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# Knowledge needed about the exchange physiology of the placenta

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ABSTRACT

There is now a basic understanding of the driving forces and mechanisms underlying rates of solute exchange across the placenta but there are still major gaps in knowledge. Here we summarise this basic understanding, whilst highlighting gaps in knowledge. We then focus on two particular areas where more knowledge is needed: (1) the electrical potential difference (PD) across the placenta and (2) the paracellular permeability of the placenta to hydrophilic solutes.

In many species a PD has been recorded between a catheter in a maternal blood vessel and one in a fetal vessel. However, the key question is whether this PD is the same as that across the placental exchange barrier. We addressed this in the human placenta using microelectrodes to measure the PD in isolated villi *in vitro*; the transtrophoblast PD so measured had a median value of −3 mV (range 0 −15 mV). There have been no subsequent studies to validate this measurement.

The syncytiotrophoblast of haemochorial placentas lacks any obvious extracellular water filled paracellular space between the syncytial nuclei. However, in mouse, rat, guinea pig and human there is an inverse relationship between the rate of diffusion of inert hydrophilic solutes across the placenta and their molecular size. The simplest explanation is that a paracellular route exists but its morphological identity is still uncertain. Areas of syncytial denudation could provide a paracellular route but this has not been proven. Answers to these and similar questions are required to fully understand the exchange physiology of the normal placenta and how this is affected in pathology.



## 1. Introduction

Exchange of nutrients and products of fetal metabolism by the placenta is essential for fetal growth. The broad mechanisms by which exchange takes place are well known. Unfortunately, much of the detailed physiology underlying these mechanisms of exchange is still not known. This lack of knowledge is a major impediment, not only to fully understand placental solute exchange in normal pregnancy, but also to understand the pathophysiology of the dysfunctional placenta in, for example, fetal growth restriction (FGR). The purpose of this review is to highlight key areas where knowledge about transplacental exchange physiology is missing. We provide an overview of the current understanding of mechanisms of exchange across the placenta, consider in detail two aspects of exchange physiology that we have investigated but for which there remains insufficient knowledge, and we provide our 'top ten' pieces of information that are still needed to fully understand the exchange physiology of the placenta.

### 1.1. Mechanisms of transfer across the placenta

There are excellent reviews providing detailed information on the various mechanisms of transfer across the placenta [1–4]; we highly recommend Faber and Thornburg's book 'Placental Physiology' [5] as essential foundation reading. Fig. 1 depicts key features of the exchange barrier in the haemomonochorial human placenta and summarises the broad categories of transfer mechanisms. The mechanisms are essentially similar in other placental types but are complicated by the additional cellular layers in e.g. haemodichorial, haemotrichorial and epitheliochorial placentas.

#### 1.1.1. Water transfer and bulk flow/solvent drag

The volume of water transfer across the placenta, as across any

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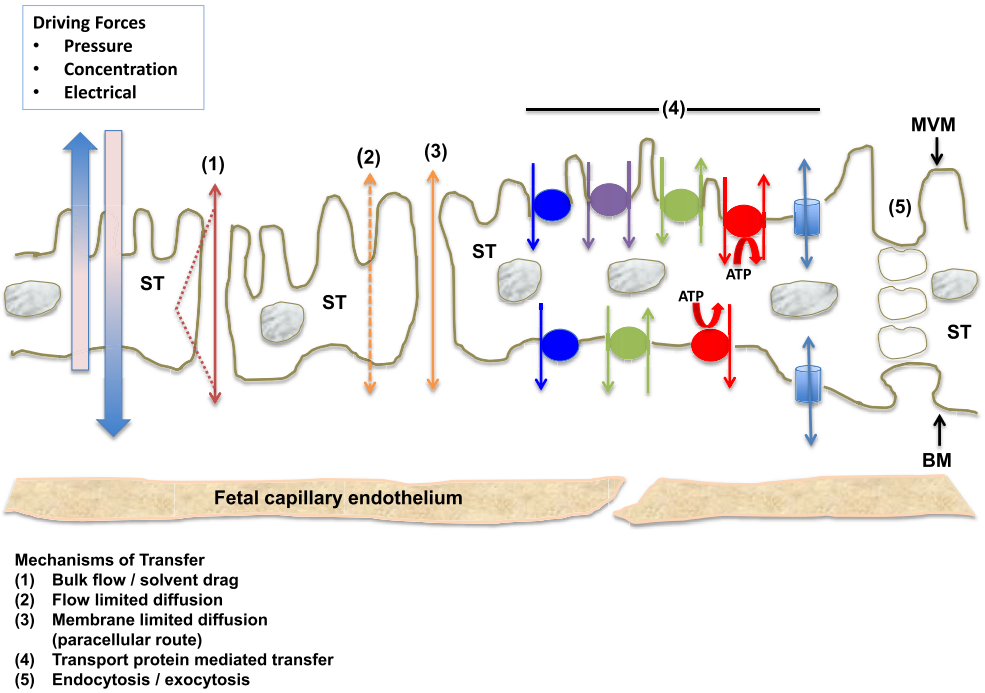


**Fig. 1.** Schematic diagram illustrating the main mechanisms of transfer across the human placenta. ST = syncytiotrophoblast; MVM = microvillous plasma membrane; BM = basal plasma membrane; ATP = adenosine triphosphate.

membrane, is by filtration and diffusion as described by the equation of Kedem and Katchalsky [6]:

$$Jv.S = Lp.S[\Delta P + \sigma RT\Delta C]$$

where $Jv$ is volume flow per $cm^2$ of membrane (cm/s). S is the surface area of the membrane ($cm^2$), Lp is the filtration coefficient (cm/s/N), ΔP is the hydrostatic pressure difference across the membrane ($N/cm^2$), σ is the reflection coefficient, ΔC (mol) is the solute concentration difference between maternal and fetal plasma at the exchange barrier, R is the gas constant and T the absolute temperature.

Flow due to filtration is driven by the hydrostatic pressure gradient across the exchange barrier (ΔP), dependent on maternal and fetal cardiac output and vascular resistance. Flow due to diffusion is driven by the concentration of water molecules between two compartments either side of a semi-permeable membrane, the inverse of the concentration of solutes between those two compartments. The solute causes an osmotic pressure gradient ($\Delta\pi$) driving water transfer and the magnitude of this is dependent both on the concentration of solute and the effective permeability of the membrane to each solute (its reflection coefficient, σ). The rate of transfer by both diffusion and filtration are dependent on the filtration coefficient of the exchange barrier for water (Lp). Mechanisms of water transfer across the human (and other species) placenta are very poorly understood as we lack knowledge of the magnitude of the key variables - osmotic pressure gradients, reflection coefficient, hydrostatic pressure gradient and filtration coefficient. Measurements of reflection coefficient and filtration coefficient are dependent on knowing the transcellular and paracellular routes by which water and solute move across the placenta but these are not clear; we consider the paracellular route later in this review. Bulk flow/solvent drag is the movement of solute and water together across the exchange barrier due to a pressure gradient. Again the quantitative contribution of bulk flow to total solute transfer *in vivo* is unknown. Studies using the *in vitro* perfused human placental cotyledon show that such transfer may be particularly important for large molecules such as alphafetoprotein (AFP), that this may occur in the fetomaternal direction [7], and that pressure gradients sufficient to cause bulk flow may arise from differential sensitivity of fetoplacental arteries and veins to vasoconstrictors [8].

### 1.1.2. Solute diffusion

The net rate of transfer across the placenta of any molecule ($J_{net}$) is the sum of the two unidirectional components:

$$J_{net} = J_{mf} - J_{fm}$$

Where $J_{mf}$ and $J_{fm}$ refer to unidirectional transfer rates in the maternofetal and fetomaternal directions respectively. Fetal growth requires that $J_{mf}$ for metabolic and synthetic substrates and water exceeds $J_{fm}$ over the course of gestation. In terms of diffusional exchange, $J_{net}$ is defined as below, but the *total* flux, in each direction, will be via diffusion *plus* that by all the other available transfer mechanisms.

Net solute diffusion across the placenta occurs if there is a maternofetal concentration difference of any molecule, or an electrochemical gradient for charged molecules.

The net rate of diffusional transfer (flux) ($J_{net}$) for a particular solute is given by Fick's equation:

$$J_{net} = AD_w/l\ ([C_m - C_f])\ mol/sec$$

where A is the surface area available for diffusion ($cm^2$), $D_w$ is the diffusion coefficient in water at 37 °C of that solute ($cm^2/s$) (directly proportional to molecular size), l is the path length over which diffusion takes place or membrane thickness (cm), $C_m$ and $C_f$ are the concentrations of solute in the intervillous space and fetal capillary (mol) respectively. The difficulty with calculating $J_{net}$ is that A, l, $C_m$ and $C_f$ are generally unknown. Any transplacental electrical potential difference (PD) can also drive diffusion of charged solutes