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The Influence of High Maternal Plasma Glucose Levels, and Maternal Blood Flow on the Placental Transfer of Glucose in the Guinea Pig

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Summary. The relationship between maternal and fetal plasma glucose concentrations and placental glucose transfer has been studied in the anaesthetised guinea pig. The fetal circulation of the placenta, left 'in situ', was perfused through the umbilical arteries, after removal of the fetus, with a low molecular weight dextran, containing physiological salts and 100 mg/100 ml glucose. The maternal plasma: fetal perfusate concentration ratio of antipyrine, infused at a constant rate into the maternal circulation, was used to monitor the changes in maternal placental blood flow. — As the maternal plasma glucose was increased from 100 to 450 mg/100 ml the perfusate concentration followed, but at a slower rate. No further increases in perfusate concentration occurred after the maternal plasma level exceeded 450 mg/100 ml which suggests a maximum capacity of the placental membrane to transport glucose, analogous to that observed for the renal tubule and blood brain barrier. — The transfer rates of glucose from the fetal to the maternal circulation were similar to those in the opposite direction, with the same linear relationship to the transplacental gradients. Transfer, in either direction across the placental membrane, was reduced when the maternal placental blood flow was impaired, as indicated by a maternal: fetal antipyrine ratio below 0.6.

Key words: High plasma glucose, blood flow, placental transfer

The glucose concentration gradient across the placental membrane is normally from mother to fetus in both animals and man, studied at vaginal delivery or Caesarian section. The values reported for the maternal: fetal concentration differences vary from 10—50% of the respective maternal blood level [1, 2, 4, 5]. It is well known also, that changes in the maternal blood concentration, within the physiological range readily influence the fetal blood values. Recently Oakley *et al.* [10] have studied these inter-relationships when the maternal plasma glucose concentrations were high. The observations were made in pregnant women in whom labour was being surgically induced at term. The maternal plasma glucose was raised to 300 mg/100 ml by intravenous infusion, and it was found that the fetal scalp blood plasma concentration never exceeded 180—200 mg/100 ml. This concentration difference between mother and fetus was particularily high in the diabetic patient. These results suggest a maximum capacity to transport glucose in the placental membrane analogous to that observed for the renal tubule and other multicellular membranes. The present experimental study was undertaken to reproduce these findings in a controlled animal model in which the fetal circulation of the placenta, left 'in situ', was artificially perfused open circuit, after removal of the fetus. The influence of changes in the maternal: fetal plasma glucose gradient and in the maternal placental blood flow on glucose transport across the placental membrane was studied.

Methods

The pregnant guinea pig was used. The membrane separating maternal and fetal blood, is similar to that of the human, and consists of syncytiotrophoblast and fetal capillary endothelium [3]. 21 placentas from 18 near term does were studied; their average weight was 1.42 kg, and the mean gestational age 61 days, with a range of 59—67 days.

The Preparation

a) Mother. The details of the whole preparation have already been fully described by Reynolds and Young [12]. Briefly, the mother was anaesthetised with intravenous pentobarbitone sodium (Nembutal 20—30 mg/kg). Constant infusions were maintained of methoxamine HCl (Vasoxine), 1.3 mg/h, to stabilize the arterial pressure without changing the plasma glucose concentration; and antipyrine (Phenazone) to follow the changes in maternal placental blood flow.

The maternal acid base status was monitored at the beginning and end of the two hour experiment; the arterial and perfusion pressures were recorded throughout the experiment.

b) Placenta. The maternal guinea-pig was supported on an inclined metal tray in a saline bath at 38°C so that her abdomen could be opened, the uterus exposed and the conceptus delivered and maintained at a constant temperature. The fetus was removed, and the fetal placenta perfused through the umbilical

arteries with 10 g/100 ml low molecular weight dextran (Lomodex) containing physiological salts and glucose; the perfusion flow was 2 ml/min and the pressure 30—40 mm Hg. The perfusate was collected continuously from the umbilical vein in graduated tubes. The average weight of the perfused placentas was 3.9 g compared with the control which was 4.1 g; the respective fetal weights were 66 g and 67 g. The mean maternal arterial pressure during the experiments ranged from 80 to 60 mm Hg., the mean arterial pH ranged from 7.40 to 7.21, the pO_2 from 89 to 81 mm Hg and pCO_2 from 35 to 36 mm Hg. These values are similar to those reported previously [12].

Experimental Procedure

A steady rise in maternal plasma glucose, from 100 mg/100 ml to 650 mg/100 ml was obtained over 90 min by infusing glucose, at the rate of 30 mg/min into the jugular vein, using a 36 g/100 ml solution. Maternal arterial blood was sampled every 15—20 min. The fetal placental perfusion fluid contained 100 mg/100 ml glucose so that the maternal: perfusate gradient would be small at the beginning of the experiment. Estimations for glucose and antipyrine were made on consecutive 4 min perfusate samples.

Alteration of the gradient in the opposite direction, from fetus to mother was studied by raising the perfusate concentration in steps of 20—50 mg/100 ml while the maternal plasma level remained constant.

Net transfer of glucose was calculated from the umbilical arterio-venous glucose concentration differences and the corresponding perfusion rate. It was expressed as mg per min per unit wet weight placenta (mg $min^{-1}g^{-1}$).

Techniques

Maternal arterial blood was collected into tubes containing dried heparin and sodium fluoride (3 mg/ml). Glucose was estimated in the plasma and in the perfusate by a modification of the glucose oxidase method [13], using the colour reaction of oxygen with 4 aminophenazone. The antipyrine method used the colour reaction with nitrous acid [8]. Both methods were run simultaneously on a Technicon Auto-Analyser, with reaction bath at 37°C. The results were both related to appropriate standard solutions and expressed in mg/100 ml. There was no interference between the two estimations.

Results

Changes in the maternal placental blood flow altered the transfer rate of the freely diffusable substance antipyrine and, therefore, its concentration in the perfusate. As the fetal side of the placenta was perfused at a constant rate, the maternal perfusate: plasma concentration ratio could be used to follow the changes in maternal placental blood flow. The ratio was usually 0.8, demonstrating adequacy of the maternal placental blood flow. A reduction in this ratio below 0.6 was regarded arbitrarily as indicating an impairment of flow and was associated with a low maternal arterial pH, below 7.29, during an experiment. The relationship between the maternal plasma and placental perfusate glucose concentrations in an individual experiment are shown in Fig. 1. As the

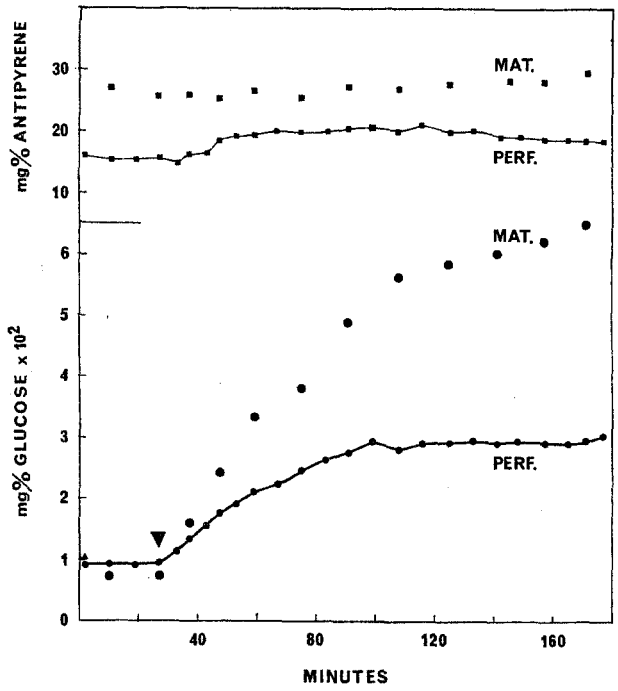

Fig. 1. The relationship between maternal plasma and placental perfusate glucose concentrations in one experiment. The perfusate concentration follows the maternal plasma concentration, but at a slower rate. When the latter exceeds 450 mg/100 ml no further increase in perfusate concentration occurs. The maternal plasma and perfusate antipyrine concentrations remain relatively constant throughout the experiment, indicating little change in maternal placental blood flow

maternal level was increased from 100—650 mg/100 ml the perfusate concentration followed, but at a slower rate. No further increase in perfusate concentration occurred after the maternal plasma concentration exceeded 450 mg/100 ml; such a pattern was observed in five experiments. The maternal plasma and perfusate antipyrine concentrations remained relatively constant throughout the experiment. Fig. 2 shows that glucose transfer rate was directly dependent upon the F:M antipyrine concentration ratio. When this ratio was about 0.8, the transfer rate was 0.16 mg $min^{-1}g^{-1}$ glucose for a 50 mg/100 ml concentration gradient between maternal arterial blood and the placental perfusion fluid.

The direct linear relationship between placental transfer rate and maternal plasma glucose concentrations below 450 mg/100 ml is shown in Fig. 3. The

regression slope 'b' = 0.0035 (r = 0.94) when the F:M antipyrine ratio was above 0.6, and was reduced to 0.0016 (r = 0.88) when this ratio fell below 0.6; there were nine experiments in each group, and the number "n" of observations were 41 and 25, respectively. Transfer in the opposite direction, from fetal perfusate into the maternal circulation occurred at a similar rate; the regression slope 'b' = 0.0037 (r =

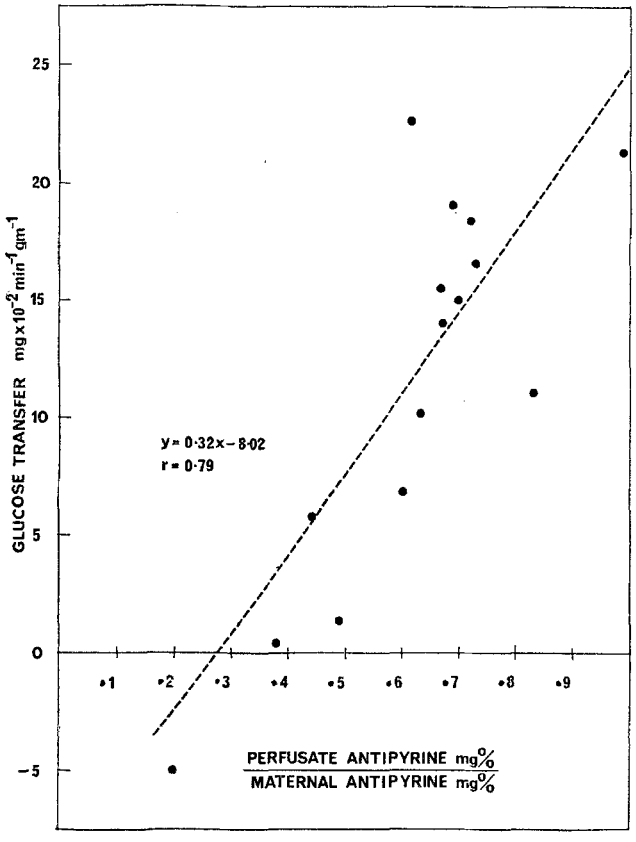

Fig. 2. The direct relationship between maternal to fetal glucose transfer (mg. $min^{-1}g^{-1}$) and fetal: maternal antipyrine ratio, representing changes in maternal placental blood flow. Each value comes from different experiments in which the maternal plasma: fetal perfusate glucose gradient was 50 mg/100 ml

0.99) with F:M antipyrine rations above 0.6 and 'b' = 0.0019 (r = 0.98) when the antipyrine ratio was below 0.6. There were four experiments in each group and "n" was 15 and 19 respectively.

Discussion

Glucose was transferred at the rate of 0.64 mg min^{-1} by the 4 g placenta, when the F:M antipyrine ratio was 0.8 and when the maternal: fetal gradient was 50 mg/100 ml. This value corresponds well with the 0.56 mg min^{-1} required for a 70 g fetus, calculated from measurements of glucose utilization rate of 8 mg kg^{-1} min^{-1} in the fetal lamb [2]. The transfer rate in the present experiments is only one third of that observed by Leichtweiss and Schröder [6] who perfused both maternal and fetal placental circulations, in the guinea pig, with an artificial fluid.

The transfer rates of glucose from maternal to fetal circulation and, in the opposite direction, from fetus to mother were very similar, with the same linear relationship to the transplancetal gradient. The linear relationship between concentration and transfer would suggest that diffusion plays the major role in the placental transport of glucose, at maternal plasma concentrations up to 450 mg/100 ml. However, in spite of this, the concentration of glucose in the perfusate effluent diverged progressively from that in the maternal plasma as this rose to 450 mg/100 ml. This shows that there was a limitation of transfer of placental origin, since the fetus had been removed. These results are quite comparable with those observed by

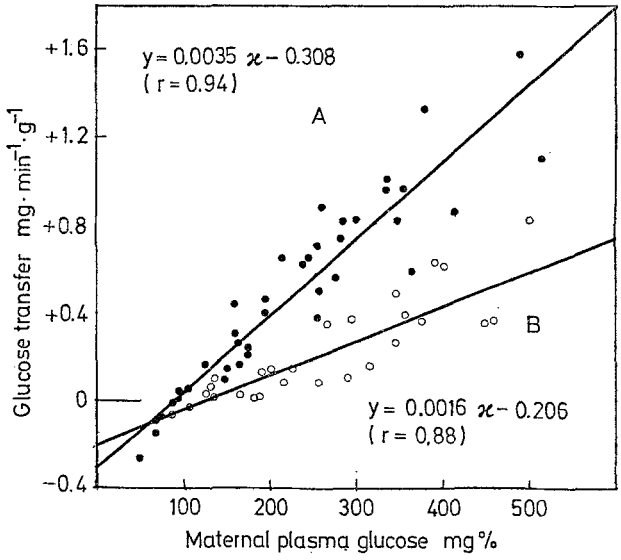

Fig. 3. The influence of maternal glucose concentration, below 500 mg/100 ml on maternal to fetal placental glucose transfer (mg. $min^{-1}g^{-1}$) with; a) good maternal placental blood flows (F:M antipyrine rations > 0.6). 'n' = 41 from 9 experiments. b) poor maternal placental blood flows (F:M antipyrine rations < 0.6). 'n' = 25 from 9 experiments

Oakley *et al.* [10] in which the fetus was present. A limitation of transfer by high plasma concentrations has also been observed for the blood brain barrier and small intestine [9, 11]. The relative parts played by diffusion limitation, saturation of the transfer process, the maternal: fetal blood flow relationships, or increased glycogen synthesis by the placenta in reducing glucose transfer rate have yet to be investigated.

The normal glucose concentration gradient, from mother to fetus across the placental membrane suggests that fetal and placental utilisation play an important role in controlling glucose transfer by creating and maintaining the gradient between the two placental blood streams. This situation is similar, but less pronounced, than that for oxygen transfer,

where the maternal: fetal tension gradient is largely due to the oxygen utilisation of both the placenta and fetus, besides the characteristics of the blood flow relationships on each side of the membrane [7].

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