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Computational modelling of placental amino acid transfer as an integrated system

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ABSTRACT

Placental amino acid transfer is essential for fetal development and its impairment is associated with poor fetal growth. Amino acid transfer is mediated by a broad array of specific plasma membrane transporters with overlapping substrate specificity. However, it is not fully understood how these different transporters work together to mediate net flux across the placenta. Therefore the aim of this study was to develop a new computational model to describe how human placental amino acid transfer functions as an integrated system. Amino acid transfer from mother to fetus requires transport across the two plasma membranes of the placental syncytiotrophoblast, each of which contains a distinct complement of transporter proteins. A compartmental modelling approach was combined with a carrier based modelling framework to represent the kinetics of the individual accumulative, exchange and facilitative classes of transporters on each plasma membrane. The model successfully captured the principal features of transplacental transfer. Modelling results clearly demonstrate how modulating transporter activity and conditions such as phenylketonuria, can increase the transfer of certain groups of amino acids, but that this comes at the cost of decreasing the transfer of others, which has implications for developing clinical treatment options in the placenta and other transporting epithelia.

1. Introduction

The placenta is the interface between the maternal and fetal circulations and plays an essential role in mediating the transfer of all the nutrients required for fetal development, including amino acids. Impaired placental transfer of amino acids during pregnancy is associated with poor fetal growth, which increases the risk of poor pregnancy outcomes such as stillbirth [1] and of chronic disease in adult life [2–4]. There are currently no effective treatments for fetal growth restriction (FGR) and a better understanding of placental transfer as a whole could potentially contribute to the development of treatment strategies for intervention and prevention of the disease.

Transfer of amino acids across the placenta is a complex process, influenced by multiple factors including placental blood flow, membrane transporters, intracellular metabolism and placental morphology [5,6]. In order to pass from the maternal intervillous space into the fetal capillaries, amino acids need to cross the placental syncytiotrophoblast, an epithelial barrier separating the two circulations. Amino acids in the maternal blood first need to be transported across the microvillous plasma membrane (MVM) of the placental syncytiotrophoblast into the cytosol. They can then either undergo metabolism or can be transported across the fetal-facing basal plasma membrane (BM), from where it is assumed they diffuse across the fetal capillary endothelium to the fetal circulation [6].

Amino acid transport across the MVM and BM is mediated by specific transport proteins [6], which operate using different energetically passive and active transport mechanisms. Accumulative transporters actively pump amino acids into the placental syncytiotrophoblast against their concentration gradient, using secondary active transport driven by the sodium electrochemical gradient. This serves as an important driving force for amino acid transfer as a whole, since fetal amino acid concentrations are higher than maternal concentrations [7] and syncytiotrophoblast cytosol concentrations are higher than both [8]. Exchangers (antiporters) are another important class of transporter, which take one amino acid from outside of the plas`ma membrane and swap it for another amino acid from inside the syncytiotrophoblast. Thus, exchangers mediate

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changes in the relative amino acid composition but not the overall net amount. Facilitative transporters on the other hand are responsible for mediating net transport to the fetus, via facilitative diffusion driven by the amino acid electrochemical gradients [9,10].

Critically, these three classes of transporter need to work together to mediate net transfer of all the required amino acids to the fetus, as it is not possible for one to do so alone [9,11]. For example, substrates taken up by the accumulative transporter across the MVM can be exchanged back to the mother to drive uptake by exchangers of amino acids that are not substrates of the accumulative transporter. Similarly, the exchangers at the BM transfer amino acids to the fetus that are not substrates of the facilitative transporters.

While many studies of amino acid transfer have focussed on individual transporters, the integrated study of the interactions between multiple transporters in the two placental plasma membranes has been limited [9,12]. There are twenty amino acids, which can either inhibit or promote each other's transport, and many distinct transporter proteins with overlapping substrate specificity. Hence, given this inherent complexity, a systems approach using mathematical modelling is necessary to help describe the transport process as a whole. Previous placental models have mainly focussed on blood flow and oxygen transport by simple diffusion, which has proved highly valuable to explain placental structure–function relationships [13–17], while models for membrane transport have been applied for the placental transfer of drugs [18] and glucose [19]. We have previously introduced a model of human placental amino acid transfer, applied to the uptake and exchange of serine and alanine [20]. However, a systematic integrated analysis of amino acid transfer is required, including more mechanistic transporter models [6,21,22].

The aim of this study was to develop a modelling framework for human placental amino acid transfer as an integrated system, to better understand (i) how different types of transporter work together, (ii) how composition of amino acids affects transport, and (iii) how specific transporter activities can drive net transfer of all amino acids to the fetus.

2. Methods

2.1. Compartmental model for the placenta

A compartmental modelling approach was adopted based on our previous work [20], in which the placenta was represented as three separate volumes, corresponding to the maternal intervillous space, syncytiotrophoblast, and fetal capillaries respectively (Fig. 1). All compartments were assumed to be well mixed, as the main focus is on the transporter interactions. The transfer of amino acids between compartments was modelled as fluxes mediated by the various types of transporters [9]. In each membrane (MVM and BM), transport by a certain type of transporter was combined and modelled as a single representative transporter. At the maternal-facing MVM these included transport by an accumulative and an exchange transporter, while at the fetal-facing BM transport by a facilitative and an exchange transporter (Fig. 1). Note that accumulative transporters are also found on the BM, but these were not included in the model as their role is thought to be limited [11]. Details of the model implementation are described below.

The rate of change in the concentration of a certain amino acid A within each placental compartment is given by:

$$\frac{d[A]^m}{dt} = \frac{1}{v_m}\left(J^m_{A,flow} - J^{m\to s}_{A,ac} - J^{m\to s}_{A,\ ex}\right) \quad (1)$$

$$\frac{d[A]^s}{dt} = \frac{1}{v_s}\left(J^{m\to s}_{A,ac} + J^{m\to s}_{A,ex} - J^{s\to f}_{A,ex} - J^{s\to f}_{A,\ fa}\right) \quad (2)$$

$$\frac{d[A]^f}{dt} = \frac{1}{v_f}\left(J^f_{A,flow} + J^{s\to f}_{A,ex} + J^{s\to f}_{A,fa}\right) \quad (3)$$

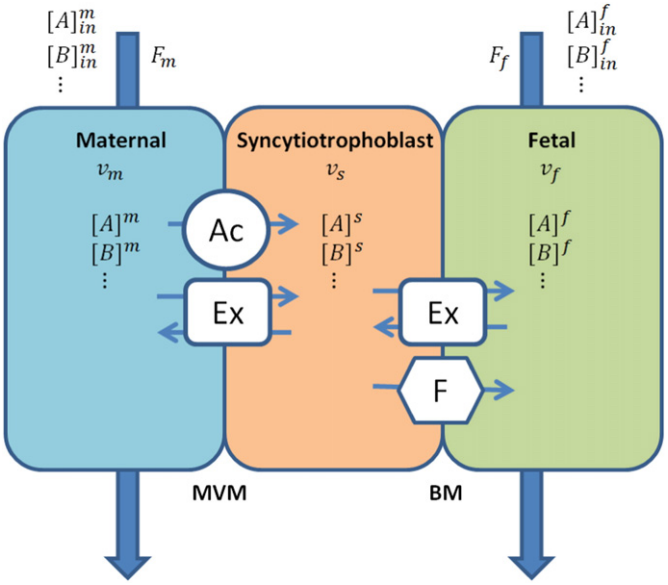

Fig. 1. Compartmental model of the placental amino acid transfer system, representing the volumes of the maternal intervillous space (v_m), placental syncytiotrophoblast (v_s), and fetal capillaries (v_f). Amino acid transporters included at the maternal-facing microvillous membrane (MVM) were accumulative transporter (Ac) and exchanger (Ex), and those at the fetal-facing basal membrane (BM) were facilitative transporter (F) and exchanger (Ex). F_m and F_f are the flow inputs (and outputs) in the maternal and fetal compartments respectively. [A] and [B] indicate amino acid concentrations in the various compartments.

where $[A]^i$ is the concentration (mol l^{-1}) of substrate A in compartment i, and v_i is the compartment volume (l). $J^{i\to j}_A$ represent the net molecular flux (mol min^{-1}) of A from compartment i to j. Here m, s, and f, are the maternal, syncytiotrophoblast and fetal compartments respectively, while ac, ex, and fa denote the accumulative, exchange, and facilitative transporters. $J^i_{A,flow}$ is the net molecular flux (mol min^{-1}) due to blood flow.

2.2. Classification of amino acids in representative groups

Amino acids were categorised according to their transporter specificity into four generic groups, to reduce complexity in the first instance. As shown in Table 1, these representative amino acid groups were AcEx, substrate of the accumulative and exchange transporters; Ex, exchange only substrate; ExF, substrate of exchange and facilitative transporters; and AcExF, substrate of all transporter types. Normal physiological concentrations of amino acids [7,8] were summed per representative group in each compartment. Glutamate and aspartate were not included in the model as these are taken up by distinct transport systems (EAATs) and their interactions with the transfer of other amino acids would be extremely limited.

2.3. Individual transporter models

Models for each type of transporter were developed based on the principles of carrier-mediated transport [21,23], to represent the simultaneous transport of multiple substrates. Briefly, parameters describing the kinetic properties were kept to the minimum required to represent the functional activity of each transporter type. Therefore, in the first instance, exchanger and facilitative transporter translocation rate constants were assumed to be symmetric and binding affinities equal on both sides of the plasma membrane. In addition, substrates of a certain type of transporter were all assumed to have identical kinetic and binding properties.