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Current Topic

Placental Chloride Channels: A Review

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ABSTRACT

The human placental syncytiotrophoblast (hSTB) is a polarized epithelial structure, that forms the main barrier to materno-fetal exchange. The chloride (Cl^-) channels in other epithelial tissues contribute to several functions, such as maintenance of the membrane potential, volume regulation, absorption and secretion. Additionally, the contributions of Cl^- channels to these functions are demonstrated by certain diseases and knock-out animal models. There are multiple lines of evidence for the presence of Cl^- channels in the hSTB, which could contribute to different placental functions. However, both the mechanism by which these channels are involved in the physiology of the placenta, and their molecular identities are still unclear. Furthermore, a correlation between altered Cl^- channels functions and pathological pregnancies is beginning to emerge. This review summarizes recent developments on conductive placental chloride transport, and discusses its potential implications for placental physiology.

1. Introduction

Transport functions in the placenta are of great importance for fetal growth and development. The human placental syncytiotrophoblast is a polarized epithelial structure that constitutes the main barrier to materno-fetal exchange. Ionic transport in the syncytiotrophoblast involves conductive pathways that are associated with numerous epithelial functions, such as maintenance of membrane potential, cell volume regulation and solute transport among others. Chloride (Cl^-) is the main anion in the extracellular fluid in the fetus, as it is in the adult, but at all gestational ages fetal Cl^- concentration is 5–6 mM higher than in maternal blood. There are no maternal–fetal differences in either Na^+ or K^+ concentrations [1]. Chloride exchange between mother and fetus in the placenta occurs *via* multiple pathways; because the hSTB is a syncytium, chloride must pass directly through both trophoblast membranes. As with intestinal mucosa and the renal epithelium, in hSTB the pathways for chloride transport could be passive or active, depending on placental permeability and electrochemical potential differences for the ion. Initially, there was considerable interest focused on Cl^- conductances in the hSTB membranes and their regulation. However, the identities of the specific ion channels underlying these conductances, including which are involved in the different placental processes, are still unknown. Recently, new evidence has emerged supporting the relationship between specific types of chloride channels and particular functions. For instance, a DIDS-sensitive conductance contributes to the resting potential of the syncytiotrophoblast microvillous membrane and is involved in volume regulation [2]. There is also strong evidence that the apical Maxi-chloride channel, a channel sensitive to DIDS, is permeable to organic anions like taurine, glutamate and aspartate. These characteristics suggest that this channel could play a role in phenomena such as volume regulation and taurine transport [3]. The biophysical characteristics of this Maxi-chloride channel are altered in preeclampsia [4], however, the consequences of this alteration for volume regulation and taurine transport in preeclampsia are open questions.

This review aims to examine the literature on chloride channels in the context of transplacental transport. After a short overview of the general cellular functions of Cl^- channels in epithelia and the molecular classifications of these channels, it will focus on the evidence for the presence of chloride channels in placental tissue and the specific characteristics of these channels, including pharmacology and possible roles in the placental physiology. This review will also discuss placental chloride channels from pathological placentae and provides a short account of the family of intracellular Cl^- channels reported in trophoblast. Finally, it will summarize the main transport mechanisms for Cl^- exchange by conductive pathways in hSTB membranes proposed to date.

2. Background of chloride channels

Anion selective channels have been classified into several group based on functional properties such as voltage dependence, single conductance, selectivity, sensitivity to blockers, kinetics, molecular structures and subcellular localization. Electrophysiological and

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families of gene studies of anion channels have revealed a wide variety of differences in their biophysical properties, for example single-channel conductance, regulation mechanisms or pharmacological sensitivity. These channels are integral proteins in biological membranes and, like other channels, the anion channels may be present and execute their functions in the plasma membrane or in intracellular organelle membranes. Ion transport through channels occurs *via* diffusional ion flux down the electrochemical gradient of the ion, meaning that a combination of the membrane potential and the difference between cytoplasmic and extracellular Cl^- concentrations, determines whether the opening of a Cl^- channel will lead to an influx or efflux of this ion. Chloride channels may conduct other anions better than they conduct chloride, but are so named because chloride is the most abundant anion in tissues. The functions of chloride channels, as well as those of other transporter proteins such as pumps, carriers and other channels, include cell volume regulation, ionic homeostasis, transepithelial transport, regulation of electrical excitability, secretion, absorption, etc. Their function and biophysical properties have determined their classification. For instance, the "apical chloride channel in absorptive epithelia" was described as a channel with a large single-channel conductance and that was active on a membrane potential near 0 mV. This channel, also present in placenta is the Maxi-chloride channel, so named for its very high conductance.

The classification of chloride channels has changed as more information has become available. Currently, several gene families of chloride channels are known. For example, the CLC family in mammals has, at least, nine members present in the plasma membrane or in intracellular organelles [5,6]. In their review "Molecular structure and physiological function of chloride channels" [7], Jentsch et al. classified channels in the CLC chloride channel family, the cystic fibrosis chloride channel, swelling active chloride channels, calcium activated chloride channels and ligand gated chloride channels.

As mentioned before, transport of anions across cellular membranes is crucial for various functions. Alterations in their structure due to mutations in Cl^- channels or in their environment can cause diseases such as the muscle disorder myotonia, cystic fibrosis, renal salt loss in Bartter syndrome, kidney stones, deafness and the bone disease osteopetrosis [8].

3. Placenta and transport

The placenta is an organ formed on the wall of the uterus during pregnancy; at term, it is approximately 20 cm in diameter and 500–700 g in mass and has a complex structure. It is the fetal–maternal interface for all mammals, including humans. It has multiples functions, among them it is responsible for the solute exchange between the mother and the fetus.

Where does this transfer process occur? The maternal side of the placenta is textured and spongy looking. The surface has 20–30 distinctive compartments named cotyledons, inside of which are the chorionic villi that form the principal functional structural unit of the placenta. These villi are complex tree-like structures that contain fetal blood. The intervillous space is filled by maternal blood. Each cotyledon contains at least one villous tree. The trophoblast separates the maternal from the fetal blood and forms the large outer surface of the villi that constitutes the area for exchange; here is where the transport processes take place. The trophoblast separates the maternal and fetal blood and thus may be viewed as an epithelium, since it effectively segregates two fluid compartments. However, the trophoblast differs from the majority of epithelial cells in that it has no lateral membranes, being a syncytium. As depicted in Fig. 1, a section of the tip of a single branch of the villous tree shows the syncytiotrophoblast as a big,

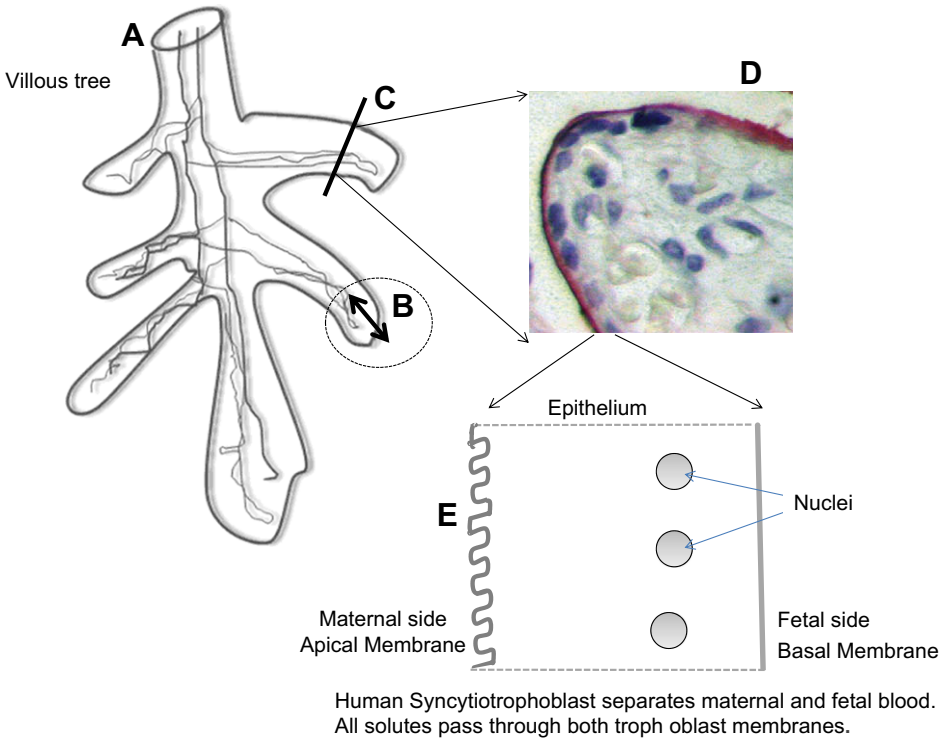

Fig. 1. Illustration showing where the exchange of solutes occurs between mother and fetus. (A) Villous tree. (B) The branch of the villi has a big surface for exchange. (C) Transverse section of a tip of a single branch. (D) Placental villous section with antibody against placental alkaline phosphatase, which marks apical membrane. The nuclei were hematoxylin-stained (image is courtesy of P. Diaz). (E) The syncytiotrophoblast forms the outer surface of the villous tree and constitutes the main placental barrier.