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Maternal Factors Modulating Nutrient Transfer to Fetus

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Abstract. Current knowledge of the modulation of maternal-fetal transfer of metabolites is reviewed and new data on the actual placental transport of *D*-glucose, *L*-alanine and glycerol in the rat are presented. Twenty-one day pregnant rats were infused with the ^{14}C-labelled substrates throughout the left uterine artery. Radioactivity appearing in fetuses was corrected by the specific dilution of the tracer at maternal arterial plasma and the uterine artery blood flow to estimate placental transfer. This parameter appeared to be 127 $\mu mol \cdot kg^{-1}$ fetal b.w. $\cdot min^{-1}$ for *D*-glucose, 23 for *L*-alanine, and 1 for glycerol – values which are much higher than those described for larger species. There is a parallelism between the magnitude of transfer to fetus and arterial concentration in mother for each studied metabolite and actually variations in their plasmatic levels affect this transport process. This is clearly seen in the case of glucose where placental transfer is reduced during fasting hypoglycemia and greatly increased in diabetes. Placental transfer of *L*-alanine and blood flow to the placenta were reduced in both 48-hour starved and streptozotocin-induced diabetic late pregnant rats. Results show the main role of maternal nutrient concentration as a modulator of their transfer to fetus, the deleterious effect of reductions of uterine blood flow on placental transport of amino acids as well as the small placental transfer of glycerol as compared to either glucose or alanine.

Maternal-fetal nutrient transfer through the placenta is accomplished by means of different mechanisms, including facilitated diffusion, active transport, and simple diffusion [for reviews, see 1–3]. The kinetic characteristics of these processes are determined by the nature of the transport mechanism involved but its magnitude is a function of or determined by other indirect factors. The most important of these factors are the nutrient concentration in both placental sides, and uterine and umbilical blood flows. This paper is intended to document the role of maternal concentration and uterine blood

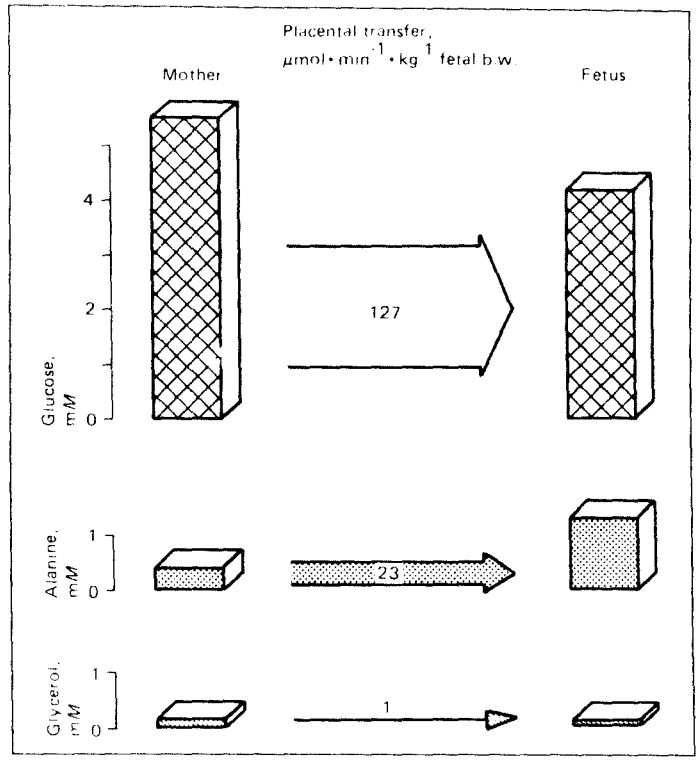

Fig. 1. Maternal and fetal plasma concentrations (bars), and placental transfer (arrows) of *D*-glucose, *L*-alanine and glycerol in the 21-day pregnant rat. Placental transfer to the fetus was determined by measuring the radioactivity that appeared in fetuses after infusing ^{14}C-labelled *D*-glucose, *L*-alanine or glycerol through the uterine artery and making proper correction of the data for specific activity dilution of the tracer, as described before [11].

flow as modulators of the transfer of some metabolites from mother to fetus by presenting some new data and reviewing current knowledge on the subject. Most of the discussion is limited to the rat, and to the transfer of glucose, amino acids, and glycerol which differ in both the specific mechanism how they cross the placenta (facilitated diffusion, active transport, and simple diffusion respectively) and in their concentration gradient between maternal and fetal blood. The magnitude of maternal-fetal transfer also differs for each of these metabolites. By measuring the umbilical venous-arterial concentration differences and the umbilical blood flow, in the conscious chronically catheterized pregnant sheep it has been estimated that the transfer to the fetus is about 17–24 μmol·kg^{-1} fetal b.w.·min^{-1} for glucose [4–6], 5 μmol·kg^{-1} fetal b.w.·min^{-1} for alanine [7], and 0.07 μmol·kg^{-1} fetal b.w.·min^{-1} for glycerol [calculated from 5 and 8]. In the 21-day pregnant rat we have determined the transfer to the fetus of these metabolites by measuring the radioactivity appearing in fetuses after infusing ^{14}C-labelled *D*-glucose, *L*-alanine or glycerol through the uterine artery and making proper correction of the data for specific activity dilution of the tracer [9–11]. The values obtained by this procedure were 127, 23 and 1 μmol·kg^{-1} fetal b.w.·min^{-1} for glucose, alanine and glycerol, respectively (fig. 1). Consequently, per kilogram of fetal body mass base, placental

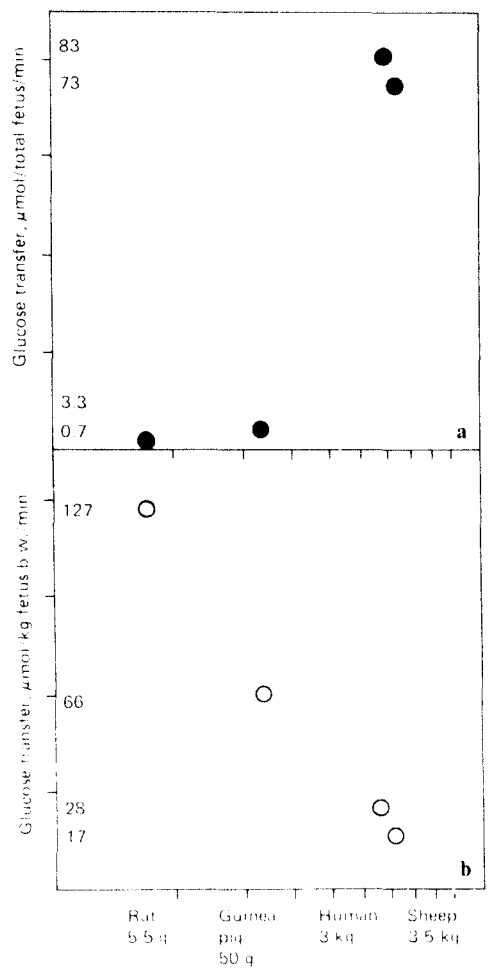

Fig. 2. Placental glucose transfer to fetus and fetal weight relationship in different species. **a** Glucose transfer is expressed per total fetus body mass. **b** Glucose transfer is expressed per kilogram of fetal body mass. Values for guinea pig, sheep and human were obtained from Simmons et al. [5].

transfer values in the rat appear much higher than in the sheep for each of these compounds. As shown in figure 2, there is an inverse correlation between the transfer of glucose per kilogram of fetus and fetal body weight when values obtained in different transfer species are plotted together (fig. 2b), whereas glucose transfer to the fetus expressed per total fetus body mass is much higher in species with larger (human, sheep) rather than smaller (guinea pig, rat) fetuses (fig. 2a). It is however worth mentioning that, in spite of these differences, the relative transfer of each of these metabolites when compared to the others is quite similar in both the sheep and the rat. This indicates that in the fed mother, among these metabolites glucose is quantitatively the main nutrient crossing the placenta, being followed by alanine which is transferred at a flux five times lower, whereas the transfer of glycerol is much lower. These comparisons parallel the order of magnitude of each of these metabolite's level in maternal plasma (fig. 1), illustrating the dependence of their placental transfer on their concentration at the maternal side.

Nutrient Concentration in Maternal Blood

Maternal-fetal concentration gradient for each metabolite is the 'pushing force' for its net transfer from mother to the fetus, and this is shown by the direct relationship that exists between fetal and maternal glycemia, both in human and in experimental animals [12–14]. By infusing ^{14}C-glucose through the left uterine artery we estimated the transfer of glucose from the mother to the fetus in hyperglycemic rats and found that it was linearly correlated with maternal glycemia even at levels of 30 m*M* [15]. These data indicate that the K_m value of placental glucose transport process is much higher than physiological circulating glucose levels and that glucose

transfer to the fetus directly depends on maternal glucose concentration. This relationship is also seen in conditions of hypoglycemia such as starvation and insulin treatment. In the unstressed ewe it has been shown that umbilical glucose extraction falls during maternal starvation proportionally to the change in uterine glucose concentration [16, 17]. In the starved condition, maternal glucose satisfies only 15% of the energy requirements of the ovine fetus, whereas it accounted for more than 50% in the fed condition [18]. In the 48-hour starved 21-day pregnant rat versus the fed one we have observed a decline in the estimated glucose transfer to fetus [Palacin et al., unpubl. observations], which can be attributed to the lower maternal supply of glucose to the placenta. In different species it has also been demonstrated that insulin-induced maternal hypoglycemia results in a decrease in the actual transfer of glucose to the fetus causing a decline in fetal circulating glucose levels [15, 19, 20]. When high doses of insulin are administered and maternal glycemia falls below 3 m*M*, the supply of glucose to the rat fetus can be estimated to be less than 60 $nmol \cdot g^{-1}$ b.w.$\cdot min^{-1}$ [11], which probably does not fulfill its metabolic needs. In these extreme situations, fetal liver glycogen is mobilized preventing fetal glycemia from lowering proportionally to maternal change [20].

Maternal plasma amino acid concentration also plays a role in their placental transfer. The transfer of maternal *L*-alanine to the 21-day rat fetus was found to be about 23 $nmol \cdot g^{-1}$ b.w.$\cdot min^{-1}$, which together with the low maternal concentration of circulating alanine compared to that of glucose (fig. 1) indicate that the alanine placental transport in the late pregnant rat is a very efficient process. The high placental amino acid transport capacity and the high apparent K_m value found in placentae from different species [3, 21, 22] suggest that changes in the circulating levels of amino acids in the mother may affect their actual transfer to the fetus. In the pregnant ewe, Morriss et al. [17] measured the uterine A-V differences for several amino acids and found that the uterine extraction of some of them was reduced by maternal starvation but the change could not be related to their concentration in maternal blood but to parallel changes in uterine blood flow. Therefore the magnitude of amino acids transfer seems to be modulated by other factors besides maternal-fetal gradient.

Placental permeability to glycerol is notably lower than to glucose or *L*-alanine [8, 23]. Besides this, under physiological conditions the concentration of glycerol in maternal blood is also lower than those metabolites. All of this accounts for the quantitatively small transfer of glycerol from mother to fetus observed in several species including the rat (fig. 1) [8, 23]. We previously found that the fetal-placental unit converts glycerol into lactate and lipids [24] contributing to maintain the glycerol concentration gradient between maternal and fetal blood [25, 26].

Maternal Blood Flow to the Placenta

In all species studied it has been found that during gestation there is a great increment in the uterine artery blood flow [27–29]. We measured uterine blood flow in the rat by injecting ^{99m}Tc-labelled microspheres and counting the radioactivity retained in the uterine structures following the methodology reported previously [30–32]. As shown

Table I. Blood flow to one uterine horn as a function of placental number in the rat

	Blood flow = a × P + b, ml/min
Virgin[1]	0.158 ± 0.012
12-day pregnant	0.116 × P + 0.021
20-day pregnant	0.890 × P + 0.331
21-day pregnant	0.868 × P − 0.030

Blood flow to the uterus was determined in pentobarbital anesthetized rats by infusing ^{99m}Tc-albumin microspheres as described [30–32]. In all but virgin animals, blood flow is expressed as a function of the number of placentae present in the uterine horn (P), which ranged between 2 and 9. Correlation coefficient between total blood flow and placental number was statistically significant ($p < 0.05$) in all pregnant animals. n = 5–7 rats/group.

[1] Values for virgin animals correspond to mean ± SEM of total blood flow.

Table II. Effect of starvation and diabetes on maternal blood flow (in ml/min) to the placenta in the rat

	Control	48 h starved	Diabetic[1]
20-day pregnant	0.89 ± 0.12[a]	–	0.36 ± 0.05[b]
21-day pregnant	0.97 ± 0.12[a]	0.44 ± 0.11[b]	–

Maternal blood flow to placentae was determined in pentobarbital anesthetized rats by infusing ^{99m}Tc-albumin microspheres as described [30–32]. Data correspond to mean ± SEM of 5–7 rats/group. Different superscripts correspond to statistically significant differences ($p < 0.001$).

[1] Rats were made diabetics by intravenous streptozotocin administration (45 mg/kg b.w.) at day 6 of gestation.

in table I, blood flow to the uterine horn, including the ovary, myometrium, endometrium, and adjacent adipose tissue is exiguous in the virgin rat and is slightly enhanced in the 12-day pregnant rat, whereas it intensely increases during late gestation. While in virgin animals blood flow to the whole uterus is less than 0.4% of the cardiac output, it accounts for about 15% at days 20 and 21 of gestation (data not shown). Note in table I that the results corresponding to pregnant animals are expressed as a function of the number of placentae (or fetuses) that are present in the uterine horn. This is because in the late pregnant rats, blood flow to the uterine horn is significantly correlated with the number of placentae (table I). In addition, it is known that the absolute flows to myometrium and decidua remain fairly constant during gestation but that to the placenta increases [28]. This mechanism seems to facilitate the placental transfer of nutrients adequate to sustain the accelerated growth of the fetus at this stage of gestation. This hypothesis is supported by the parallel change in placental blood flow and nutrients transfer found in the late pregnant rat [33]. Nevertheless, as placental transfer of nonmetabolizable glucose and amino acid analogs are also positively correlated with placental and fetal weights [34], more direct studies are required to establish the relative contribution of all these factors to the actual transfer of nutrients to the fetus.

The magnitude of the effect of uterine blood flow on placental transfer depends on the extraction coefficient of the substrate by uterine structures [35]. This is, for example, the case for oxygen as it has been demonstrated that a reduction in uterine blood flow

may result in fetal hypoxia due to restriction in the delivery of this gas from the mother [36, 37]. We tested whether reduced placental nutrient transfer in the starved condition could be influenced by parallel changes in uterine blood flow. Results obtained after the infusion of ^{99m}Tc-microspheres to fed and 48-hour starved 21-day pregnant rats are summarized in table II. It can be seen that starvation in the rat produces an intense reduction in the blood supply to the placenta (table II) and we believe that this is the major factor responsible, together with the changes in maternal circulating metabolite levels, for the diminished supply of nutrients to the fetus in the fasting state.

We previously reported that in severely diabetic late pregnant rats placental *D*-glucose transfer is several times higher than in fed normal rats while transfer of *L*-alanine is half [38]. These changes coincide with profound circulatory alterations reported in diabetic rats [32, 38, 39]. As shown in table II, in the 20-day pregnant rat made diabetic by streptozotocin treatment there is an intense reduction in placental blood flow when compared to the controls. Although the effect of reduced blood flow on the actual placental glucose transfer was not directly studied in these rats, the fact that it increased linearly with maternal glycemia indicates that reduction in maternal blood flow to placenta does not alter much the transfer of glucose to the fetus [11]. In contrast, the reduced transfer of *L*-alanine to fetuses in this maternal diabetic condition seems to be very much dependent on the change in placental blood flow as it may not be explained by changes in the concentration of this amino acid in both maternal and fetal plasmas nor by any other known factor [38]. The sensitivity of the placental transfer of amino acids to the placental blood flow has been also proposed by others [17, 40, 41] and interestingly, it has been shown that a reduction in uterine blood flow has more negative repercussions on the placental transfer of certain alpha-amino acids than on glucose [33, 40–42].

In summary, the available evidence indicates the main role of both maternal concentration and blood flow to the placenta as modulators of the nutrient transfer to the fetus. It has been the intention of the authors to emphasize the absolute dependence of the transfer of *D*-glucose to the fetus on the maternal concentration of this nutrient and the deleterious effect of the reduction of the uterine blood flow on the placental transfer of amino acids. In certain conditions this may represent an imbalance in the supply of nutrients for the fetus which can upset its normal growth.

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