Original article

Effects of meal intake on materno-foetal exchanges of energetic substrates in the pig

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Abstract — Catheters were implanted in 18 gilts at 99 days of pregnancy to study the effects of meal intake on uterine and umbilical uptake of energetic substrates in the conscious pig. Blood samples were withdrawn at 105 days of pregnancy from 10 min before and up to 90 min after feeding of a 2.5-kg meal. Plasma glucose was 2.2 to 2.5 times lower and blood lactate 2 to 3 times higher in the foetus than in the sow. Glucose and lactate increased after the meal. Their umbilical uptake amounted to 0.32 and 0.26 mmol·L^{-1}, respectively. Fructose was found in large amounts in foetal plasma (4.3 mmol·L^{-1}), but it did not seem to be metabolised by the foetus. Meal intake decreased plasma levels of FFA and glycerol in the sows, whereas they increased in the foetuses. A small FFA and glycerol umbilical uptake was recorded (14 and 6 μmol·L^{-1}, respectively). Most features of the materno-foetal exchanges in the porcine species resemble those of other species, especially ruminants.

materno-foetal exchange / energetic substrate / meal intake / pig

Résumé — **Effets de la prise alimentaire sur les échanges materno-fœtaux de substrats énergétiques chez le porc.** Des cathéters ont été implantés sur 18 truies à 99 jours de gestation afin d'étudier chez l'animal vigile les effets d'une prise alimentaire sur la capture de substrats énergétiques par l'utérus et le fœtus. Des échantillons de sang ont été prélevés à 105 jours de gestation entre 10 min avant et 90 min après la distribution d'un repas de 2,5 kg. La glycémie était 2,2 à 2,5 fois plus faible et la lactatémie 2 à 3 fois plus élevée chez le fœtus que chez la mère. Elles augmentaient après le repas. La capture de glucose et de lactate par le fœtus était respectivement de 0,32 et 0,26 mmol·L^{-1}. Les concentrations sanguines de fructose étaient élevées chez le fœtus (4,3 mmol·L^{-1}), mais ce substrat ne semblait pas métabolisé. La consommation du repas provoquait une diminution des teneurs plasmatiques en AGL et en glycérol des truies alors qu'elles augmentaient chez les fœtus. Une faible

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capture d'AGL et de glycérol était notée chez les fœtus (respectivement 14 et 6 µmol·L^{-1}). La plupart des caractéristiques des échanges materno-fœtaux chez le porc sont similaires aux autres espèces, en particulier aux ruminants.

échange materno-fœtal / substrat énergétique / prise alimentaire / porc

1. INTRODUCTION

During the first days of life of piglets there is an important loss of animals which is in great part attributable to the fact that new-borns have limited energy body stores (glycogen and 1 to 2% lipids which are almost structural) to meet their tremendous thermoregulatory requirements. Many attempts have been made to improve the glycogen and fat stores of pig foetuses during late pregnancy. Increased energy allowance to pregnant sows [30], supplementation with fat of the pregnant sow diet [39], and induction of diabetes in late pregnancy (see for instance Ezekwe and Martin [15]) have been tested, but they have all led to variable results. This could be partly explained by a lack of knowledge regarding the transfer of nutrients from the mother to the foetus, as well as the control of foetal nutrient utilisation. Due to technical difficulties, these studies were undertaken in species in which the females carry foetuses of large size and which are also less prone to abortion such as the cow [8] and sheep [28, 29]. Some information has also been gained in smaller species like rabbits [24], guinea pigs [57, 58] or rats [23], using labelled substrates. The conclusions which were drawn from these studies do not however necessarily apply to the foetal pig because of its lower fatness at birth and the different placenta. To our knowledge, the studies undertaken in pigs allow to gain access to the metabolism of the pregnant uterus, but excepted Fowden et al. [21], they do not give any information about the foetal metabolism. A chronic catheterisation method has been developed to allow the study of nutrition and metabolism in conscious and unstressed pig foetus [38]. The present experiment was therefore undertaken to evaluate the foetomaternal exchanges of energetic nutrients in the fasting and fed state.

2. MATERIALS AND METHODS

2.1. Animals and diets

The foetomaternal exchanges of nutrients were measured on eighteen Large White gilts. They were inseminated at 254 ± 5 days of age and 147 ± 4 kg body weight (mean ± se) with semen from Large White boars. They were kept in farrowing crates and fed 2.5 kg·day^{-1} of a diet based on cereals and soybean oil meal providing 3.0 Mcal DE·kg^{-1}, 13.1% crude protein, and 0.65% lysine. Animals were fed a single meal each morning at 9:00 hours.

2.2. Experimental procedure and measurements

Surgery was performed under general anaesthesia maintained with 2 to 5% halothane (Fluothane, Pitman-Moore, 77100 Meaux, France) in oxygen (1 to 2 L·min^{-1}), at 99 days of pregnancy. Details concerning catheterisation of blood vessels supplying or draining the uterus and foetus have been previously reported [38]. Briefly, a foetoplacental unit (part of the uterus corresponding to one foetus and its placenta) was exteriorised. A 2-cm incision was made through the uterus and the membranes for inserting two catheters (0.64 mm o.d., 0.28 mm i.d.) in the foetus which was kept

in the uterus. The first one was inserted in the femoral artery and advanced into the aorta, near the junction with the umbilical arteries. The second catheter was floating and implanted in the umbilical vein by using a divisible needle. A maternal catheter (1.65 mm o.d., 0.76 mm i.d.) was introduced into a small collateral vein of the uterus, and advanced in the main uterine vein draining the foetoplacental unit corresponding to the catheterised foetus. A fourth catheter was implanted in the maternal abdominal aorta. Post-surgical recovery, as assessed by the sows' appetite, required 2 to 3 days. Catheters were flushed daily with saline containing 250 IU heparin·mL^{-1}.

Animals were studied after an overnight fast at 105 ± 1 days of pregnancy. Each experiment consisted of a 10 min control period and a 90 min sampling period that followed consumption of the 2.5 kg meal during 10 to 15 min. Blood samples (1 mL) were drawn simultaneously through the four catheters. During the fasting period, samples were obtained 10 min before and just before the meal of the sow, and just before the meal only for the foetus in order to avoid over-bleeding. The subsequent blood samples were drawn in the dam and in the foetus at 15, 30, 45, 60, 75, and 90 min after the meal distribution. They were immediately divided into three subsamples and kept on ice. The first one was centrifuged and plasma samples were recovered for glucose, free fatty acids (FFA), glycerol and insulin determinations. The second one was deproteinized with perchloric acid 0.6 mol·L^{-1} for lactate analysis, and the third one was deproteinized by adding zinc sulphate 10% (wt/vol) and NaOH 0.5 N for fructose determination. All the subsamples were centrifuged at 3 °C, and supernatants were stored at – 20 °C until analysed.

Glucose, lactate, fructose, FFA, and glycerol were determined with commercial kits by automated enzymatic methods adapted to a Cobas Mira apparatus (Roche, Basel, Switzerland). The sensitivity was

19, 10, 3, 3 and 4 µmol·L^{-1} for these determinations, respectively. Concentration of insulin was measured by validated radioimmunoassay [42]. The sensitivity was 8 µU·mL^{-1}.

2.3. Calculations and statistical analysis

Arterio-venous differences of blood substrate concentrations were determined across the uterus and umbilical cord. Extraction coefficients were calculated as the differences between the arterial and venous substrate concentrations in percent of the substrate concentration in the arterial blood for the sow, or in the umbilical venous blood for the foetus. Paired comparisons of the substrate concentrations in arterial and venous blood in the sow and in the foetus were performed by using the t-test of the MEANS procedures of SAS [50]. Variation with time of concentrations, concentration differences and extraction coefficients were analysed by variance analysis with the GLM procedure of SAS [50] taking into account the effects of the sow and time, and the means were separated by F-protected LSD.

3. RESULTS

3.1. Glucose

Maternal arterial glycaemia was 5.03 ± 0.11 mmol·L^{-1} after an overnight fast. It increased significantly 15 min after meal ingestion (5.45 ± 0.11 mmol·L^{-1}) and reached a maximum value at 60 min (7.28 ± 0.24 mmol·L^{-1}) (Fig. 1). It did not differ significantly during the time interval between 45–90 min. Variations of glycaemia in the uterine vein paralleled those of the artery but remained significantly lower throughout the sampling period. The arterio-venous difference across the uterus did not vary with time ($P > 0.10$) and amounted to 0.35 ± 0.02 mmol·L^{-1} as a mean, which corresponds to an extraction coefficient of
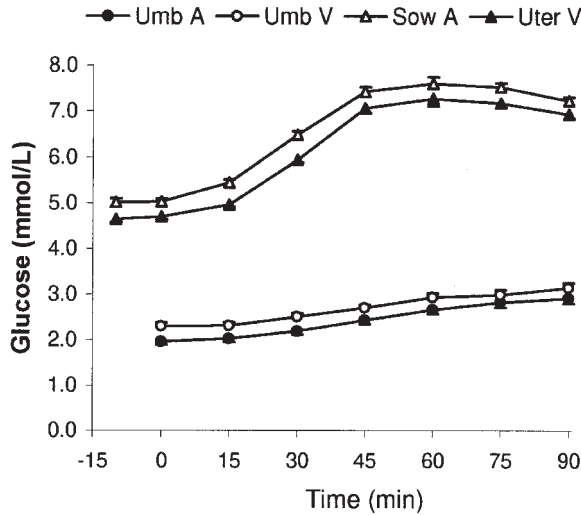
Figure 1. Variation with time of plasma glucose in the umbilical vein (Umb V), the foetal aorta (Umb A), the maternal aorta (Sow A) and the uterine vein (Uter V) ($n = 18$).
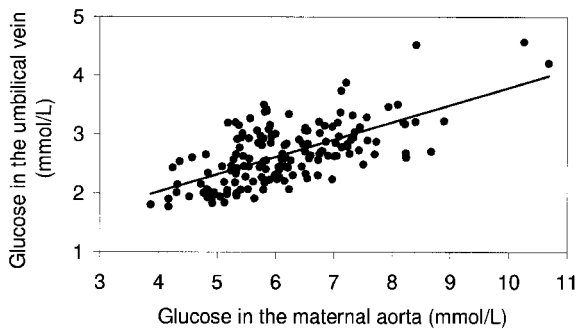

Figure 2. Relationship between plasma levels of glucose in the maternal aorta and in the umbilical vein.

$5.7 \pm 0.3\%$. Foetal glycaemia was 2.2 to 2.5 times lower than in the dam. The basal level of glucose in the umbilical vein was significantly higher than in the artery (2.30 ± 0.08 vs. 1.96 ± 0.07 mmol·L^{-1}; $P < 0.001$). Meal intake induced a significant and progressive increase in plasma glucose concentration in the foetal vessels. Foetal hyperglycaemia seemed to be slightly delayed compared to the mother since it was significantly increased only at time 30 min. Then, plasma glucose level progressively increased during the rest of the study period. Note that the level was always significantly higher in the umbilical vein than in the foetal artery ($P < 0.001$). The arterio-venous difference of glucose and the extraction coefficient across the foetus did not change significantly during

the period studied (0.32 ± 0.02 mmol·L^{-1} and $12.3 \pm 0.6\%$, respectively).

There was a fairly good linear relationship between plasma glucose concentration in the umbilical vein and in the maternal aorta (Fig. 2): foetal glucose = 0.86 (± 0.17) + 0.29 (± 0.03) × maternal glucose ($R^2 = 0.42$; $P < 0.001$), with foetal and maternal glucose in mmol·L^{-1}.

3.2. Insulin

The mean fasting insulin levels in plasma were 20 ± 3 and 13 ± 2 µU·mL^{-1} in the maternal aorta and the uterine vein, respectively (Fig. 3). Fifteen min after meal ingestion, insulin levels were significantly higher
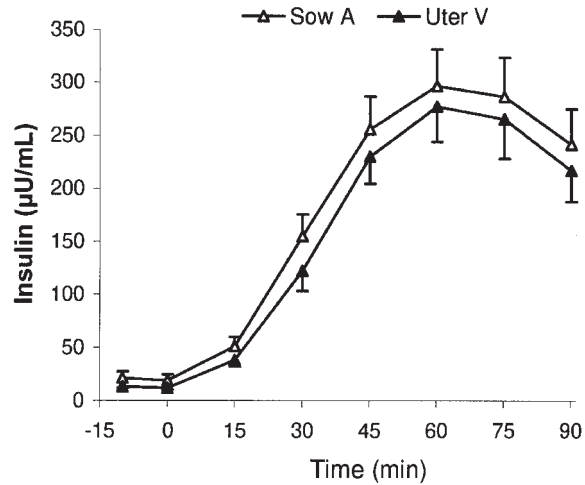
Figure 3. Variation with time of plasma insulin in the maternal aorta (Sow A) and the uterine vein (Uter V) ($n = 18$).

compared to the basal values (51 ± 9 and 38 ± 6 μU·mL^{-1}, respectively). Then they progressively increased and reached their maximum values at 60 min (297 ± 35 and 277 ± 33 μU·mL^{-1}). In the time interval from 45 and 90 min, insulinemia did not differ significantly in either maternal vessels. Throughout the study period, plasma insulin level in the artery was significantly higher than in the uterine vein. However, the arterio-venous difference of insulin was significantly higher ($P < 0.001$) from 30 to 90 min after the meal than earlier (14 to 21 vs. 1 to 4 μU·mL^{-1}), but the uterine

extraction coefficient remained constant over time ($7.4 \pm 0.8\%$). Foetal plasma insulin was practically undetectable using the radioimmunoassay for maternal insulin determination.

3.3. Lactate

The fasting levels of lactate amounted to 0.82 ± 0.07, 0.83 ± 0.06, 2.14 ± 0.14, and 2.45 ± 0.17 mmol·L^{-1} in the maternal aorta, the uterine vein, the umbilical artery and the umbilical vein, respectively (Fig. 4).
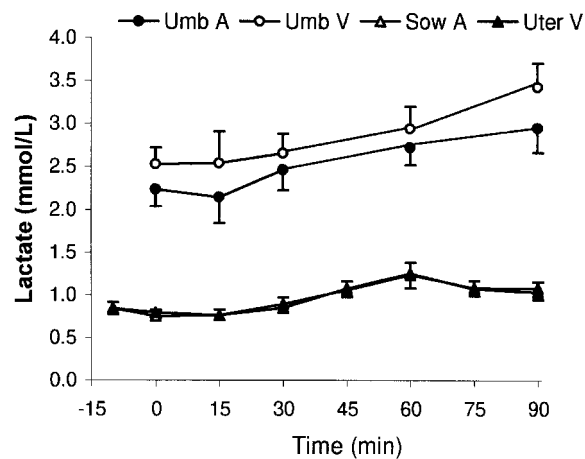

Figure 4. Variation with time of blood lactate in the umbilical vein (Umb V), the foetal aorta (Umb A), the maternal aorta (Sow A) and the uterine vein (Uter V) ($n = 12$).

Foetal blood lactate level was about two to three times higher than that measured in the dam. In the sow, 30 min after the meal, the lactate level increased and attained a maximum value at 60 min (1.26 ± 0.14 and 1.24 ± 0.15 mmol·L^{-1} in the artery and in the uterine vein, respectively). The lactate level did not differ significantly between 45 and 90 min after the meal. The arterio-venous difference of concentration and the extraction coefficient of lactate across the uterus did not differ significantly from zero. In the foetus, 30 min after the meal, blood lactate increased in the umbilical cord, and was maximal at 90 min (3.28 ± 0.29 and 2.82 ± 0.18 mmol·L^{-1} in the umbilical vein and artery, respectively). In order to avoid over-bleeding, lactate was not measured at 45 and 75 min after the meal in the foetus. Throughout the study period, the concentration of lactate was significantly higher in the umbilical vein than in the artery. The difference did not vary significantly with time and amounted to 0.26 ± 0.03 mmol·L^{-1}, which corresponds to a coefficient of lactate extraction of $10 \pm 1\%$ by the foetus. Lactate levels in the maternal aorta and in the umbilical vein were correlated ($r = 0.70$; $P < 0.001$).

3.4. Fructose

Fructose was not detected in gilts blood. In contrast, its level in the foetus was very high (about 4.3 mmol·L^{-1}) and did not vary with time. The arterio-venous difference of fructose concentration in the umbilical cord was not significantly different from zero at all sampling times.

3.5. Free fatty acids

The levels of plasma FFA in the fasting state in the sow averaged 612 ± 46 and 592 ± 45 μmol·L^{-1} in the maternal aorta and uterine vein, respectively (Fig. 5). They progressively decreased after the meal and at 90 min they averaged 214 ± 25 and 218 ± 24 μmol·L^{-1}, in the aorta and uterine vein respectively. The plasma levels of FFA were significantly higher in the maternal aorta than in the uterine vein only in the fasting state and over the first 15 min following meal ingestion. The uterine uptake of FFA averaged $4.5 \pm 1.1\%$ during that period and did not differ significantly from zero thereafter. The concentrations of plasma FFA in the umbilical vein and artery increased
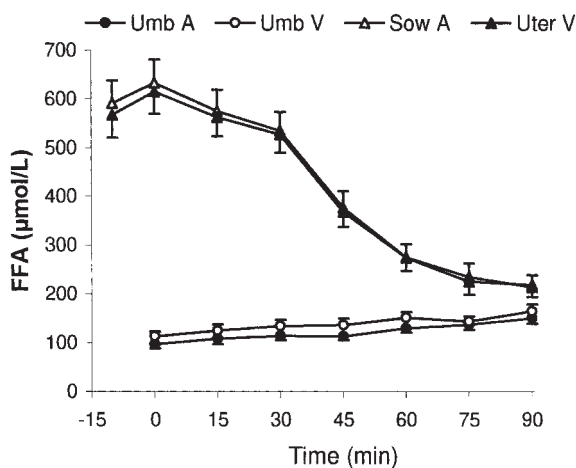

Figure 5. Variation with time of plasma free fatty acids (FFA) in the umbilical vein (Umb V), the foetal aorta (Umb A), the maternal aorta (Sow A) and the uterine vein (Uter V) ($n = 18$).

progressively from the fasting values (114 ± 9 and 97 ± 9 $\mu mol \cdot L^{-1}$, respectively) to a maximum at 90 min post-meal (165 ± 14 and 151 ± 11 $\mu mol \cdot L^{-1}$, respectively). They were significantly higher in the umbilical vein than in the artery, up to 15 min and at 60 min after the meal, whereas there was only a tendency at 30, 45 and 90 min ($P < 0.10$) after the meal. The mean arterio-venous difference of concentration across the umbilical cord averaged 14 ± 2 $\mu mol \cdot L^{-1}$. The extraction coefficient by the foetus differed from zero up to 15 min and at 60 min, with a mean of $7.8 \pm 2.5\%$ during the whole experiment.

3.6. Glycerol

Plasma levels of glycerol in the sow in the fasting state averaged 70.5 ± 5.7 and 67.8 ± 5.4 $\mu mol \cdot L^{-1}$ in the aorta and uterine vein, respectively (Fig. 6). From 15 min to 45 min after meal ingestion, there was a progressive decline in plasma level and during the time interval 45–90 min it was steady (time 90 min: 19.3 ± 1.5 and 19.2 ± 1.5 $\mu mol \cdot L^{-1}$, in the aorta and uterine vein respectively). Plasma glycerol tended to be higher in the artery than in the uterine vein, but the difference was only significant in the fasting state and during the first 15 min following meal ingestion and it averaged

3.2 ± 0.4 $\mu mol \cdot L^{-1}$. The extraction coefficient of glycerol by the uterus did not vary with time ($3.9 \pm 1.2\%$). The plasma level of glycerol in the foetus increased steadily from the fasting state (43.4 ± 2.0 and 36.1 ± 1.3 $\mu mol \cdot L^{-1}$ in the umbilical vein and artery, respectively) until 90 min after the meal (53.1 ± 2.6 and 47.1 ± 4.0 $\mu mol \cdot L^{-1}$, respectively). The levels in the foetal vessels were similar between 45 and 90 min after the meal, and significantly higher than before 30 min. The plasma levels of glycerol were always significantly higher in the umbilical vein than in the artery. The mean difference of concentration averaged 6.0 ± 0.6 $\mu mol \cdot L^{-1}$. The extraction coefficient of glycerol across the umbilical cord did not differ with sampling time ($12.2 \pm 1.2\%$).

4. DISCUSSION

Measurements of blood substrate levels in pig foetuses were made either from the umbilical blood during a caesarean operation in anaesthetised animals [1, 9, 35, 46–49, 59], or from foetuses with catheters implanted in the jugular vein or in the carotid artery [20, 44, 45]. An attempt of measuring substrate balances across the foetoplacental unit was also performed in the gilt [10]. The present experiment provides a view of
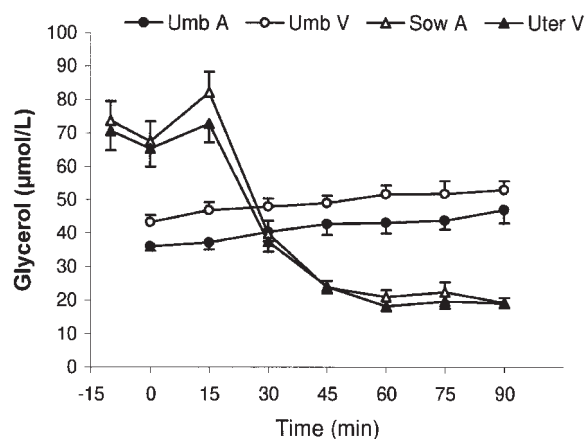

Figure 6. Variation with time of plasma glycerol in the umbilical vein (Umb V), the foetal aorta (Umb A), the maternal aorta (Sow A) and the uterine vein (Uter V) ($n = 9$).

substrate exchange between conscious sows and foetuses during the transition from a fasting to a postprandial state. This model, which is original in this species, allows the measurement of arterio-venous differences of substrates across the foetoplacental unit as a whole and the foetus as a part of the foetoplacental unit in several physiological conditions. Quantification of substrates utilised or produced by the uterus and foetus would require simultaneous measurement of uterine and umbilical blood flow. However, values in pigs are scare and, at our knowledge, the only available data show that, in the last third of pregnancy, umbilical and uterine blood flow per foetus are in the same range (0.31 and 0.38 L·min^{-1} respectively, Reynolds et al. [48]).

Fasting plasma levels of glucose in the maternal artery were within the same range as those previously reported in sows [1, 10, 18, 20, 44, 47, 48], cows [16, 17], ewes [7, 36], and rabbits [24]. The arterio-venous difference of glucose across the uterus was within the range of those reported earlier in conscious gilts at a similar stage of pregnancy after an overnight fast [1, 10, 18, 44]. Foetal glycaemia was much lower than in the dam which was in agreement with experiments involving sows [1, 20, 44] and other species [5, 26]. The arterio-venous difference of glucose across the umbilical cord and the corresponding extraction coefficient were not affected by the meal intake of the sow (0.32 mmol·L^{-1} and 12.3%, respectively). This is in keeping with the data obtained in foetuses from anaesthetised sows [1, 9, 47, 48] or before meal intake [44]. As a consequence of the hyperglycaemia induced by meal intake in the sow, we observed an elevation of foetal glycaemia, since the placental transfer of glucose depends on the concentration difference of glucose between the mother and the foetus [3]. The slope of the relationship between maternal and foetal plasma glucose averaged about 0.29 which was in the same range with that reported in sheep (0.32, Philipps et al. [41]; 0.38, Hay et al. [28]).

These relatively low values underline the poor glucose transfer efficiency of the epitheliochorial placenta of pigs and ruminants relative to the hemochorial placenta [4]. The delay (about 15 min) between the increase of glycaemia in the pig foetus and in its mother also suggests a low permeability of the pig placenta.

There was no significant change in the arterio-venous difference of insulin across the uterus throughout the study period, in agreement with Fowden et al. [20]. By contrast, in rabbits, there is a consistent insulin uptake by the uterus, with the extraction coefficient ranging from 20 to 30% [24]. The insulin level in the pig foetus was much lower than that of the mother as well as in an earlier study [20]. This is a feature of many species [19, 25, 33, 37, 40]. The mean level of insulin in the foetal pig, even in the chronically catheterised animal, is lower than the values reported for most other species studied [20]. Note that the plasma level of insulin in the foetus was below 8 µU·mL^{-1} and could not be measured, even after meal-induced hyperglycaemia. Depression of pancreatic β cell function through catecholamine release was shown during anaesthesia and surgery in the foetal pig, but not when it was chronically catheterised [20]. It was demonstrated that the pancreatic β cells of the foetal pig are functional before term [20]. However, glucose infusion to the chronically catheterised pig foetus leading to a 4 mmol·L^{-1} glycaemia increase elicits an extremely low insulinemia increase of about 6 µU·L^{-1} [20]. Moreover, insulin levels are very low in pigs at birth [31]. In our experiment, a lack of detectable change could then be explained by the poor insulin assay sensitivity.

The fasting levels of lactate in sows and foetuses agree with earlier data [9, 10, 55]. As in other species [26], the blood level of lactate was two to three times higher in the foetus than in the sow. Meal intake induced a progressive increase of the blood lactate level in the sow and in the foetus. It should

be pointed out that the lactate concentration in the umbilical vein was always higher than in the umbilical artery. The difference in lactate level across the umbilical circulation was 0.26 mmol·L^{-1} over the whole experiment. Slightly lower values were reported in pigs (0.19 mmol·L^{-1}, Comline et al. [9]), sheep (0.16 mmol·L^{-1}; Burd et al. [6]), and cows (0.10 mmol·L^{-1}; Comline and Silver [8]). As in ruminants, it seems reasonable to assume that foetal metabolism also relies on foetal lactate [27].

In agreement with earlier reports in sows [1, 47] and ewes [51], fructose was not detected in significant amounts (< 0.1 mmol·L^{-1}) in maternal blood at any sampling times. By contrast, elevated levels of fructose were found in foetuses which is in keeping with previous data obtained in late pregnant sows [1, 45–47] and in other species [54, 60, 61]. It seems reasonable to assume that the fructose in the foetal blood originates from a placental production as it has been shown in sheep [2, 32]. The fate of this substrate in the foetus is questionable because there was no arterio-venous difference of fructose across umbilical circulation, therefore suggesting that there is no net utilisation of the substrate by the foetus. Similar results were reported in pigs [47], sheep [60, 61], cows and horses [53]. On the whole, these data support the view that fructose is not an important substrate of foetal energy metabolism in normal conditions, especially in the fed state.

As in other species, maternal plasma levels of FFA were higher than in foetal plasma [26]. Important differences of FFA transfer to the foetus have been demonstrated between species in relation to their placentation. Maternal FFA are readily transferred in several species like rabbits [11, 12, 24, 56] or guinea pigs [57, 58], although in sheep the placenta displays poor permeability to this substrate [13]. This latter observation can be extended to the pig since after meal ingestion the maternal plasma FFA drop and it is not accompanied by a corresponding change in the foetal plasma. In pigs, Duée et al. [10] found a small arterio-venous difference of FFA across the uterus (7 to 10 μmol·L^{-1}) and concluded that FFA are not significantly extracted by the uterus. Only trace amounts of labelled fatty acids were found in foetal plasma lipids following the injection of labelled fatty acids to anaesthetised sows [59], and some direct transfer of maternal fatty acids to the foetus was demonstrated in pigs [22, 52]. In the present experiment, FFA were extracted by the uterus only when their levels were elevated. After the meal, FFA increased in the foetus despite they were no more taken up by the uterus. Most of the umbilical fatty acid uptake is not directly derived from sow FFA [14] and metabolism of FFA has been demonstrated in the porcine placenta [34, 43]. Fœtal levels of FFA could then result from de novo synthesis utilising glucose and lactate as the major precursors.

Transfer of glycerol across the uterus has been shown in sows after an overnight fast at a similar stage of pregnancy [10]. In the present experiment, after meal ingestion both in the mother and the foetus, plasma glycerol levels paralleled those of FFA. It should be pointed out that during the marked drop in maternal plasma level there was no concomitant change in foetal plasma level therefore suggesting a poor placental transfer of glycerol. In rat and rabbit placenta, transfer of glycerol has been demonstrated by intravascular injection of [^{14}C]glycerol to the mother in late pregnancy [23].

5. CONCLUSION

The intravascular catheterisation technique developed in the foetal pig and sow allows to chronically measure nutrient exchange in conscious and unstressed sows. This methodology permits to follow temporal responses to a variety of maternal or foetal perturbations. The present study shows that several features of uterine and foetal metabolism are similar among species

studied previously. Compared to hemochorial placenta of primates and rodents, the transfer efficiency of the porcine epitheliochorial placenta appears to be as low as that of ruminants. Glucose is taken up by the uterus and partly converted into lactate by the placenta. Glucose is the most important energetic fuel of the foetus and is followed by lactate, whereas fructose does not seem to be metabolised in our experimental conditions. Limited amounts of free fatty acids and glycerol are taken up by the uterus and cross the placental barrier, mainly in fasting conditions. The contribution of amino acids to energy metabolism, which is important in other species [5], needs to be evaluated.

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