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Intracellular and extracellular pH dynamics in the human placenta from diabetes mellitus

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ABSTRACT

The placenta is a vital organ whose function in diseases of pregnancy is altered, resulting in an abnormal supply of nutrients to the foetus. The lack of placental vasculature homeostasis regulation causes endothelial dysfunction and altered vascular reactivity. The proper distribution of acid- (protons (H^+)) and base-equivalents through the placenta is essential to achieve physiological homeostasis. Several membrane transport mechanisms that control H^+ distribution between the extracellular and intracellular spaces are expressed in the human placenta vascular endothelium and syncytiotrophoblast, including sodium (Na^+)/H^+ exchangers (NHEs). One member of the NHEs family is NHE isoform 1 (NHE1), whose activity results in an alkaline intracellular pH (high intracellular pH (pHi)) and an acidic extracellular pH (pHo). Increased NHE1 expression, maximal transport activity, and turnover are reported in human syncytiotrophoblasts and lymphocytes from patients with diabetes mellitus type I (DMT1), and a positive correlation between NHEs activity and plasma factors, such as that between thrombin and platelet factor 3, has been reported in diabetes mellitus type II (DMT2). However, gestational diabetes mellitus (GDM) could result in a higher sensitivity of the human placenta to acidic pHo. We summarized the findings on pHi and pHo modulation in the human placenta with an emphasis on pregnancies in which the mother diagnosed with diabetes mellitus. A potential role of NHEs, particularly NHE1, is proposed regarding placental dysfunction in DMT1, DMT2, and GDM.

1. Introduction

The placenta is the vital connection between the foetus and the mother, permitting nutrient uptake, waste removal, and respiration [1,2], which delimits a healthy pregnancy and a positive neonatal outcome. Acid–base homeostasis is essential for a positive perinatal outcome because changes in the pH microenvironment alter maternal and foetal functions (see reviews [2] and [3]). The acute control of extracellular (pHo) and intracellular (pHi) pH is required, and altered pH modulation in pathologies, including diabetes mellitus type I (DMT1) and type II (DMT2) [4,5], are described. An early review highlighted this phenomenon in the placenta and its consequences for intrauterine growth restriction (IUGR) [2]. However, the role of pHi and pHo in the aetiology of DMT1, DMT2 or gestational diabetes mellitus (GDM) has not been reported [2,4–6]. An update of the findings reported for these diseases is required to complement those in IUGR [2] or preeclampsia [7,8].

One mechanism regulating pHi and pHo includes the activity of plasma membrane transporters, in terms of proton (H^+) efflux and

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base equivalents influx [3,6]. These transport systems include sodium (Na^+)/H^+ exchangers (NHEs), vacuolar H^+-ATPases (V-ATPase), and H^+/potassium (K^+) ATPases. The bidirectional monocarboxylate transporters regulate the intracellular content of the conjugate base lactate, and the Na^+/$HCO3^-$ transporters regulate both Na^+ and HCO_3^-. NHEs play a role in the removal of intracellular H^+ in most organs [6], including the human placenta (Fig. 1) [2,7–10]. NHEs activity in the syncytiotrophoblast (STB) is likely to result in extracellular acidification; however, NHE1, NHE2, and NHE3 isoforms expressed in the human syncytiotrophoblast (STB) [7,9,10] and their impact on pHo in the intercellular space between STB and placental microvasculature has not yet been reported. Thus, a microperfusion approach may potentially resolve this question.

NHEs comprise a family of electroneutral membrane transporters, including 11 members with NHE1, that are the most characterized due to their potential role in the diseases of pregnancy [2,8], cancer [11], and hypertension, among others [12,13]. Under physiological pHi, NHE1 remains a monomer, but following intracellular acidification or after stimulation by growth factors, a homodimer is formed, resulting in increased H^+ affinity [14]. Although the key role of pH homeostasis in modulating cell function is well known, the consequences of a change in pH, particularly in pHi, and NHEs involvement at the single-cell level and its physiological implications for tissue homeostasis in the human placenta from diabetes mellitus pregnancies, are not well understood. We reviewed information on the potential involvement of changes in foetoplacental pHi and pHo microenvironments in pregnancies in mothers with DMT1, DMT2, or GDM. We focused on the potential role of NHEs expression and activity modulating placental pHo and pHi and whether changes in these parameters correlate with pregnancies in mothers with diabetes mellitus.

2. Role of pH in the human placenta

Foetal organ function may be compromised by an abnormal function of blood buffering systems. Altered acid–base control affects the foetal central nervous and cardiovascular systems, among other systems [15]. Maternal blood acidosis is associated with a poor perinatal outcome, a lower Apgar score, and reduced pHo (i.e., acidification) in foetal circulation [16]. Foetal respiratory acidosis appears early in foetal development due to reduced umbilical vein blood flow [17]. This phenomenon results in lower pHo due to reduced oxygen tension-associated hypoxemia and hypercapnia. Acidic foetal blood is associated with a non-reassuring foetal status (including repetitive variable decelerations, foetal tachycardia or bradycardia, late decelerations, or low biophysical profile), compared with foetal development at physiological pH [18].

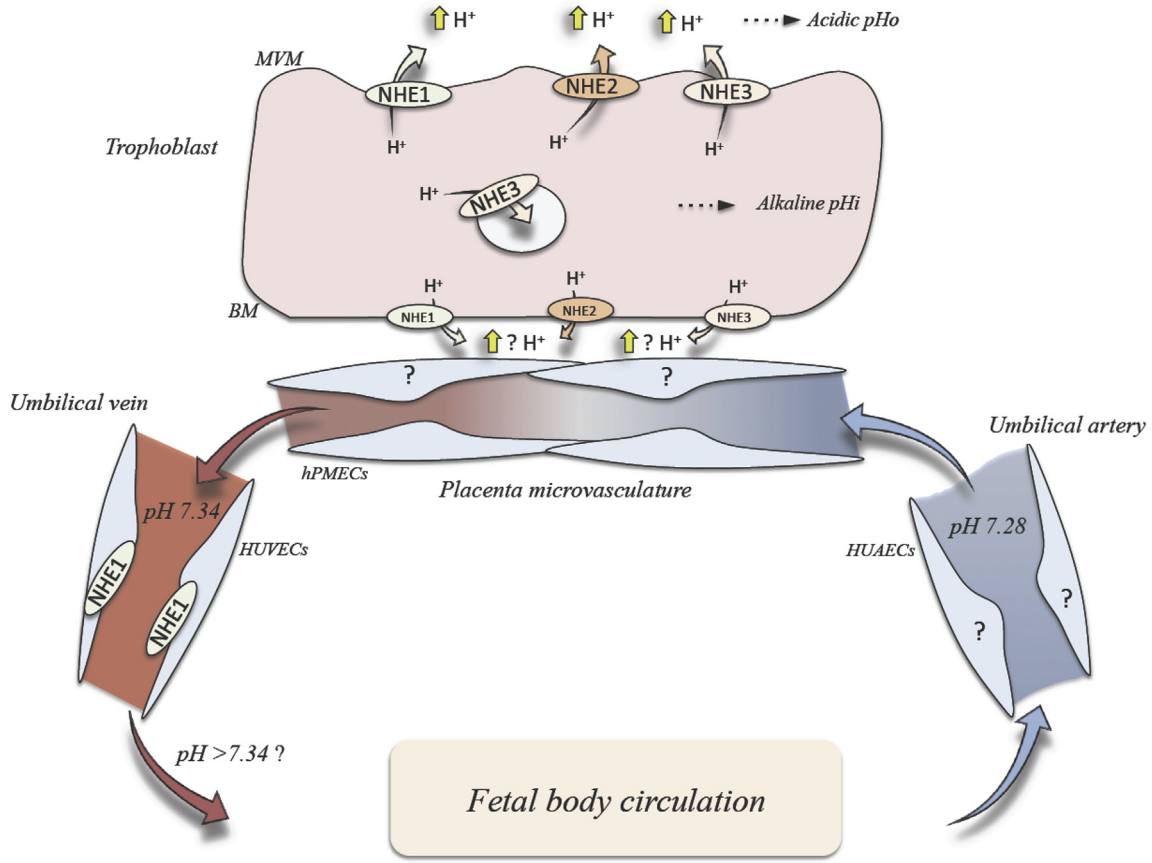

Fig. 1. Proton transport in the human placenta. Na^+/H^+ exchanger 1 (NHE1), 2 (NHE2), and 3 (NHE3) are expressed at the microvillous (MVM) and basal (BM) plasma membrane of human trophoblast (*Trophoblast*). NHEs remove intracellular H^+ increasing (⇧) its extracellular concentration causing an acidic extracellular (*Acidic pHo*) and alkaline intracellular (*Alkaline pHi*) pH. Whether this phenomenon occurs in the interphase trophoblast-microcirculation is unknown (?). NHE3 locates at intracellular microsomes contributing to an alkaline pHi. NHE1, NHE2, and NHE3 protein expression at BM is lower than MVM, but expression in the microvasculature (*Placenta microvasculature*) is unknown (?). Functional NHE1 is expressed in umbilical vein endothelium (*Umbilical vein*) contributing to pHi/pHo in these cells and umbilical vein blood pH (pH *7.34*). If the passage of blood microcirculation through the umbilical vein reaching the foetus (*Foetal body circulation*) generates alkalization is unknown (pH > *7.34* ?). NHEs expression or activity in umbilical artery endothelium and their role in modulating umbilical artery blood pH (pH *7.28*) is also unknown (?). HUVECs, human umbilical vein endothelial cells. HUAECs, human umbilical artery endothelial cells. hPMECs, human placenta microvascular endothelial cells.