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What factors determine placental glucose transfer kinetics?☆

P.E. Day, J.K. Cleal, E.M. Lofthouse, M.A. Hanson, R.M. Lewis*

Institute of Developmental Sciences, University of Southampton, Faculty of Medicine, Southampton SO16 6YD, United Kingdom

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ABSTRACT

Introduction: Transfer of glucose across the human placenta is directly proportional to maternal glucose concentrations even when these are well above the physiological range. This study investigates the relationship between maternal and fetal glucose concentrations and transfer across the placenta.
Methods: Transfer of D-glucose, ^{3}H-3-o-methyl-D-glucose (^{3}H-3MG) and ^{14}C-L-glucose across the isolated perfused human placental cotyledon was determined for maternal and fetal arterial D-glucose concentrations between 0 and 20 mmol/l.
Results: Clearance of ^{3}H-3MG or ^{14}C-L-glucose was not affected by maternal or fetal D-glucose concentrations in either circulation.
Discussion: Based on the arterial glucose concentrations and the reported K_M for GLUT1, the transfer of D-glucose and ^{3}H-3MG would be expected to show signs of saturation as D-glucose concentrations increased but this did not occur. One explanation for this is that incomplete mixing of maternal blood and the rate of diffusion across unstirred layers may lower the effective concentration of glucose at the microvillous membrane and subsequently at the basal membrane. Uncertainties about the affinity of GLUT1 for glucose, both outside and inside the cell, may also contribute to the difference between the predicted and observed kinetics.
Conclusion: These factors may therefore help explain why the observed and predicted kinetics differ and they emphasise the importance of understanding the function of transport proteins in their physiological context. The development of a computational model of glucose transfer may improve our understanding of how the determinants of placental glucose transfer interact and function as a system.
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1. Introduction

Placental glucose transfer is essential to sustain fetal growth and metabolism. Insufficient glucose transfer will result in fetal growth restriction (FGR) while too much is associated with fetal macrosomia [1]. FGR and macrosomia are associated with complications at birth and an increased burden of chronic diseases in adulthood [2]. As such, it is important to understand factors that determine glucose availability to the fetus in pregnancies with normal and abnormal maternal glucose levels.

Glucose transport across the microvillous (MVM) and basal (BM) membranes of the human placental syncytiotrophoblast at term has been shown to be a transporter mediated process [3]. It is thought that glucose transfer is predominantly mediated by the transporter GLUT1 (SLC2A1) which mediates facilitated diffusion [3,4]. GLUT1 levels are lower on the BM which also has a smaller surface area and, as a result, is thought to be rate-limiting for placental glucose transfer [4]. Glucose transporters other than GLUT1 may play important roles earlier in gestation, especially GLUT3 [5,6]. The consensus K_M for D-glucose transport by GLUT1 in human erythrocytes is reported to be around 3 mmol/l although lower and higher K_M values have been reported, ranging from 1 to 17 mmol/l [7,8]. Glucose uptake by human placental MVM and BM membrane vesicles is very rapid suggesting a high capacity for glucose transport in the placenta [9]. Net glucose transfer across the placenta will be the sum of paracellular and transcellular routes, less any metabolised in the placenta. Although the paracellular route across the syncytiotrophoblast is poorly defined, it has been demonstrated using L-glucose which is not transported by glucose transporters [8,10,11].

The rate of glucose transfer across the human placenta is thought to be primarily determined by the maternal to fetal glucose gradient and transfer is directly proportional to this gradient up to maternal glucose concentrations well above physiological [10,12,13]. Evidence of transporter saturation in the perfused placenta has been reported with glucose concentrations above 20 mmol/l suggesting

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* Corresponding author. Tel.: +44 (0)2380798663; fax: +44 (0)2380795255.
E-mail addresses: rohan.lewis@southampton.ac.uk, rml2@soton.ac.uk (R.M. Lewis).

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an apparent K_M for placental glucose transport higher than that reported for GLUT1 [3]. Maternal and fetal blood flow will maintain the concentration gradient by delivering glucose enriched blood to the maternal side and removing the glucose transported to the fetal circulation. Evidence that glucose transfer is flow-limited is consistent with the idea that glucose transfer increases linearly with maternal–fetal glucose gradients [14]. This is interesting as a high affinity transporter such as GLUT1, which is believed to have a K_M below physiological glucose concentrations, would be expected to be increasingly independent of maternal glucose concentrations as they rise above the K_M as illustrated in Fig. 1A. If there are more transporters in the membrane then V_{max} will be higher and the capacity for glucose transfer across the placenta will be greater. However, increasing V_{max} will not change the glucose concentration at which transporter saturation will occur (Fig. 1B).

Given the difference between the observed glucose transfer in the human placenta and what would be predicted based on the kinetics of GLUT1, we explored the extent to which glucose transfer is transporter-limited. We also addressed the role of paracellular glucose transfer in the human placenta.

2. Methods

Human placentas from uncomplicated term deliveries were obtained immediately after delivery from Princess Anne Maternity Hospital. Ethical approval was given by the South and West Hants Local Research Ethical Committee.

3. Placental perfusion methodology

Placentas were perfused using the methodology of Schneider [15] as adapted in our laboratory [16]. All placentas used for the studies had a fetal arterial flow rate recovery of 95% or greater. Earle's Bicarbonate Buffer (EBB, 1.8 mM $CaCl_2$, 0.4 mM $MgSO_4$, 116.4 mM NaCl, 5.4 mM KCl, 26.2 mM $NaHCO_3$, 0.9 mM NaH_2PO_4 and a variable concentration of glucose as stated below) gassed with 5% CO_2 and 95% O_2 was perfused through the fetal catheter going into the chorionic plate fetal artery at 6 ml/min and the five maternal catheters at 14 ml/min using a roller pump. Buffers containing D-glucose, ^{14}C-L-glucose and ^{3}H-3-o-methyl-D-glucose (^{3}H-3MG) (Perkin Elmer, Massachusetts, USA), were then perfused as described below. When sampling approximately 1.5 ml of venous exudate was collected from maternal and fetal venous outflows. At the end of the experiments, the perfused mass of placental cotyledon that assumed a white colour was obtained by trimming off the non-perfused tissue, then blotted and weighed.

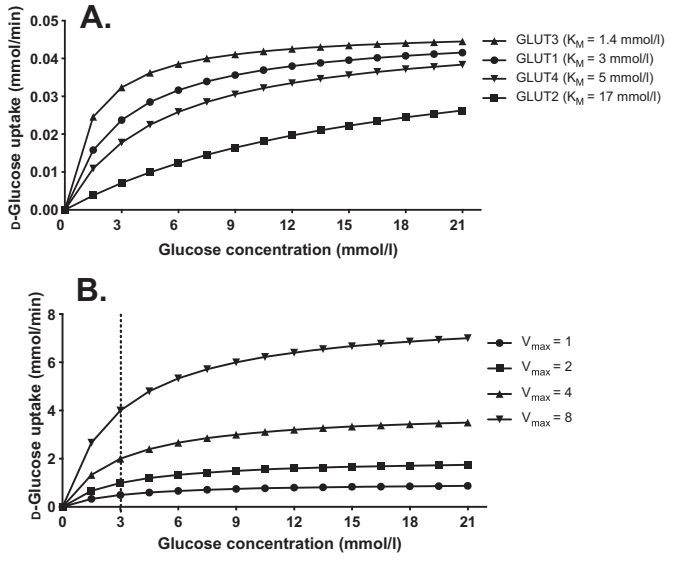

Fig. 1. The predicted effect of K_M and V_{max} on glucose transport based on simple Michaelis Menten Kinetics. A, The effect of K_M on glucose uptake using the K_Ms for GLUT1-4 as examples [7]. Glucose transfer by GLUTs with a lower K_M would be less dependent on maternal glucose concentration. B, Glucose uptake is directly proportional to V_{max} but only proportional to maternal glucose levels where these are less than K_M. Note that the K_M for all curves is 3 mmol/l (dotted line) regardless of the V_{max}.

4. Glucose perfusions

In initial experiments increasing concentrations of D-glucose were perfused through the maternal artery (from 0 to 18 mmol/l in 3 mmol/l steps for 20 min each) with no glucose added to the fetal catheters going into the chorionic plate fetal artery.

Subsequently, experiments were performed using 0.8 μCi/l of ^{14}C-L-glucose as a measure of paracellular diffusion and 8 μCi/l ^{3}H-3MG were perfused into the maternal intervillous space or the fetal artery. L-glucose is not transported by GLUT1 [8]. The non-metabolisable glucose analogue 3MG is reported to have a K_M of 1.8 mmol/l in human erythrocytes in line with the consensus values for the K_M of D-glucose [17], although a higher K_M is reported in *Xenopus* oocytes of 17.6 mmol/l for 3MG which is again comparable to the K_M D-glucose of 17 mmol/l in this system [8]. In the maternal-side tracer experiments maternal and fetal arterial D-glucose concentrations were: 0:0, 3:0, 6:0, 9:0, 9:3, 6:3, 3:3, 0:3, 0:6, 3:6, 6:6, 9:6 and 12:6 (maternal:fetal (mmol/l)) for 20 min at each step. In the fetal tracer experiments maternal and fetal arterial D-glucose concentration were: 0:3, 3:3, 6:3, 9:3, 9:6, 6:6, 3:6, 0:6, 0:9, 3:9, 6:9, 9:9, 15:9 and 15:20 (maternal:fetal (mmol/l)) for 20 min at each step. Maternal and fetal venous samples were analysed by liquid scintillation counting (Packard–Perkin Elmer, Massachusetts USA) and an enzymatic glucose assay (Alpha Laboratories, Eastleigh, UK) according to the manufacturer's instructions.

4.1. Analysis and statistics

Clearance was calculated so that transfer from maternal to fetal and fetal to maternal circulations could be compared. Clearance of ^{3}H-3MG or ^{14}C-L-glucose from one circulation to the other was calculated using the formula clearance $= [V_R].F_R/[A_D]$. Where $[V_R]$ = recipient arterial tracer activity (cpm), F_R = recipient circulation flow rate, $[A_D]$ = donor circulation arterial tracer activity (cpm).

Using simple Michaelis Menten Kinetics, predicted transport curves for GLUT1, 2, 3 and 4 were generated using literature K_M values for each transporter (Fig. 1A) [7]. This calculation assumed that donor side glucose concentrations were homogeneous and equal to the arterial concentration. Michaelis Menten Kinetics were determined using the following formula: $v_0 = V_{max}[S]/(K_M+[S])$ where v_0 is the initial rate, $[S]$ is the substrate concentration, K_M is the substrate concentration at which there is the half maximal flux and V_{max} the maximal rate of uptake. Where predictions are compared to data the V_{max} of the prediction was adjusted so that the predicted and experimental data aligned in the early part of the curve.

Transporter-mediated clearance was calculated by subtracting clearance of L-glucose (representing paracellular glucose transfer) from clearance of 3MG (which is transferred by both paracellular diffusion and transcellular transport).

Maternal venous to fetal venous and fetal venous to maternal venous ratios were calculated by dividing the venous concentration in the recipient circulation by that in the donor circulation (the circulation into which the tracer or glucose was added).

Statistical analyses were carried out using PASW SPSS19 (IBM, Chicago, IL, USA). Clearance of ^{3}H-3MG and L-glucose were analysed

by univariate analysis of variance with maternal arterial D-glucose concentration, fetal arterial D-glucose concentration and donor circulation as fixed factors. All data are presented as mean and standard error of the mean (SEM). A P value of less than 0.05 was considered to be statistically significant.

5. Results

In the maternal side tracer perfusion experiments mean (SEM) fetal flow recovery was 6.0 (0.03) ml/min and cotyledon weight was 32.2 (8.3) g. In the fetal side tracer perfusion experiments mean (SEM) fetal flow recovery was 5.9 (0.03) ml/min and cotyledon weight was 35.6 (4.4) g. There was no significant difference in cotyledon weight or flow between the groups. In experiments where tracer was added to the maternal circulation average tracer recoveries (mean (SEM)) were 94 (3.9) % for ^{14}C-L-glucose and 96 (3.1) % for ^{3}H-3MG. In experiments where tracer was added to the fetal circulation average tracer recoveries were 102 (2.4) % for ^{14}C-L-glucose and 104 (2.1) % for ^{3}H-3MG.

5.1. Predicted glucose transfer kinetics

Predicted glucose transfer based on simple Michaelis Menten kinetics were calculated for increasing K_M (Fig. 1A) and V_{max} values (Fig. 1B).

5.2. Glucose transfer to the fetal vein

Transfer of D-glucose from the maternal circulation to the fetal vein (venous concentration × flow rate) was positively correlated to maternal arterial D-glucose concentration, $n = 5$ placentas (Fig. 2). The curve of the line for D-glucose transfer was significantly different from that predicted by Michaelis Menten Kinetics for GLUT1 with a K_M of 3 mmol/l ($P < 0.01$). As glucose concentrations in the artery may be higher than those at the membrane we calculated how low the glucose concentrations at the membrane would need to be in order to explain the observed data if glucose concentration at the membrane were the only explanation for the observed data. It was determined that if GLUT1 had a K_M 3 mmol/l, a membrane concentration equivalent to 10% of the arterial glucose concentration would be necessary for the observed and predicted curves to overlap. Some reports indicate a higher K_M for GLUT1 of 17 mmol/l and in this case a membrane concentration equivalent to 50% of the arterial glucose concentration would be necessary for the observed and predicted curves to overlap.

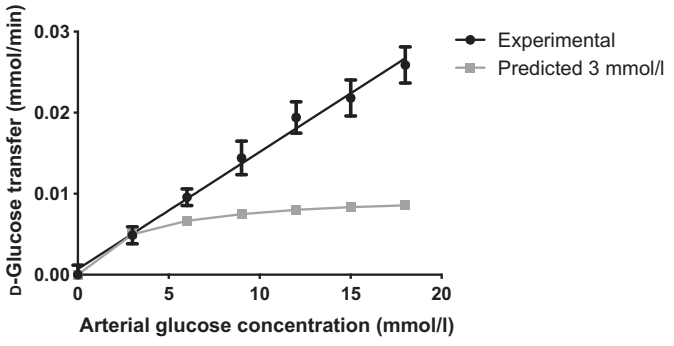

Fig. 2. Transfer of D-glucose from the maternal circulation to the fetal circulation vs predicted glucose uptake. The linear relationship between maternal arterial glucose concentration and experimental transfer ($R^2 = 0.74$) suggests that there is no transporter saturation. The experimental data and predicted data were significantly different ($P < 0.01$). Experimental data is mean and SEM, $n = 5$ perfusions per point.

5.3. Clearance of L-glucose and ^{3}H-3MG

Clearance of ^{14}C-L-glucose from the maternal circulation into the fetal circulation was not affected by either maternal ($P = 0.99$) or fetal ($P = 0.60$) glucose concentrations, $n = 5$ placentas (Fig. 3A). Fetal to maternal L-glucose clearance was significantly higher than maternal to fetal clearance, $n = 5$ placentas ($P = 0.03$). There were no significant interactions between the factors ($P > 0.82$ in all cases).

Clearance of ^{3}H-3MG from the maternal circulation into the fetal circulation was not affected by either maternal ($P = 0.31$) or fetal ($P = 0.09$) glucose concentrations (Fig. 3B). Clearance of ^{3}H-3MG in the maternal to fetal direction was higher than in the fetal to maternal directions ($P = 0.03$). There were no significant interactions between the factors ($P > 0.18$ in all cases).

Transporter mediated clearance of ^{3}H-3MG was not affected by either maternal ($P = 0.94$) or fetal ($P = 0.89$) glucose concentrations (Fig. 3C). Transporter mediated clearance from the maternal to the fetal circulation was significantly greater than from the fetal to the maternal circulation ($P = 0.001$). There were no significant interactions between the factors ($P > 0.90$ in all cases).

6. Discussion

This study found that placental clearance of the non-metabolisable glucose analogue ^{3}H-3MG from the maternal to fetal circulation or from the fetal to maternal circulation was not inhibited by increasing D-glucose concentrations to well above physiological concentrations. These observations are in line with previous studies but in apparent contrast with the pattern of transfer we predicted using simple Michaelis Menten kinetics [3,10,12,13]. These predictions were based on a number of assumptions, including that donor side glucose concentrations were homogeneous and equal to the arterial concentrations. The experimental data suggest that there are factors that we did not initially consider which affect the kinetics of placental glucose transfer.

The difference between the observed and predicted glucose and ^{3}H-3MG transfer could be explained if the reported K_M for GLUT1 is lower than the actual K_M. While the K_M for glucose transport by GLUT1 is generally believed to be around 3 mmol/l, values of up to 17 mmol/l have been reported (equivalent to GLUT2 on Fig. 1A). If the K_M for GLUT1 was 17 mmol/l this would not in itself explain our observations although the difference would be smaller. However, a higher intracellular K_M in combination with a lower glucose concentration at the membrane could explain the difference. The intracellular face of GLUT1 is reported to have a 2.9 fold lower affinity for glucose under zero-trans conditions (intracellular K_M 4.6 mmol/l vs extracellular K_M 1.6 mmol/l) [18]. In order to be transferred to the fetus, glucose must cross the BM from the intracellular side so a higher intracellular K_M may also in part explain our observations.

If these observations were to be explained by glucose concentrations alone then if concentrations at the MVM were 10%–50% (depending on the actual K_M for GLUT1) of those in the maternal artery then the predicted and observed transfers would match. Factors which reduce the glucose concentration at the membrane compared to arterial blood include the efficiency of mixing of glucose rich arterial blood with glucose depleted blood, diffusion across the unstirred layer around the villi and the progressive transport of glucose out of maternal blood as it passes through the intervillous space.

Mixing of maternal blood is a particularly important determinant of the glucose available for transport. The A-V difference across the intervillous space (at maternal and fetal arterial glucose concentrations of 6 and 3 mmol/l respectively) was 11% suggesting that glucose concentrations within the intervillous space remain

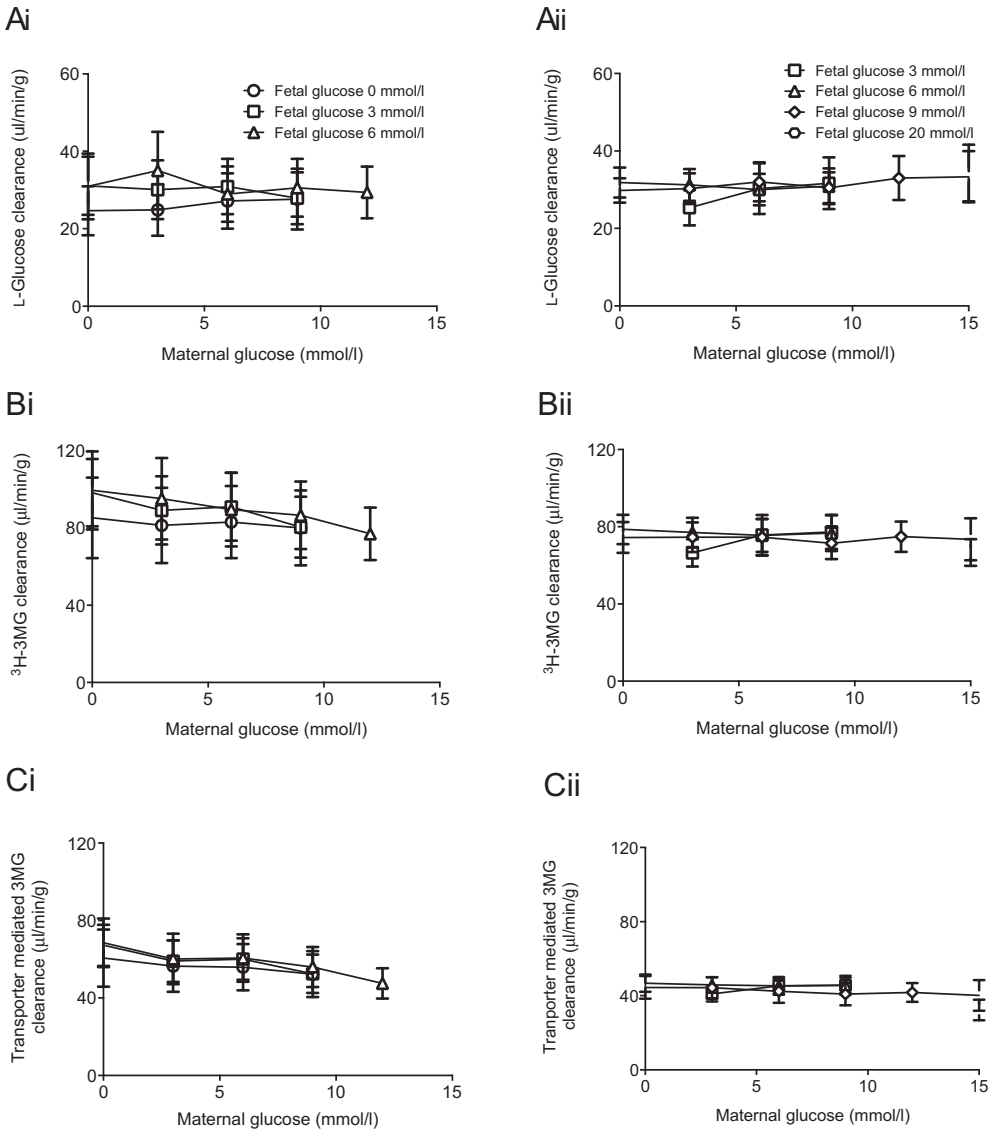

Fig. 3. Clearance of (A) L-glucose, (B) ^{3}H-3MG and (C) transporter mediated ^{3}H-3MG from the (i) maternal and (ii) fetal circulations of the isolated perfused human placental cotyledon. A, Maternal or fetal D-glucose concentrations did not affect L-glucose clearance nor did the direction of transfer. B, Clearance of ^{3}H-3MG was not affected by maternal or fetal D-glucose concentrations but was higher in the maternal to fetal direction ($P = 0.03$). C, Transporter mediated clearance (^{3}H-3MG transfer − ^{14}C-L-glucose). Maternal or fetal D-glucose concentrations did not affect transporter mediated ^{3}H-3MG clearance but this was greater in the maternal to fetal direction ($P = 0.001$). Data is mean and SEM, $n = 4–5$ perfusions at each point.

relatively high. However if there were a shunt within the intervillous space, a region where maternal blood did not mix effectively on its way to the vein, then effective glucose concentrations may be lower than implied by venous concentrations [19].

The human placenta is postulated to have a multivillous arrangement of maternal and fetal blood flow although this has not been determined experimentally [20]. Under some circumstances a multivillous blood flow system could allow for solute concentrations in the fetal vein to be higher than in the maternal vein even though transfer is by diffusion [20]. In the perfusion model the normal patterns of maternal blood flow may not represent those *in vivo* and this may affect the observed transfer. The perfused placenta may have a lower flow rate and viscosity which may affect mixing within the intervillous space and therefore the glucose concentrations at the membrane. This means we cannot assume that our data will be directly comparable to the *in vivo* situation.

Blood flows through the intervillous space but at the fluid tissue interface there will be an unstirred layer through which glucose must diffuse (Fig. 4). As glucose will be transported across the membrane on the other side of this layer, the balance between the rate at which glucose can diffuse in and the rate at which it is transported out will determine the concentration at the membrane.

These factors are likely to cause the glucose concentration at the membrane to be lower than in the artery as well as regional differences across the placenta. For this reason, the kinetics of transfer at the MVM should ideally be worked out using a spatial mean, an average glucose concentration across the surface of the placental exchange area.

Placental glucose metabolism would decrease transfer rate of D-glucose by decreasing its intracellular concentration and therefore affecting its transfer kinetics. As 3MG is not phosphorylated its transfer represents glucose transfer activity independent of placental metabolism and in this regard it will be different from D-glucose or 2-deoxyglucose transfer.

As GLUT1 protein abundance and activity are lower on the BM, the V_{max} of the BM will be lower than that of the MVM and thus, as

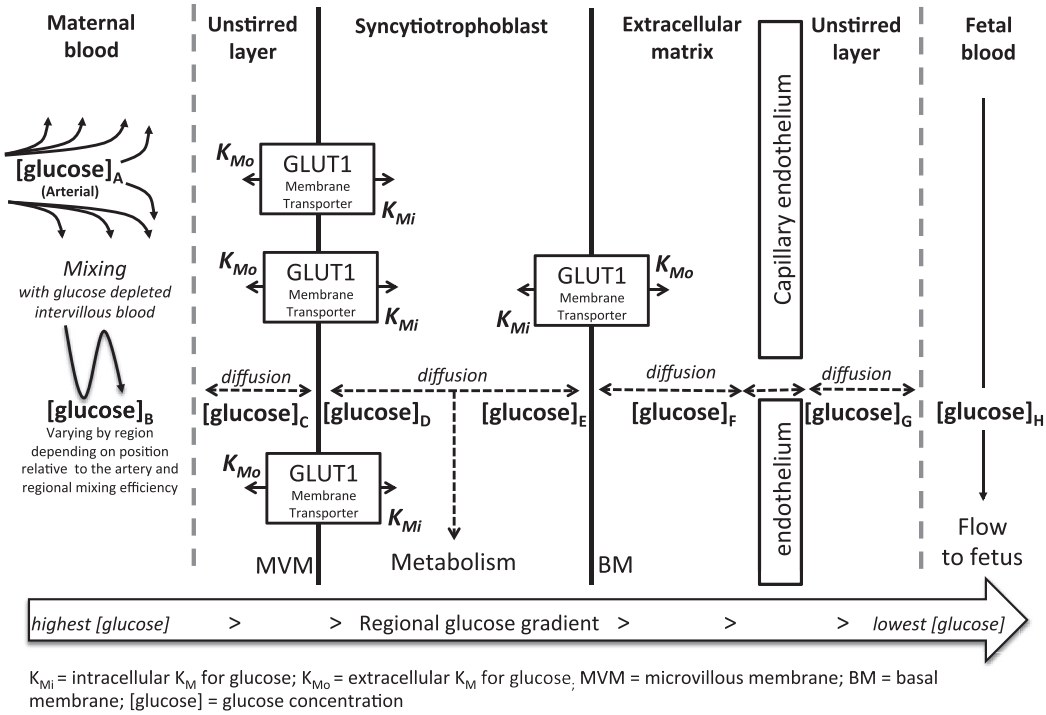

Fig. 4. Factors which may affect glucose transfer kinetics across the human placenta. Glucose will diffuse, or be transported by facilitative transporters from regions of high to low concentration. Maternal diet and hepatic glucose release keep maternal glucose high while fetal consumption reduces fetal levels. Glucose concentrations decrease progressively from the maternal artery to vein and from [glucose]A > [glucose]B > [glucose]C >… > [glucose]H (note that [glucose]B may vary in different regions of the placenta). The glucose concentration in any region will be determined by the rate at which glucose diffuses out in the fetal direction and the rate at which new glucose diffuses in from the maternal side. Glucose metabolism within the syncytiotrophoblast and uptake by other placental cells will also affect glucose concentrations in specific regions. It should be noted that there is no fixed relationship between the direction of maternal blood flow and blood flow within the villi.

has been suggested previously, it is likely that the BM will be rate-limiting for glucose transport [4,10]. Given that glucose concentrations at the intracellular face of the BM will be lower than at the MVM and that the intracellular K_M may be higher, the BM may have a significant influence on the kinetics of glucose transfer (Fig. 4).

Previous theoretical studies have developed models of glucose transport and to fully explain our observations the modelling approach needs to be developed further in combination with experimental studies [21]. We have previously used an approach which couples modelling with experimental data to study amino acid transfer and the similar development of an experimentally validated model for glucose transfer would also prove useful [22,23]. While there is an extensive literature on the K_M for GLUT1 and most studies suggest a K_M around 3 mmol/l there is wide discrepancy in the literature [7,8]. Further data on both intracellular and extracellular K_M for GLUT1, preferably obtained under equilibrium exchange conditions, would be very helpful in this regard.

6.1. Paracellular diffusion

We found significant unidirectional paracellular fluxes of L-glucose which suggests a significant capacity for transfer of glucose by paracellular diffusion. However it should be noted that paracellular diffusion in the perfusion system may be higher than *in-vivo* as has been suggested from studies in guinea pigs [24,25]. In contrast to a previous study where L-glucose flux was greatest in the fetal to maternal direction we did not see any difference in the clearance of L-glucose in either direction [10]. This may reflect differences in the placental perfusion setup between laboratories.

7. Conclusion

The fact that the predicted and experimental glucose transfer kinetics did not match suggests that factors we did not initially consider are important determinants of placental glucose transfer. This illustrates the need for a systems biology approach to understanding the kinetics of placental glucose transport and the importance of understanding transporter activity in its physiological context. Understanding the determinants of placental glucose transfer is important if we are to explain how glucose transfer may be affected in pathological pregnancies with either fetal growth restriction or fetal macrosomia.

Acknowledgements

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