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Review: Transport across the placenta of mice and women

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ABSTRACT

Since the advent of technologies to produce genetic knockout and transgenic mice, the number of mouse strains suggested to be useful as models for pregnancy-related complications in the human has risen substantially. Some of these share features in common with fetal growth restriction (FGR) and preeclampsia (PE) and could be useful for investigating aetiologies and for testing potential therapeutics to improve outcome in these diseases. However, since placental pathology is a major underlying factor in both FGR and PE, it is important to understand the similarities and differences in structure and function of the placenta between mice and women. The main aim of this review is to directly compare placental exchange physiology between human and mouse. The review will compare human and mouse in both normal and pathological circumstances, to attempt to answer the question of whether placental studies in the mouse can be translated to the human. The review includes descriptions of placental structure between the species, comparisons of nutrient transport, including amino acids, glucose and calcium, and evidence of how these transport systems are altered in both human FGR and mouse models of this disease. Finally, our review will conclude by examining studies in which mouse models of FGR/PE have been treated with drugs of potential therapeutic value in women and consider whether data obtained in mice can be a prelude for clinical trials in human.

1. Introduction

There exists an ever-increasing number of animal models of pregnancy-related disease. The mouse has become prevalent in this regard, particularly since the advent of technologies to produce genetic knockout and transgenic strains that target specific gene pathways. The mouse has several practical advantages over other species, including relatively low costs to house and maintain, sound understanding of its genetics and overall physiology, with short gestation periods and large litter sizes allowing relatively quick data collection. However, a pre-requisite for an appropriate model for human pregnancy is that many of the physiological characteristics of pregnancy, in health and disease, should be comparable between the species. This review will compare the mouse and human, focussing on placental structure and functions related to nutrient exchange, to help answer the question of whether the mouse is an appropriate species for research into human pregnancy, and specifically placental transport mechanisms in poor outcomes such as fetal growth restriction (FGR) and preeclampsia (PE). This review will also consider studies where mouse models of these diseases have been used to test potential drug therapies for use in women. Although it is acknowledged that there are important dietary and surgical models of FGR, this review will focus on genetic mouse models.

2. Morphological comparison of the mouse and human placenta

Mouse and human placentas are both of the haemochorial type, meaning that the fetally-derived trophoblast tissue is directly bathed in maternal blood, as summarized in [1]. However, in contrast to the human placenta, the mouse placenta is organized into two major zones, termed the junctional and labyrinthine zones. The junctional zone consists primarily of spongiotrophoblast and glycogen cells and is associated with endocrine function [2]. The labyrinthine zone is the maternofetal exchange layer and is a variation on the villous architecture of the human placenta [3]. Unlike in the human, where villi extend into the maternal blood

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space, the maternal blood spaces and fetal capillaries in the mouse are arranged in a labyrinth-like arrangement. A schematic of the placental structure of mice and human can be seen in Fig. 1.

The mouse placenta is haemotrichorial, with three trophoblast layers between the maternal and fetal circulations compared to the single layered (haemomonochorial) syncytiotrophoblast of the human placenta. The three layers in the mouse are denoted I, II and III (Fig. 1) with layer I adjoining the maternal blood spaces. Layer I is thought to consist of an intermittent layer of trophoblast giant cells which should be highly permeable to most small molecular weight solutes. Thus, layer II, which is syncytial, is thought to present the initial barrier to maternofetal exchange [1,4]. Whilst there are differences in the number of trophoblast layers between species, localization studies suggest there are similarities between specific membranes in human and mouse. Using electron microscopy, alkaline phosphatase staining was localized to the apical (maternal facing) plasma membrane of trophoblast layer II in the mouse [1,4] as depicted in Fig. 2. This fits well with the data demonstrating localized alkaline phosphatase staining to the microvillous (maternal facing) plasma membrane (MVM) of human syncytiotrophoblast [5]. In addition, isolation of the apical membrane of the mouse trophoblast layer II and subsequent transporter studies (see below) strongly suggest this membrane is analogous to the human MVM. Trophoblast layers II and III of the mouse placenta are connected via gap junctions with the fetal facing plasma membrane of layer III, given its proximity to the fetal capillaries, suggested to be analogous to the human basal plasma membrane (BM) of the syncytiotrophoblast. However, how well the basal (fetal facing) plasma membrane of mouse layer III relates to this BM is unclear at the present time. We are not aware of comparative studies of this membrane between the two species, indeed no techniques currently exist to allow isolation of the BM of the mouse placenta, unlike the human [6]. Thus direct comparisons of transporter identification and abundance between the species is not yet possible. That said, there is evidence showing that transporters known to be localized to both the MVM and the BM in human, such as the glucose transporter GLUT-1, and transporters with much greater abundance in the human BM, such as plasma membrane calcium ATPase (PMCA) [7], are also present in mouse placenta [8,9]. This suggests that nutrient transport between the two species may occur by similar mechanisms; this is examined in greater detail in relation to specific transporter systems later in this review.

3. Comparison of placental exchange physiology between the normal mouse and human

Comprehensive reviews of placental exchange physiology may be found in [10,11]. The focus of this section is on the comparison of transfer mechanisms between mouse and human placentas, with specific focus on diffusional and transporter-protein mediated exchange mechanisms.

3.1. Diffusional exchange

All solutes in maternal and fetal blood will be able to diffuse across the exchange barrier of the placenta. The rate of diffusion will depend on the molecular properties of the molecule in question, the concentration gradients between maternal and fetal plasma, and the surface area and thickness of the exchange barrier itself [12]. In human placenta, the first barriers, in terms of maternal to fetal transfer, are the MVM and BM of the single layered syncytiotrophoblast. As discussed above this appears analogous in the mouse to the maternal and fetal facing plasma membranes of syncytial layer II and III respectively, although the exact contribution of layers I and III is not known. The fetal capillary endothelium is the next barrier component in the human and has wide intercellular spaces through which molecules below about 1500 molecular weight will diffuse quite rapidly [13]; the mouse placenta has a morphologically similar fetal capillary endothelium although its permeability properties have not been directly examined.

Molecular size and lipophilicity of individual molecules will have a major effect on the rate of diffusion. The diffusion of small lipophilic molecules, such as respiratory gases, will be rapid because they will be able to diffuse across the lipid bilayers of the barrier. As the concentration gradients of such molecules will consequently rapidly equilibrate in the circulations on either side of the barrier, the rate of diffusion will largely be dependent upon blood flow rates in uterine and umbilical circulations [10] delivering and extracting the molecules. It is possible to measure blood flow velocity in the uterine and umbilical arteries of mice using Doppler ultrasound and studies have demonstrated waveforms in mice that appear similar to humans for both uterine [14] and umbilical arteries [15].

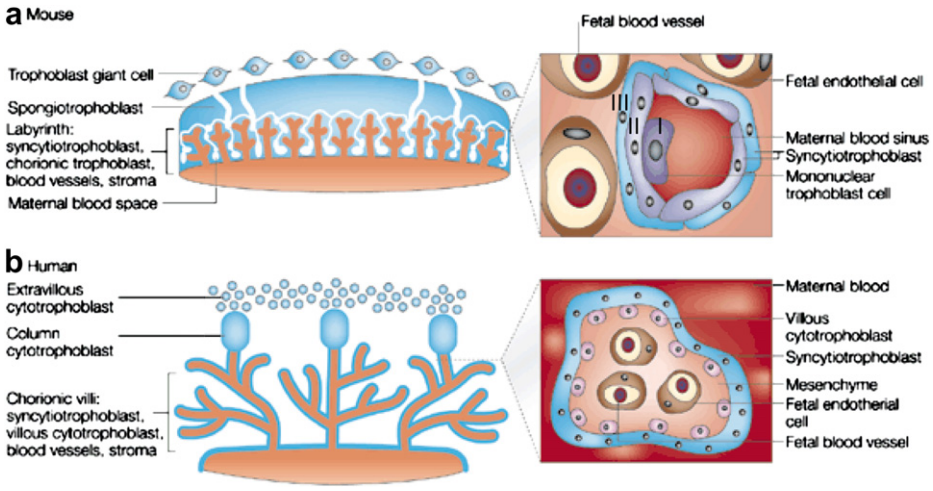

Fig. 1. Comparison of mouse and human placental structure. (a) Structure of the mouse placenta including the spongiotrophoblast (Junctional zone) and labyrinth. The inset details the fetal–maternal interface in the labyrinth and demonstrates the three trophoblast layers, layer I (mononuclear trophoblast cell layer) and layers II and III (syncytiotrophoblast). (b) Structure of the human placenta. The inset image shows a cross-section through a chorionic villus; trophoblast-derived structures (blue) and mesoderm-derived tissues (orange). The inset images illustrate the number and type of cell layers between the maternal and fetal blood. Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Genetics* (Rossant J and Cross JC (2001); placental development: Lessons from mouse mutants; 2:538–548), copyright 2001.

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