptake) or arteriovenous concentration difference (excretion) across the umbilical circulation.

The fetal rates of utilization and production of glucose, CO_2 production from glucose carbon, and the fraction of the net umbilical oxygen uptake used for oxidation of glucose carbon by the fetus, were calculated according to the following equations (Hay et al. 1981, 1983; Fowden & Hay, 1988).

\[
\text{Fetal glucose utilization (μmol min}^{-1}\text{)} = \frac{\text{Net fetal tracer uptake (d.p.m. min}^{-1}\text{)}}{\text{Fetal arterial glucose specific activity (d.p.m. (μmol glucose)}^{-1}\text{)}} \tag{1}
\]

where:

\[
\text{Net fetal tracer uptake} = \text{Tracer glucose infusion rate} - \text{Net umbilical tracer glucose excretion rate}. \tag{2}
\]

Oxidation of fetal glucose carbon was calculated as the rate of ^14CO_2 production.

\[
\text{CO}_2 \text{ production from the oxidation of fetal glucose carbon (μmol min}^{-1}\text{)} = \frac{\text{Net umbilical } ^{14}\text{CO}_2 \text{ excretion rate (d.p.m. min}^{-1}\text{)}}{\text{Fetal arterial blood glucose specific activity (d.p.m. (μmol glucose carbon)}^{-1}\text{)}}. \tag{3}
\]

The glucose carbon oxidation fraction and the fraction of oxygen consumption used to oxidize glucose carbon in the fetus were then calculated as follows.

\[
\text{Glucose carbon oxidation fraction} = \frac{\text{Net umbilical } ^{14}\text{CO}_2 \text{ excretion rate (d.p.m. min}^{-1}\text{)}}{\text{Net fetal tracer glucose uptake (d.p.m. min}^{-1}\text{)}} \tag{4}
\]

The glucose carbon oxidation fraction is the fraction of fetal glucose carbon utilization rate that is oxidized.

\[
\text{Fraction of oxygen uptake used for oxidation of glucose carbon} = \frac{\text{Amount of O}_2 \text{ used to oxidize fetal glucose carbon (μmol min}^{-1}\text{)}}{\text{Net umbilical O}_2 \text{ uptake rate (μmol min}^{-1}\text{)}} \tag{5}
\]
METABOLISM OF THE FETAL PIG

where:

\[
\text{Amount of } O_2 \text{ used to oxidize} = \text{Amount of } CO_2 \text{ produced by this fetal glucose carbon oxidative process (eqn (3)).}
\]

Endogenous glucose production by the fetus was calculated as follows.

\[
\text{Endogenous glucose production} = \text{Fetal glucose utilization} - \text{Umbilical glucose uptake.}
\]

All metabolic rates have been expressed per kilogram fetal body weight. Body weight at the time of the study was estimated from the weight of the piglet at birth (Table 1) and known growth rates in late gestation (Becker, 1978).

Statistical analyses

Mean values (± S.E.M.) have been used throughout. Statistical analyses were made according to the methods of Armitage (1971). Correlation coefficients were calculated by linear regression analyses. Statistical significance was assessed by Student’s paired and unpaired t tests or Fisher’s test, where appropriate. Probabilities of less than 5% were considered significant. The values observed in the fetus studied 14 days after surgery were similar to those seen in the fetuses examined after 2–3 days of catheterization; hence, the data from all animals have been combined for subsequent analyses.

RESULTS

Basal values

Insertion of umbilical venous as well as arterial catheters in the fetal pig appeared to have no adverse effects on its well-being in utero or its viability at birth. All fetuses were alive at delivery and their birth weights were similar to those published previously for catheterized and unoperated newborn piglets (Randall, 1977; Silver, Barnes, Comline, Fowden, Clover & Mitchell, 1979). Fetal arterial blood pH and gas tensions in the chronic preparations in the present study (Table 2) were also similar to those observed in earlier studies of fetal pigs with indwelling catheters in either arterial or venous vessels (Randall, 1977; Silver et al. 1979). In addition, the mean arterial concentrations of blood glucose and lactate in the fetal pigs in the present study (Table 2) were within the normal range of values reported previously for chronically catheterized animals (Randall, 1977; Fowden, Comline & Silver, 1982). Umbilical blood flow in the present study (231 ± 14 ml min⁻¹ kg⁻¹, n = 7) was also similar to

<table>
<thead>
<tr>
<th>pH</th>
<th>(P_{O_2}) (mmHg)</th>
<th>(P_{CO_2}) (mmHg)</th>
<th>PCV (%)</th>
<th>(O_2) content (mmol l⁻¹)</th>
<th>[Glucose] (mmol l⁻¹)</th>
<th>[Lactate] (mmol l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV</td>
<td>7.452 ± 0.013</td>
<td>53.0 ± 2.5</td>
<td>44.2 ± 1.3</td>
<td>4.69 ± 0.23</td>
<td>3.45 ± 0.19</td>
<td>0.90 ± 0.06</td>
</tr>
<tr>
<td>UV</td>
<td>7.459 ± 0.013</td>
<td>47.6 ± 1.0</td>
<td>44.3 ± 2.3</td>
<td>25.0 ± 2.0</td>
<td>3.12 ± 0.25</td>
<td>2.93 ± 0.25</td>
</tr>
<tr>
<td>FA</td>
<td>7.431 ± 0.011</td>
<td>24.9 ± 0.6</td>
<td>51.7 ± 0.6</td>
<td>24.5 ± 2.0</td>
<td>1.61 ± 0.21</td>
<td>2.76 ± 0.28</td>
</tr>
<tr>
<td>UV–FA</td>
<td>0.018 ± 0.005*</td>
<td>22.7 ± 1.5*</td>
<td>7.6 ± 1.3*</td>
<td>0.3 ± 0.6</td>
<td>1.52 ± 0.07*</td>
<td>0.17 ± 0.03*</td>
</tr>
</tbody>
</table>

* \(n = 7\) fetuses; \(n = 5\) sows. * \(P < 0.01\), significant umbilical venous–arterial difference (Student’s paired t test).
Table 3. Mean (± s.e.m.) rates of umbilical uptake and utilization of glucose, and of CO₂ production from glucose carbon, and mean values of the glucose carbon oxidation fraction in chronically catheterized fetal piglets, foals and lambs during late gestation (≥90% gestation)

<table>
<thead>
<tr>
<th></th>
<th>Umbilical glucose uptake (μmol min⁻¹ kg⁻¹)</th>
<th>Glucose utilization (μmol min⁻¹ kg⁻¹)</th>
<th>CO₂ production from glucose carbon (μmol min⁻¹ kg⁻¹)</th>
<th>Glucose carbon oxidation fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglet</td>
<td>7 38.4 ± 4.0*</td>
<td>41.3 ± 5.2*</td>
<td>126.9 ± 12.6**</td>
<td>0.530 ± 0.081</td>
</tr>
<tr>
<td>Foal†</td>
<td>5 38.2 ± 4.1</td>
<td>37.2 ± 2.5</td>
<td>119.4 ± 31.1</td>
<td>0.515 ± 0.103</td>
</tr>
<tr>
<td>Lamb‡</td>
<td>8 28.8 ± 2.1</td>
<td>28.8 ± 2.0</td>
<td>83.9 ± 8.1</td>
<td>0.497 ± 0.049</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01, significantly different from the values in the fetal lamb. Data from: † Fowden & Silver (1995a); ‡ Fowden & Silver (1995b).

that measured previously using microspheres over the same range of gestational ages (Macdonald, Heymann, Llanos, Pesonen & Rudolph, 1985).

Oxygen metabolism

A venous–arterial difference in O₂ content was observed across the umbilical circulation in all seven fetuses (Table 2); the mean value was significant (Table 2). The mean rate of umbilical O₂ uptake was therefore 340 ± 13 μmol min⁻¹ kg⁻¹ (n = 7). There was no correlation between umbilical O₂ uptake and gestational age (r = 0.459, n = 7, P > 0.05) or between umbilical O₂ uptake and the fetal arterial concentration of blood glucose (r = 0.368, n = 7, P > 0.05).

Glucose metabolism

Metabolic rates. The mean rates of umbilical uptake and utilization of glucose, and of CO₂ production from glucose carbon, in the fetal pigs are shown in Table 3, together with their glucose carbon oxidation fractions. No change in any of these parameters was observed with increasing gestational age towards term (n = 7, P > 0.05, all cases). Fetal glucose utilization was not significantly different from umbilical glucose uptake; hence, endogenous glucose production was negligible in the fetal pig when the sow was in the fed state (2.9 ± 3.0 μmol min⁻¹ kg⁻¹, n = 7, P > 0.05). The mean rate of CO₂ production from glucose carbon was approximately half the rate of glucose carbon utilization by the fetal tissues (Table 3) and accounted for 37.3 ± 3.4% (n = 7) of the umbilical O₂ uptake. There was no gestational trend in the fraction of O₂ uptake used to oxidize glucose carbon in utero (n = 7, P > 0.05). No significant correlations were observed between the fetal arterial concentration of blood glucose and the rates of umbilical glucose uptake (r = −0.631, n = 7, P > 0.05), fetal glucose utilization (r = −0.545, n = 7, P > 0.05) and CO₂ production from glucose carbon (r = 0.498, n = 7, P > 0.05). There was also no significant correlation between the arterial blood glucose level and the glucose carbon oxidation fraction in the individual fetuses (r = 0.697, n = 7, P > 0.05).

Distribution of labelled glucose. There was a net flux of tracer glucose from the fetus to the uteroplacental tissues (umbilical excretion) in every animal (Fig. 2). The mean rate of tracer glucose uptake by the uteroplacental tissues expressed as a percentage of the infusion rate into
the fetus was 78.1 ± 4.5% (n = 7, Fig. 2) and did not differ significantly with increasing gestational age towards term (P > 0.05). The rate of tracer uptake by the uteroplacental tissues was positively correlated with the fetal arterial concentration of blood glucose (r = 0.782, n = 7, P < 0.05). Of the tracer carbon remaining in the fetus, 53.0 ± 8.1% (n = 7) was metabolized to radioactively labelled CO₂, which accounted for 9.8 ± 0.9% of the total infusion rate of tracer into the fetus (Fig. 2).

Lactate metabolism

There was a significant mean venous–arterial concentration difference in blood lactate across the umbilical circulation when the values from all seven fetuses were combined (Table 2). Consequently, there was a significant umbilical uptake of lactate in the fetal piglet during late gestation (32.6 ± 10.4 μmol min⁻¹ kg⁻¹, n = 7, P < 0.05). The rate of umbilical lactate uptake was not related to the levels of glucose or lactate in either fetal or maternal blood (P > 0.05, all cases).

DISCUSSION

This is the first study in which metabolic rates have been quantified in the fetal pig in utero. The results show that, in common with other domestic species (Hay et al. 1983; Fowden & Silver, 1995a, b), the fetal pig uses glucose for both oxidative and non-oxidative processes in utero. The rates of uptake and utilization of glucose, and of CO₂ production from glucose carbon, by the fetal piglet were significantly higher than the corresponding values in the fetal lamb at the equivalent stage of gestation but were similar to those measured in the fetal foal using identical methodology in the same laboratory (Table 3). The mean rates of glucose metabolism found in the fetal pig in the present study were also higher than the range of mean values for umbilical glucose uptake (17.2–33.1 μmol min⁻¹ kg⁻¹), glucose utilization (25.8–38.1 μmol min⁻¹ kg⁻¹) and CO₂ production from glucose carbon (81.2–91.7 μmol min⁻¹ kg⁻¹) observed previously in
fetal sheep under similar conditions in other laboratories (Hay et al. 1983; Bloch, Menon & Sperling, 1988; Owens, Falconer & Robinson, 1989; Hay, DiGiacomo, Meznarich, Hirst & Zerbe, 1989). The weight-specific rate of umbilical O₂ uptake in the fetal pig was at the upper end of the range of values observed in fetal sheep (295–340 µmol min⁻¹ kg⁻¹) but was 10–15% higher than the value observed in fetal foals at a similar stage of gestation (Hay et al. 1983, 1989; Owens, 1991; Thureen, Trembler, Meschia, Makowski & Wilkening, 1992; Fowden & Silver, 1995a, b). Certainly, the relatively high rates of glucose metabolism observed in the fetal piglet in the present study are consistent with previous findings that the piglet is much more dependent on glucose as a metabolic fuel in the immediate postnatal period than the newborn lamb (Randall, 1978; Mellor, 1988).

These species differences in fetal metabolic rates suggest that maternal nutrition and placental morphology may, indeed, have an important role in determining nutrient utilization in utero. Fetal rates of glucose utilization were greatest in the pig and horse, which are non-ruminant herbivores with a dietary source of glucose and higher maternal glucose levels than found in ruminants. The pig and horse also have diffuse placentae, which previous studies have indicated are more efficient at nutrient transfer than the cotyledonary placenta of the sheep (Silver et al. 1973). Alternatively, the different fetal metabolic rates may be explained by species differences in the demand for nutrients either by individual fetal tissues or by the fetus as a whole. Tissues such as the brain, which have an obligatory glucose requirement, account for a significantly higher proportion of body weight in fetal piglets than lambs during late gestation (Dickerson & Dobbing, 1967; Owens, 1991). Similarly, the fetal piglet accumulates much more glucose carbon as glycogen in its liver and muscles during the prepartum period than the fetal lamb or foal (Table 4). The fetal pig is also comparatively active in utero and has a higher incidence of breathing movements than the fetal lamb at a similar stage of gestation (Harding, Fowden & Silver, 1991; Fowden et al. 1992). Since paralysis of the sheep fetus reduces O₂ consumption by 20–30% (Rurak & Gruber, 1983), the increased activity of the respiratory and other muscles in the fetal pig is likely to contribute to its relatively high rates of glucose and oxygen utilization.

In common with other species (Hay et al. 1983; Fowden & Silver, 1995a), the rates of umbilical uptake and utilization of glucose did not change with increasing gestational age towards term when values were expressed on a weight-specific basis. There was also no significant difference between the rates of umbilical uptake and fetal utilization of glucose in

Table 4. Comparison of the supply of carbon as carbohydrates, and of the carbon requirements for oxidation and glycogen deposition, in the fetal piglet, foal and lamb on a weight-specific basis during late (≥90%) gestation

<table>
<thead>
<tr>
<th></th>
<th>Supply (g day⁻¹ kg⁻¹)</th>
<th>Requirements (g day⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose</td>
<td>Lactate</td>
</tr>
<tr>
<td>Piglet</td>
<td>4.28</td>
<td>1.70</td>
</tr>
<tr>
<td>Foal</td>
<td>3.86</td>
<td>0.64</td>
</tr>
<tr>
<td>Lamb</td>
<td>2.99</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data from references as follows. Piglet: this study and Randall & L’Ecuyer (1976); foal: Fowden, Mijovic, Ousey, McGladdery & Silver (1991a) and Fowden & Silver, (1995a); lamb: Hay et al. (1983) and Fowden (1995).
the present study. Endogenous glucose production was therefore negligible in the fetal piglet when the sow was in the fed state. In the fetal lamb, significant glucose production has been observed just before delivery, when the hepatic glucogenic capacity is high (Fowden, Mundy & Silver, 1991b; Townsend, Rudolph & Rudolph, 1991). However, in the present study, glucogenesis was still undetectable in the one fetal piglet studied within 36 h of spontaneous delivery at term. Since the glucogenic capacity of the fetal piglet is high compared with other species in late gestation (Fowden, Apatu & Silver, 1995), the present findings probably reflect differences in the hormonal stimulus to glucogenesis, since the plasma concentrations of cortisol and adrenaline in the fetal piglet are lower than those observed in the fetal lamb during the immediate prepartum period (Silver, Fowden, Comline, Knox & Bloom, 1985; Silver & Fowden, 1988; Townsend et al. 1991).

In contrast to findings in the fetal foal and lamb (Hay, Meznarich, DiGiacomo, Hirst & Zerbe, 1988; Hay et al. 1989; Fowden & Silver, 1995a, b), there was no relationship between the rate of glucose utilization and the glucose concentration in the fetal pig in the present study. In sheep and horses, fetal glucose levels are determined primarily by the maternal nutritional state, while in pigs, they are also influenced by the relative placental mass of the fetus and the number of fetuses in the litter (Widdowson, 1971; Comline et al. 1979; Fowden, 1995). Hence, any relationship between glucose utilization and glucose levels in utero may have been obscured by variations both within and between litters in the present study. Only by varying glucose levels in individual fetuses will it be possible to demonstrate whether glucose utilization is determined by the glucose level in the fetal pig, as is the case in other species (Hay et al. 1988; Fowden & Silver, 1995a).

Oxidation of glucose carbon accounted for only 35–40% of the umbilical O₂ uptake in the chronically catheterized fetal pigs in the present study. Substrates other than glucose must therefore be oxidized by the fetal pig to account for its total rate of O₂ consumption. In normal conditions, the chronically catheterized sheep fetus oxidizes lactate and amino acids, as well as glucose, but relatively little, if any, fructose or free fatty acids (Battaglia & Meschia, 1988; Fowden, 1995). There was a significant umbilical uptake of lactate in the chronically catheterized fetal pigs which, if completely oxidized, would account for 20–30% of the umbilical O₂ uptake. The pig, like the horse and sheep, is a fructogenic species and significant amounts of fructose are detected in the circulation of the fetal pig during late gestation (Aherne et al. 1969; Randall & L’Ecuyer, 1976). Since oxidation of fructose carbon contributes about 6% of the CO₂ produced by the sheep fetus (Meznarich, Hay, Sparks, Meschia & Battaglia, 1987), oxidation of carbohydrate could account in total for up to 75% of the oxygen taken up by the fetal piglet. This value is higher than those observed in the fetal lamb (50%) and foal (60%) at similar stages of gestation (Fowden & Silver, 1995a, b). The remaining 25% of the oxygen taken up by the chronically catheterized fetal pig is probably used to oxidize amino acids and fat. Urea, the main deamination product of amino acid catabolism, is produced by the fetal pig but its concentration in utero is low in chronic preparations (Silver, 1981). The total α-amino nitrogen level in the chronically catheterized fetal pig is also low and the fetomaternal gradients in α-amino nitrogen and urea in the pig are small compared with those found in the sheep during late gestation (Silver, 1981; Battaglia & Meschia, 1988). Amino acids may therefore provide less carbon for oxidation in the fetal piglet than seen in the fetal lamb close to term. Lipids appear to be no more plentiful in the fetal pig. The body fat content of the fetal pig is relatively low at term (Widdowson, 1971) and preliminary measurements of free fatty acid levels in fetal porcine plasma suggest that concentrations are only 5–10% of
those seen in the fetal lamb and foal during late gestation (Randall, 1977; Fowden, 1995; Fowden & Silver, 1995a; A. L. Fowden & M. Silver, unpublished observations). But, since these molecules have a high carbon content, even a very small umbilical uptake of lipid may provide a physiologically significant supply of oxidative substrate.

The origin of the lactate taken up by the umbilical circulation in the fetal pig is probably the uteroplacental tissues. These tissues are known to produce lactate and release it into the umbilical and uterine circulations in other domestic species (Battaglia & Meschia, 1988) and a positive venous–arterial concentration difference in lactate has been observed across the uterine circulation of chronically catheterized pregnant sows in an earlier study (Randall, 1977). In the present study, the weight-specific rate of umbilical lactate uptake was higher and accounted for a greater proportion of the known supply of carbohydrate carbon in the fetal pig (≈ 30%) than seen in either the fetal foal (≈ 15%) or lamb (≈ 20%) at equivalent stages of gestation (Table 4). However, in contrast to previous findings (Aherne et al. 1969; Randall, 1977), lactate levels were similar to, and not higher than, glucose concentrations in fetal arterial blood in the present study.

In pregnant sheep, the nutrients required for the metabolic activities of the uteroplacental tissues are provided by both the fetus and mother (Hay, 1994). In the present study, there was a net flux of tracer glucose from the fetus to the uteroplacental tissues in the sow, which suggests that these tissues also derive glucose from the fetal circulation in this species. The percentage of tracer glucose lost to the uteroplacental tissues in the pig was similar to that observed in the horse (65–70%) but greater than that seen in the sheep (40–50%), which is consistent with the greater glucose permeability of the diffuse placenta (Silver et al. 1973; Hay et al. 1981; Owens, 1991; Fowden & Silver, 1995a, b). The relatively high umbilical supply of lactate in the chronically catheterized fetal pig may therefore offer a strategy for conserving carbohydrate carbon for use specifically by the fetal tissues, since uteroplacental tissues appear to be much less permeable to lactate than to glucose (Hay, 1994).

In the chronically catheterized fetal pig, the rates of umbilical uptake of glucose and lactate would provide a carbon supply of 5.98 g day\(^{-1}\) (kg fetal body weight\(^{-1}\), which is greater than the corresponding values calculated for the fetal lamb and foal at similar stages of gestation (Table 4). The carbon requirement for oxidation and glycogen deposition in the fetal piglet during late gestation (7.22 g day\(^{-1}\) (kg fetal body weight\(^{-1}\)) is also greater than that seen in the other two species when values are expressed on a weight-specific basis (Table 4). Although no allowances have been made for fetal uptake and losses of carbon in forms other than carbohydrate or for the carbon accumulated as new structural tissue, these figures show that carbohydrate is a major source of carbon to the fetus in all three species, although the relative importance of glucose and lactate to the total carbohydrate carbon supply differs between species (Table 4). Since the lactate taken up by the umbilical circulation is probably of uteroplacental origin, the increased dependence of the fetal pig on lactate as a carbon source may ensure that a carbon supply can be maintained to an individual fetus in a polytocous species in which littermates compete for a finite supply of maternal glucose carbon. The sources of the remaining carbon required by the fetal pig have yet to be identified.

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Glucose, lactate and oxygen metabolism in the fetal pig during late gestation
AL Fowden, AJ Forhead, M Silver and AA MacDonald

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