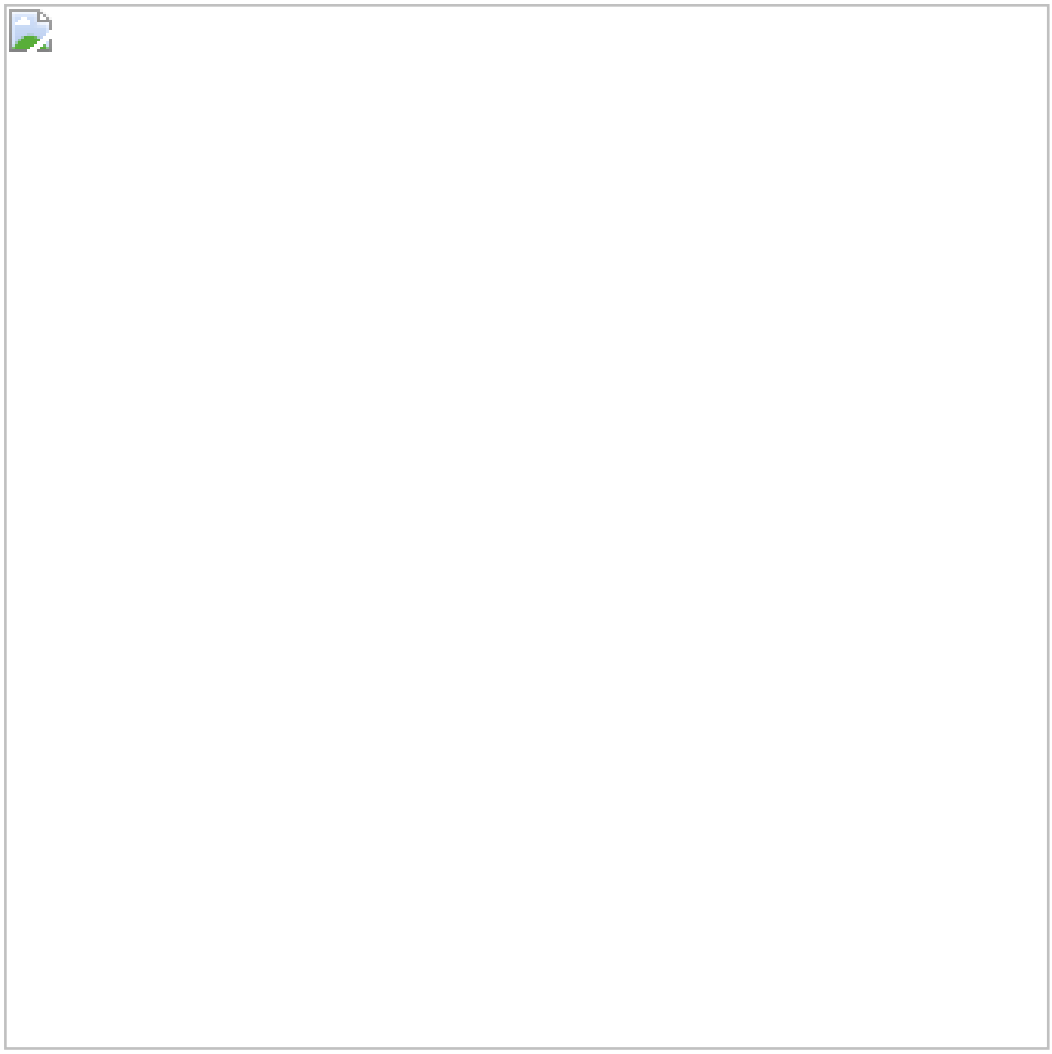

Placental ion channels: potential target of chemical exposure

Authors: Zhao, Yi, Pasanen, Markku, and Rysä, Jaana

Source: Biology of Reproduction, 108(1) : 41-51

Published By: Society for the Study of Reproduction

URL: https://doi.org/10.1093/biolre/ioac186

Biology of Reproduction, 2023, **108(1)**, 41–51
https://doi.org/10.1093/biolre/ioac186
Advance access publication date 29 September 2022
Review

Placental ion channels: potential target of chemical exposure

Yi Zhao[1], Markku Pasanen[2] and Jaana Rysä[2,*]

[1]Department of Obstetrics, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China
[2]School of Pharmacy, University of Eastern Finland, Kuopio, Finland

*__Correspondence:__ School of Pharmacy, University of Eastern Finland, POB 1627, Kuopio 70211, Finland. Tel: +358403552412; E-mail: jaana.rysa@uef.fi

Abstract

The placenta is an important organ for the exchange of substances between the fetus and the mother, hormone secretion, and fetoplacental immunological defense. Placenta has an organ-specific distribution of ion channels and trophoblasts, and placental vessels express a large number of ion channels. Several placental housekeeping activities and pregnancy complications are at least partly controlled by ion channels, which are playing an important role in regulating hormone secretion, trophoblastic homeostasis, ion transport, and vasomotor activity. The function of several placental ion channels (Na, Ca, and Cl ion channels, cation channel, nicotinic acetylcholine receptors, and aquaporin-1) is known to be influenced by chemical exposure, i.e., their responses to different chemicals have been tested and confirmed in experimental models. Here, we review the possibility that placental ion channels are targets of toxicological concern in terms of placental function, fetal growth, and development.

Summary Sentence

Ion channels participate in regulating key placental functions. The effects of chemicals affecting ion channels have rarely been studied although theoretically these compounds could cause pregnancy complications.

Keywords: placenta, ion channel, trophoblast, smoking, chemical exposure, pharmaceuticals

Introduction

The human placenta is a complex organ between the mother and the fetus. The primary function of the placenta is the exchange of nutrients, gases, and other substances between the mother and the fetus. Placenta also serves as a fetal nutrient storage site and produces hormones such as estrogen and progesterone, placental lactogen, and human chorionic gonadotropin (hCG). In addition, the placenta has defensive and immunomodulatory capabilities. Placenta has the semipermeability of membrane barrier selection, and it synthesizes immunomodulatory factors such as cytokines to protect the fetus. Finally, the placenta also regulates fetal metabolism, especially during the early and mid-term stages of pregnancy [1, 2].

Exposure to chemicals during pregnancy, such as maternal smoking, medication, consumer chemical products, and through environmental pollution, may affect the placental function and, in the worst case, may even result in an adverse pregnancy outcome [3]. Many chemical compounds can cross the placental barrier and gain further access to the fetal compartment [4]. The transfer is conducted through the chorionic membrane barrier, a polarized epithelial structure, which develops from the syncytiotrophoblast cells and has several specific transport mechanisms including ion channels and transporters [5]. Ion channels are specialized membrane-spanning, pore-forming protein macromolecules, which facilitate the rapid transmembrane transfer of water-soluble molecules such as inorganic ions [6]. Owing to the different functions in different tissues and organs, the distribution of ion channels and subtypes tend to be organ specific. Although the activation of an ion channel is selective for its particular ions, its physiological consequences can be diverse.

Placental housekeeping activities are susceptible to chemicals and at least partly controlled by ion channels [5]. Consequently, these channels have great physiological and pathological significance. The objective of this review was to provide an update and comprehensive insight into placental ion channels. We review the information on expression of ion channels in human placental tissue and primary cells. Furthermore, we highlight the possibility that placental ion channels are targets of toxicological concern in terms of placental function, fetal growth, and development based on studies obtained in different placental platforms.

Placental ion channels

Ion channels have two major characteristics: the first is selectivity—one type of channel preferentially passes certain ions, whereas other ions cannot easily pass through that channel. The second characteristic is an ability to switch; ion channels exist in two states, open and closed states. Ion channels can be divided into various ion channel subtypes depending on the type of ion and activation [6]. Human placenta expresses a large number of ion channels. The data on ion channels in

Received: July 3, 2022. **Revised:** September 23, 2022. **Accepted:** September 29, 2022

human placental tissue and primary placental cells are shown in Table 1. The studies include placental tissue or primary cells from all trimesters of pregnancy, and also from abnormal pregnancies. For many ion channel types, the data on the human placenta are limited to mRNA expression studies. Among the most studied ion channels in placental platforms are nicotine acetylcholine receptors (nAchR), transient receptor potential channels (TRPs) TRPP2, TRPV5, and TRPV6, aquaporins (AQP) 3, 8, and 9, and connexin 43 (Cx43).

Calcium channels

Calcium transfer in the human placenta mainly occurs through the syncytiotrophoblasts and calcium channels are the most widely distributed type of ion channel in the placenta [116,117]. In placenta, voltage-gated L-type Ca channel isoforms ($Ca_v1.1$, $Ca_v1.2$, and $Ca_v1.3$), and Cav1.4 have been detected in syncytiotrophoblasts [63,64], where these channels would also have a role in cell signaling and protein secretion [117]. In placental blood vessels, voltage-gated L-type Ca channels are mainly involved in regulating the hypoxic fetoplacental vasoconstriction [118] and in syncytiotrophoblasts, these channels would have a role in also in cell signaling and hormone secretion in addition to cellular Ca^{2+} entry [63–65].

Transient receptor potential channels

Human placenta expresses several isoforms of TRPs [116], of which transient receptor potential cation channel subfamily C (TRPCs) may have a role in store-operated calcium entry (i.e., activated by intracellular calcium released particularly from the endoplasmic reticulum store) in the placenta. In addition, TRPV5 and – 6 are calcium selective channels that seem to be strongly involved in the calcium transport from the mother to the fetus [15]. In fact, mutations in TRPV6 coding gene were shown to interfere with calcium transport through the placenta and cause fetal calcium deficiency, hyperparathyroidism, and metabolic bone disease [119]. In addition, a non-selective, voltage-dependent TRPP2 channel (polycystin-2) is located at the apical membrane of the syncytiotrophoblasts with a high permeability to Ca^{2+} but also permeable to Na^+ and K^+ [53]. It may be important for Ca^{2+} transport but also for regulation of other ions transport in the placenta [53–56].

Chloride channels

Placental chloride channels are important for chloride transport at the plasma membrane. The members of chloride intracellular channel (CIC) proteins are ubiquitously expressed and involved in the transplacental passage of chloride but also in the regulation of several other cellular processes including proliferation, differentiation, and apoptosis although their role is not completely understood [89–91]. However, the expression of these chloride channels is increased in placentae of pre-eclamptic (PE) and intra-uterine growth retardation pregnancies (IUGR), but it remains to be studied whether they contribute to pathological processes of these conditions [65,90]. Maxi-chloride channel is a complex with solute carrier organic anion transporter family member 2A1 (SLCO2A1) as pore-forming component and two auxiliary regulatory proteins, annexin 2 and S100 calcium binding protein A10 (S100A10) [115] Maxi-chloride channel has been shown to be regulated by arachidonic acid, fatty acids and steroid hormones [120]. In addition to chloride, the maxi-chloride channel is permeable to amino acids and it may have a role in placental volume regulation [121].

Potassium channels

Potassium channels play important physiological roles in the human placenta including membrane permeability to K^+ ions, the control of fetoplacental blood flow, and hormone secretion [122]. With respect to the identified potassium channels, many members of voltage-gated, calcium and sodium - activated and 2-pore domain potassium channels participate in hormone secretion in the placenta [33,36,42,46,48,123–125]. Many K-channels distributed in the placental blood vessels are oxygen-sensitive and participate in controlling the vascular tone of the placental blood vessels [42,125,126]. In fetal growth restriction, gene expression of voltage dependent potassium channel $K_V9.3$ and $K_V2.1$ was increased in placental tissue and veins, respectively [34]. Similarly, the expression of Kv2.1, inwardly rectifying potassium channel Kir2.1 increased in the basal membrane of placentas from PE and IUGR pregnancies compared to placentas of healthy pregnancies, where these channels were mainly present in the apical membrane [33]. In addition, during the differentiation of cultured human trophoblasts, the expression of K_V7 channel subunits (KCNQ1, KCNE1, KCNE3, and KCNE5) was decreased by hypoxia and induced in an oxygen-rich environment [42]. Altogether, the changes in the expression of potassium channels in vasculature and trophoblasts, and their localization between apical and basal membranes in pathological conditions such as PE and IUGR [33,34,42] suggest that these ion channels may have a role in regulating placental physiology.

Other ion channels

Several subunits and receptor subtypes of nicotinic acetylcholine receptors nAChR are expressed in the placenta. In PE, expression of several mAChR subunits is dysregulated [17,18]. Placenta also expresses an epithelial sodium channel (ENaC), which is located in the apical membrane of cytotrophoblasts [7]. The expression of ENaC is regulated by aldosterone and a reduced amount of ENaC is reported in PE [127]. In addition to control of the intracellular flow of sodium ions, ENaC may promote cell migration in the placenta [127,128]. In addition, the expression of π subunit of the ion channel gamma-aminobutyric acid (GABA) A receptor (GABRP) is also increased in the placentas of patients with PE. In HTR-8/SVneo trophoblastic cells, GABRP was shown to promote apoptosis and inhibit the invasion of trophoblastic cells that could have a role in the onset of PE [12]. Furthermore, a special type of ATP-activated ion channels called the purinergic receptors are expressed in human cytotrophoblast cells. Ligand-gated P2X4, P2X7, and G protein-coupled P2Y2 and P2Y6 have been reported to modulate the intracellular concentration of Ca^{2+} and K^+ efflux in cytotrophoblasts [24,25] although their significance in the control of placental electrolyte transport is not studied in detail and consequently their role in the placenta is not yet known. In addition, several aquaporins (AQPs), water channels that also have an additional ion channel function, are expressed in the human placenta on placental trophoblasts, chorionic villi, and fetal membrane [129]. In the placenta, as water channels, they have a role as a regulator of maternal-fetal fluid flow but the ion channel roles remain to be defined [130].

Table 1. The distribution of ion channels in human placental tissue and primary human placental cells

Name	Gene name	Expression in placenta			References
		mRNA*	Protein**	Localization***	
Ligand-gated ion channels					
Epithelial sodium channels					
ENaCα	*SCNN1A*	+	+	Cytotrophoblasts, syncytiotrophoblasts	[7–11]
ENaCβ	*SCNN1B*	+	+	Syncytiotrophoblasts	[7,10]
ENaCγ	*SCNN1C*	+	+	Syncytiotrophoblasts	[7,9,10]
GABA-type receptors					
GABA A	*GABRP*	+	+	Cytotrophoblasts, syncytiotrophoblasts.	[12–14]
Inositol 1,4,5-trisphosphate receptors (IP3R)					
IP3R1	*ITPR1*	+	–	–	[15]
IP3R2	*ITPR2*	+	–	–	[15]
IP3R3	*ITPR3*	+	–	–	[15]
Nicotine acetylcholine receptors					
nAchRα1 subunit	*CHRNA1*	+	–	–	[16]
nAchRα2 subunit	*CHRNA2*	+	+	Syncytiotrophoblasts, villi	[16–19]
nAchRα3 subunit	*CHRNA3*	+	+	Syncytiotrophoblasts, blood vessels	[16–19]
nAchRα4 subunit	*CHRNA4*	+	+	Syncytiotrophoblasts, blood vessels	[16–19]
nAchRα5 subunit	*CHRNA5*	+	+	Syncytiotrophoblasts, blood vessels	[16–19]
nAchRα6 subunit	*CHRNA6*	+	+	–	[16,17,19]
nAchRα7 subunit	*CHRNA7*	+	+	Cytotrophoblasts, syncytiotrophoblasts, villi, blood vessels	[17–21]
nAchRα9 subunit	*CHRNA9*	+	+	Syncytiotrophoblasts, villi, blood vessels	[16–19]
nAchRα10 subunit	*CHRNA10*	+	+	Syncytiotrophoblasts, blood vessels	[16,17,19]
nAchRβ1 subunit	*CHRNB1*	+	+	Villi	[16–18,22]
nAchRβ2 subunit	*CHRNB2*	+	+	Villi	[16–18]
nAchRβ3 subunit	*CHRNB3*	+	–	–	[16]
nAchRβ4 subunit	*CHRNB4*	+	–	–	[16,17]
nAchRδ subunit	*CHRND*	+	+	Villi	[16–18]
nAchRγ subunit	*CHRNG*	+	–	–	[16]
nAchRε subunit	*CHRNE*	+	–	–	[16,17]
P2X receptors					
P2X1	*P2RX1*	+	–	Blood vessels	[23]
P2X4	*P2RX4*	+	+	Cytotrophoblasts, blood vessels	[23–25]
P2X5	*P2RX5*	+	–	Blood vessels	[23]
P2X6	*P2RX6*	+	–	Blood vessels	[23]
P2R7	*P2RX7*	+	+	Cytotrophoblasts, blood vessel	[23,24]
ZAC					
ZAC	*ZACN*	+	–		[26]
Potassium channels					
Calcium- and sodium-activated potassium channels					
K_{Ca}1.1	KCNMA1 KCaα	+	+	Blood vessels	[27–29]
	KCNMB1 BKCaβ	+	+	Blood vessels	[30]
K_{Ca}2.1	KCNN1 SKCa1, SK1	+	+	Blood vessels	[31]
K_{Ca}2.3	KCNN3 SKCa3,	+	–	Blood vessels	[28]
K_{Ca}3.1	KCNN4 IKCa, IK1, IKCa3.1, SKCa4	+	+	Cytotrophoblasts, blood vessels	[28,31,32]
Inwardly rectifying potassium channels					
K_{ir}2.1	*KCNJ2*	+	+	Syncytiotrophoblasts, blood vessels	[33–35]
K_{ir}6.1	*KCNJ8*	+	+	Syncytiotrophoblasts, blood vessels	[29,34,36]
K_{ir}6.2	*KCNJ11*	+	–	Blood vessels	[36]
Two P domain potassium channels					
K_{2p}2.1 (TWIK)	*KCNK1*	+	–	–	[37]
K_{2p}2.1 (TREK1)	*KCNK2*	+	+	Cytotrophoblasts, syncytiotrophoblasts	[33,38]

(continue)

Table 1. Continued.

Name	Gene name	Expression in placenta			References
		mRNA*	Protein**	Localization***	
K_{2p}3.1 (TASK1)	*KCNK1*	+	+	Cytotrophoblasts, syncytiotrophoblasts, blood vessels	[29,33,38]
K_{2p}4.1 (TRAAK)	*KCNK4*	+	–	–	(Lesage, Maingret and Lazdunski, 2000)
K_{2p}5.1 (TASK2)	*TASK2 KCNK5*	+	–	–	[38]
K_{2p}6.1 (TWIK2)	*KCNK6*	–	+	Blood vessels	[39]
K_{2p}7.1 (TWIK3)	*KCNK7*	–	+	Blood vessels	[39]
K_{2p}9.1 (TASK3)	*KCNK9*	–	+	Blood vessels	[39]
K_{2p}13.1 (TASK5)	*KCNK15*	+	–	–	[38]
K_{2p}17.1 (TALK2, TASK4)	*KCNK17*	+	–	–	[38,40]
K_{2p}18.1 (TRESK-2)	*KCNK18*	+	–	–	[41]
Voltage-gated potassium channels					
Kv1.5	*KCNA5*	+	+	Blood vessels	[27]
Kv2.1	*KCNB1*	–	+	Syncytiotrophoblasts, blood vessels	[27,29,33,34]
Kv3.1	*KCNC1*	–	+	Blood vessels	[27]
	KCNE1	+	+	–	[42–44]
	KCNE2	+			[43,44]
	KCNE3	+	–	–	[42–44]
	KCNE4	+	–	–	[42,44]
	KCNE5	+	–	Syncytiotrophoblasts, blood vessels	[42–44]
Kv6.2	*KCNE6*	–	+		[45]
Kv7.1	KCNQ1	+	+	Blood vessels	[42–44,46,47]
Kv7.2	KCNQ2	+	+	Blood vessels	[43,44,47]
Kv7.3	KCNQ3	+	+	Syncytiotrophoblasts, blood vessels	[42–44,46,47]
Kv7.4	KCNQ4	+	+	Blood vessels	[43,44,46,47]
Kv7.5	KCNQ5	+	+	Blood vessels	[42,43,46,47]
Kv9.3	KCNS3	+	+	Syncytiotrophoblasts, blood vessels	[29,34,48]
Ryanodine receptors					
RyR1	*RYR1*	+	–	Cytotrophoblasts, syncytiotrophoblasts	[15,49]
RyR2	*RYR2*	+	–	–	[15]
RyR3	*RYR3*	+	–	Cytotrophoblasts, syncytiotrophoblasts	[15,49]
Transient receptor potential cation channels					
TRPC1	*TRPC1*	+	+	–	[50]
TRPC3	*TRPC3*	+	–	Cytotrophoblasts, syncytiotrophoblasts	[50]
TRPC4	*TRPC4*	+	+	Cytotrophoblasts, syncytiotrophoblasts	[50]
TRPC5	*TRPC5*	+	–	–	[50]
TRPC6	*TRPC6*	+	+	Syncytiotrophoblasts	[50]
TRPM2	*TRPM2*	+			[51]
TRPM4	*TRPM4*	+			[51]
TRPM7	*TRPM7*	+			[51]
TRPP (polycystin) family					
TRPP1	*PKD2*	+	+	Trophoblasts	[52]
TRPP2	*PKD2L1*	+	+	Syncytiotrophoblasts, trophoblasts	[52–59]
TRPV (Vanilloid) family					
TRPV1	*TRPV1*	+	+	Cytotrophoblasts, syncytiotrophoblasts	[60,61]
TRPV4	*TRPV4*	+	+	Cytotrophoblasts, syncytiotrophoblasts	[62]
TRPV5	*TRPV5 (ECaC1, CaT2)*	+	+	Syncytiotrophoblasts, villi	[15,63–65]
TRPV6	*TRPV6 (ECaC2, CaT1)*	+	+	Syncytiotrophoblasts, villi	[15,63,65,66]
Voltage-gated calcium channels					
Ca_V1.1	*CACNA1S*	+	+	Syncytiotrophoblasts, villi	[65]
Ca_V1.2	*CACNA1C*	+	+	Syncytiotrophoblasts, villi, blood vessels	[39,63,65]
Ca_V1.3	*CACNA1D*	+	–	–	[63]
Voltage-gated sodium channels					
Na_v1.8	*SCN10A*	+	–	–	[67]
Other ion channels					
Aquaporins					
AQP1	*AQP1*	+	+	Cytotrophoblasts, villi blood vessels	[68–71]
AQP2	*AQP2*	–	+	Syncytiotrophoblasts, trophoblasts	[72]

(continue)

Table 1. Continued.

Name	Gene name	Expression in placenta			References
		mRNA*	Protein**	Localization***	
AQP3	*AQP3*	+	+	Cytotrophoblasts, syncytiotrophobasts, villi	[68–71,73–77]
AQP4	*AQP4*	+	+	Syncytiotrophoblasts, villi, endothelial cells	[68,71,78,79]
AQP5	*AQP5*	+	–	Villi	[68]
AQP8	*AQP8*	+	+	Cytotrophoblasts, syncytiotrophoblasts, villi	[68,70,71,80–83]
AQP9	*AQP9*	+	+	Cytotrophoblasts, syncytiotrophoblasts, villi	[68,70,71,73,80,81,83–88]
AQP11		+	–	Villi	[68]
Chloride channels					
ClC (CLC)-family					
CIC-1	*CLCN1*	+	+	Trophoblasts	[89]
CIC-3	*CLCN2*	+	+	Cytotrophoblasts, syncytiotrophoblasts, trophoblasts	[90,91]
CIC-4	*CLCN4*	+	+	Trophoblasts, villi	[89]
CIC-5	*CLCN5*	+	+	Trophoblasts, villi	[89,91]
CFTR-family					
CFTR	*CFTR*	+	+	–	[11,92–95]
Maxi chloride channels					
Maxi-Cl^-	#	–	+	Syncytiotrophoblasts, trophoblasts	[96]
Connexins and pannexins					
Cx26	*GJB2*	+		Syncytiotrophoblasts	[97]
Cx31	*GJB3*	+		Syncytiotrophoblasts	[97]
Cx32	*GJB1*	+	+	Cytotrophoblasts, syncytiotrophoblasts, trophoblasts	[97–99]
Cx37	*GJA4*	+		Syncytiotrophoblasts	[97,99]
Cx40	*GJA5*	+	+	Cytotrophoblasts, syncytiotrophoblasts, endothelial cells	[97,99–102]
Cx43	*GJA1*	+	+	Cytotrophoblasts, syncytiotrophoblasts, trophoblasts, villi	[97–100,102–111]
Cx45	*GJC1*	+	+	Syncytiotrophoblasts	[97,99]
Cx46	*GJA3*	+		Syncytiotrophoblasts	[97]
Px1	*Panx1*	+	+	Syncytiotrophoblasts	[97,112]
Px2	*Panx2*	+		Syncytiotrophoblasts	[97]
Px3	*Panx3*	+		Syncytiotrophoblasts, trophoblasts, villi	[97,105]
Piezo channels					
Piezo1	*PIEZO1*	+		Endothelial cells	[113]
Orai channels					
Orai1	*Orai1*	+		–	[114]

*In situ hybridization, Northern Blot, RT-PCR were used to measure mRNA levels, **western blot to detect protein and ***immunohistochemistry, immunocytochemistry and immunofluorescence as well as cell fractions and vesicles were used to report localization of ion channels. #A complex with solute carrier organic anion transporter family member 2A1 as a core pore-forming component and two auxiliary regulatory proteins, annexin A2 and S100 calcium binding protein A10 [115]. CaV, voltage-gated calcium channel; CFTR, cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7); CLC, chloride channel; Cx, connexin; K_{2P}, two-pore domain potassium channel; KCa, calcium-activated potassium channel; K_{ir}, inwardly rectifying potassium channel; nAchR, nicotinic acetylcholine receptor; Na_V, voltage-gated sodium channel; P2X, purinergic receptor P2X Px, pannexin; Ryr, ryanodine receptor; TRPM, transient receptor potential cation channel subfamily M; TRPP, transient receptor potential cation channel subfamily P; TRPV, transient receptor potential cation channel subfamily V; ZAC, zinc-activated channel.

The effect of chemical exposure on placental ion channels

Chemicals in tobacco products

Effects of chemical exposure on ion channels have been studied in multiple placental platforms. We have reviewed the findings on experimental models including cell lines and experimental animal studies in Table 2. Smoking during pregnancy is the most common type of chemical exposure to placenta, e.g., leading to disturbed trophoblast morphology and invasion, reduction in placental development, and ultimately retarded fetal growth [131,132]. Studies with the term placentas have indicated that cigarette smoke and nicotine can dysregulate levels of nAchR subtypes in the placenta [16,18,133–137]. In addition, nicotine competes with endogenous acetylcholine for binding to nAChRs [138]. In fact, nAChRs in rat trophoblast cells are responsive at nicotine concentrations similar to nicotine plasma levels detected among moderate to heavy cigarette smokers [16,19,137]. One of the possible mechanisms by which nicotine impairs placental function could be increased endoplasmic reticulum stress via nAChR [138]. In addition, nicotine has been shown to suppress placental cytokine production mediated through the nAChR pathway [136].

In addition, heavy metals such as cadmium, which are also present in tobacco smoke, can inhibit placental leptin synthesis, partly explaining the endocrine-disrupting effects of cadmium [147]. In a study using a human embryonic kidney HEK293 cell line, cadmium significantly inhibited calcium ion

Table 2. Effects of smoking and chemical exposure on ion channels obtained in different placental platforms

Chemical	Ion channel	Material	Experimental results	References
Cigarette smoke	nAchR	Full term human placenta	Increased expression of nAChRα9 and β1 subunits	[18]
Nicotine	nAchR	Full term human placenta	Increased levels of nAChRα9 subunit and decreased levels of nAChRδ	[16]
Nicotine	nAchR	HTR-8/SVneo cells	Suppressed invasiveness of human trophoblasts by downregulation of CXCL12 expression through nAChRα7 subunit	[134]
Nicotine	nAchR	BeWo cells	Increased expression of nAChRα9 subunit	[135]
Nicotine	nAchR	Rat placental explants	Regulated increased expression of nAChRα7 subunit in placenta after lipopolysaccharide treatment	[133]
Nicotine	nAchR	In vivo in rats, rat trophoblast Rcho-1 cell line	Increased expression of nAChRα4 subunit	[137]
Nicotine	nAchR	Rat trophoblast Rcho-1 cell line	Increased endoplasmic reticulum stress via nAChR.	[138]
Nicotine	nAchR	Primary human placental cells	Inhibited cytokine production via nAChR pathway	[136]
Aflatoxin B1	TRPs	Placental JEG-3 cells	Increased mRNA levels of TRP subtypes C3, C4, C6, V5, P2 TRPC3 mediated AFB1 induced increase in COX-2 expression	[139]
Zeranol	TRPs	Placental JEG-3 cells	Increased mRNA levels of TRP subtypes C3, C6, P2 TRPC3 mediated zeranol induced increase in COX-2 expression	[140]
Bisphenol A, octylphenol	TRPV6	Mouse placenta	Decreased mRNA levels of TRPV6	[141]
Bisphenol A	ENaCα	Mouse fetal membrane	Decreased ENaCα protein levels	[142]
Aroclor 1254	AQP1	Mouse placenta Human HTR8 cells	Reduced AQP1 protein levels	[143]
ROS	TRPP2	Human syncytiotrophoblasts	Inhibited TRPP2 activity	[58]
Aldosterone	ENaC	BeWo cells	Modulated ENaC currents	[128,144]
Aldosterone	ENaCα	Human HTR8/SVneo cell line	Upregulated ENaCα protein expression ENaC activity was important for trophoblast cells invasion	[8]
Prolactin, hGC	ENaCα	Human HTR8/SVneo cell line	Upregulated ENaCα protein expression	[8]
Verapamil, nifedipine	Calcium channel	Human first trimester placental tissue	Inhibited GnRH-stimulated hCG secretion	[145]
17-beta-estradiol, tamoxifen	Maxi-Cl- channel	Human placental apical membrane vesicles	Steroid hormones may regulate transplacental chloride transport	[146]
Bicuculline	GABA type A receptor	Human first trimester trophoblasts	Inhibited hCG secretion	[13]
Capsasin	TRPV1	Human cytotrophoblasts	Inhibited hCG secretion Impaired the spontaneous in vitro differentiation of cytotrophoblasts into syncytiotrophoblasts	[60]
Leptin	AQP9	Human placental explants	Upregulated AQP9 expression	[84]

CXCL12, C-X-C Motif Chemokine Ligand 12; GnRH, Gonadotropin-releasing hormone; JEG-3, Human choriocarcinoma cell line; nAchR, Nicotinic acetylcholine receptor; TRPV5/6, Transient receptor potential cation channel subfamily V member 5/6.

flow into the cells, and this was attributed to a competitive inhibition of two important ion channels TRPV5 and TRPV6 [148], both of which are important in fetal placental calcium transport as well [149], indicating that cadmium could directly affect fetal bone development via these ion channels.

Environmental contaminants

Several common environmental pollutants such as dichlorodiphenylethylene (DDE), bisphenol A, brominated flame retardants, polychlorinated biphenyls, and fungal metabolites such as aflatoxins can be detected in the placenta [3]. Studies with the JEG-3 cell line demonstrated that endocrine-disrupting chemicals (EDCs), aflatoxin B1, and zeranol can significantly increase the mRNA levels of TRPC3 ion channel and increase intracellular calcium levels [139,140]. In addition, the experiments in pregnant mice demonstrated that bisphenol A and octylphenol significantly reduced placental TRPV6 mRNA levels, and furthermore disturbed fetal bone development in mice [141]. In another study, after intervention with bisphenol A, the expression of epithelial sodium channel alpha (ENaCα) protein in the decidua was significantly down-regulated detected by immunohistochemistry [142]. Thus, it has been suggested that exposure to BPA leads to impaired decidualization through a reduced serum glucocorticoid-induced kinase 1-mediated downregulation of ENACα [142,150]. In epidemiological studies, polychlorinated biphenyls (PCB) and other chlorides have been linked with serious adverse effects on maternal health and fetal development including growth restriction [151] impaired immune response [152] and neurobehavioral deficits [153] in the child. Finally, there is convincing evidence that aquaporin 1 (AQP1) is involved in the production of fetal amniotic fluid [154]. In the placenta of pregnant mice exposed to PCB, the protein expression of placental AQP1 was significantly downregulated in comparison to normal

wild-type mice, and the amount of amniotic fluid was significantly increased [143].

Pharmaceuticals

Several well-known pharmaceuticals even act via ion channels and some of them have been shown to affect placental function. A class of antihypertensive drugs, i.e., dihydropyridines have been shown to stimulate the secretion of hCG via calcium channels. Inhibited hCG secretion was also seen in response to capsaisin in human primary cytotrophoblasts, where capsaisin impaired differentiation of cytotrophoblasts into syncytiotrophoblasts by activating TRPV1 [60]. In addition, also GABA-A receptor agonis bicuculline can inhibit hCG secretion [13]. On the other hand, hCG, prolactin, and aldosterone were able to upregulate ENaCα protein expression in human extravillous trophoblast cell line [8].

Placenta is a highly active endocrine organ, and several ion channels are regulated by hormones. For example, 17β-estradiol (and tamoxifen) have been shown to regulate the Maxi-chloride channel in apical membranes from human placental syncytiotrophoblasts [146]. Furthermore, exogenous progesterone was shown to upregulate TRPV5 and TRPV6 mRNAs in ovine placentome [155] and an energy metabolism-regulating hormone leptin upregulated AQP9-expression in human trophoblast explants [84]. Finally, human term cytotrophoblast expresses the mineralocorticoid-responsive genes including ENaCα ja ENaCγ subunits [9] and it has been shown that aldosterone can promote cell migration via ENaC in BeWo cells [128,144].

Concluding remarks

A large number of ion channels are distributed in the placenta where they have several important functions (1) to regulate the synthesis and secretion of hormones, (2) to ensure homeostasis of trophoblasts, (3) to control the transport of trace elements between mother and fetus, and (4) to regulate vascular contraction and relaxation. It has been confirmed that the placental ion channels exposed to chemicals can undergo functional and quantitative changes, which in turn could affect the normal function of the placenta and the growth and development of the fetus. However, so far, there are rather few reports on the effects of the chemical compounds on placental ion channels. The responses of placental ion channels to chemical exposure, which may be either direct or indirect, can potentially lead to pregnancy complications such as abortion, premature delivery, fetal growth restriction, fetal development abnormalities, *etc.* Further focused investigations using placental platforms are needed to clarify the potential role of chemical-induced ion channels medicated effects on placental housekeeping functions and whether pharmaceuticals acting *via* ion channels can become potential therapies in selected obstetric complications.

Conflicts of interest

The authors have declared that no conflict of interest exists.

Authors' contributions

All authors contributed to the study, and read and approved the submitted version.

Acknowledgment

This paper belongs to the studies carried out by the Kuopio Birth Cohort Consortium (www.KuBiCo.fi).

References

1. Syme MR, Paxton JW, Keelan JA. Human placenta. *Clin Pharmacokinet* 2004; **43**:487–514.
2. Myllynen P, Pasanen M, Vähäkangas K. The fate and effects of xenobiotics in human placenta. *Expert Opin Drug Metab Toxicol* 2007; **3**:331–346.
3. Vähäkangas K. Chemical exposure as etiology in developmental origin of adult onset human cancer. *Front Pharmacol* 2011; **2**: 1–5.
4. Audus KL. Controlling drug delivery across the placenta. *Eur J Pharm Sci* 1999; **8**:161–165.
5. Riquelme G. Placental syncytiotrophoblast membranes - domains, subdomains and microdomains. *Placenta* 2011; **32**:S196–S202.
6. Alexander SPH, Mathie A, Peters JA, Veale EL, Striessnig J, Kelly E, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Davies JA *et al.* The concise guide to pharmacology 2021/22: ion channels. *Br J Pharmacol* 2021; **178**:S157–S245.
7. Marino GI, Kotsias BA. Expression of the epithelial sodium channel sensitive to amiloride (ENaC) in normal and preeclamptic human placenta. *Placenta* 2013; **34**:197–200.
8. Yang Y, He G, Xu W, Liu X. ENaC mediates human extravillous trophblast cell line (HTR8/SVneo) invasion by regulating levels of matrix metalloproteinase 2 (MMP2). *Placenta* 2015; **36**: 587–593.
9. Driver PM, Rauz S, Walker EA, Hewison M, Kilby MD, Stewart PM. Characterization of human trophoblast as a mineralocorticoid target tissue. *Mol Hum Reprod* 2003; **9**:793–798.
10. Wang S, He G, Yang Y, Liu Y, Diao R, Sheng K, Liu X, Xu W. Reduced expression of Enac in placenta tissues of patients with severe preeclampsia is related to compromised trophoblastic cell migration and invasion during pregnancy. *PLoS One* 2013; **8**: 1–8.
11. Zhou M, Fu J, Huang W, Shen L, Xiao L, Song Y, Liu Y. Increased cystic fibrosis transmembrane conductance regulators expression and decreased epithelial sodium channel alpha subunits expression in early abortion: findings from a mouse model and clinical cases of abortion. *PLoS One* 2014; **9**:1–8.
12. Lu J, Zhang Q, Tan D, Luo W, Zhao H, Ma J, Liang H, Tan Y. GABA A receptor subunit promotes apoptosis of HTR-8/SVneo trophoblastic cells: Implications in preeclampsia. *Int J Mol Med* 2016; **38**:105–112.
13. Licht P, Harbarth P, Merz WE. Evidence for a modulation of human chorionic gonadotropin (Hcg) subunit messenger ribonucleic acid levels and hcg secretion by γ-aminobutyric acid in human first trimester placenta in vitro. *Endocrinology* 1992; **130**: 490–496.
14. Karvas RM, McInturf S, Zhou J, Ezashi T, Schust DJ, Roberts RM, Schulz LC. Use of a human embryonic stem cell model to discover GABRP, WFDC2, VTCN1 and ACTC1 as markers of early first trimester human trophoblast. *Mol Hum Reprod* 2020; **26**:425–440.
15. Haché S, Takser L, Lebellego F, Weiler H, Leduc L, Forest JC, Giguère Y, Masse A, Barbeau B, Lafond J. Alteration of calcium homeostasis in primary preeclamptic syncytiotrophoblasts: effect on calcium exchange in placenta. *J Cell Mol Med* 2011; **15**: 654–667.
16. Machaalani R, Ghazavi E, Hinton T, Waters KA, Hennessy A. Cigarette smoking during pregnancy regulates the expression of specific nicotinic acetylcholine receptor (nAChR) subunits in the human placenta. *Toxicol Appl Pharmacol* 2014; **276**:204–212.
17. MacHaalani R, Ghazavi E, David RV, Hinton T, Makris A, Hennessy A. Nicotinic acetylcholine receptors (nAChR) are increased

in the pre-eclamptic placenta. *Hypertens Pregnancy* 2015; **34**: 227–240.
18. Machaalani R, Ghazavi E, Hinton T, Makris A, Hennessy A. Immunohistochemical expression of the nicotinic acetylcholine receptor (nAChR) subunits in the human placenta, and effects of cigarette smoking and preeclampsia. *Placenta* 2018; **71**: 16–23.
19. Lips KS, Brüggmann D, Pfeil U, Vollerthun R, Grando SA, Krummer W. Nicotinic acetylcholine receptors in rat and human placenta. *Placenta* 2005; **26**:735–746.
20. Alwazzan A, Mehboob R, Gilani SA, Hassan A, Perveen S, Tanvir I, Waseem H, Ehsan K, Ahmad FJ, Akram J. Immunohistochemical Expression of the Alpha Nicotinic Acetylcholine Receptor 7 in the Human Normal, Diabetic, and Preeclamptic Placenta and Products of Conception. *Front Physiol* 2020; **11**:1–6.
21. Kwon JY, Kim YH, Kim SH, Kang MH, Maeng YS, Lee KY, Park YW. Difference in the expression of alpha 7 nicotinic receptors in the placenta in normal versus severe preeclampsia pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2007; **132**:35–39.
22. Aishah A, Hinton T, Machaalani R. Cellular protein and mRNA expression of β1 nicotinic acetylcholine receptor (nAChR) subunit in brain, skeletal muscle and placenta. *Int J Dev Neurosci* 2017; **58**:9–16.
23. Valdecantos P, Briones R, Moya P, Germain A, Huidobro-Toro JP. Pharmacological identification of P2X1, P2X4 and P2X7 nucleotide receptors in the smooth muscles of human umbilical cord and chorionic blood vessels. *Placenta* 2003; **24**:17–26.
24. Roberts VHJ, Greenwood SL, Elliott AC, Sibley CP, Waters LH. Purinergic receptors in human placenta: Evidence for functionally active P2X4, P2X7, P2Y2, and P2Y6. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**:1374–1386.
25. Roberts VHJ, Webster RP, Brockman DE, Pitzer BA, Myatt L. Post-translational modifications of the P2X4 purinergic receptor subtype in the human placenta are altered in preeclampsia. *Placenta* 2007; **28**:270–277.
26. Davies PA, Wang W, Hales TG, Kirkness EF. A novel class of ligand-gated ion channel is activated by Zn2+. *J Biol Chem* 2003; **278**:712–717.
27. Hampl V, Bíbová J, Straák Z, Wu X, Michelakis ED, Hashimoto K, Archer SL. Hypoxic fetoplacental vasoconstriction in humans is mediated by potassium channel inhibition. *Am J Physiol Hear Circ Physiol* 2002; **283**:2440–2449.
28. Brereton MF, Wareing M, Jones RL, Greenwood SL. Characterisation of K+ channels in human fetoplacental vascular smooth muscle cells. *PLoS One* 2013; **8**:e57451.
29. Wareing M, Bai X, Seghier F, Turner CM, Greenwood SL, Baker PN, Taggart MJ, Fyfe GK. Expression and function of potassium channels in the human placental vasculature. *Am J Physiol Regul Integr Comp Physiol* 2006; **291**:R437–R446.
30. He M, Li F, Yang M, Fan Y, Beejadhursing R, Xie Y, Zhou Y, Deng D. Impairment of BKca channels in human placental chorionic plate arteries is potentially relevant to the development of preeclampsia. *Hypertens Res* 2018; **41**:126–134.
31. Li FF, He MZ, Xie Y, Wu YY, Yang MT, Fan Y, Qiao FY, Deng DR. Involvement of dysregulated IKCa and SKCa channels in preeclampsia. *Placenta* 2017; **58**:9–16.
32. Díaz P, Wood AM, Sibley CP, Greenwood SL. Intermediate conductance Ca2+− activated K+ channels modulate human placental trophoblast syncytialization. *PLoS One* 2014; **9**:1–12.
33. Riquelme G, De Gregorio N, Vallejos C, Berrios M, Morales B. Differential expression of potassium channels in placentas from normal and pathological pregnancies: targeting of the Kir 2.1 channel to lipid rafts. *J Membr Biol* 2012; **245**:141–150.
34. Corcoran J, Lacey H, Baker PN, Wareing M. Altered potassium channel expression in the human placental vasculature of pregnancies complicated by fetal growth restriction. *Hypertens Pregnancy* 2008; **27**:75–86.
35. Mylona P, Clarson LH, Greenwood SL, Sibley CP. Expression of the Kir2.1 (inwardly rectifying potassium channel) gene in the human placenta and in cultured cytotrophoblast cells at different stages of differentiation. *Mol Hum Reprod* 1998; **4**:195–200.
36. Lybaert P, Hoofd C, Guldner D, Vegh G, Delporte C, Meuris S, Lebrun P. Detection of KATP channels subunits in human term placental explants and evaluation of their implication in human placental lactogen (hPL) and human chorionic gonadotropin (hCG) release. *Placenta* 2013; **34**:467–473.
37. Pountney DJ, Gulkarov I, Vega-Saenz De Miera E, Holmes D, Saganich M, Rudy B, Artman M, Coetzee WA. Identification and cloning of TWIK-originated similarity sequence (TOSS): a novel human 2-pore K+ channel principal subunit. *FEBS Lett* 1999; **450**:191–196.
38. Bai X, Bugg GJ, Greenwood SL, Glazier JD, Sibley CP, Baker PN, Taggart MJ, Fyfe GK. Expression of TASK and TREK, two-pore domain K+ channels, in human myometrium. *Reproduction* 2005; **129**:525–530.
39. Ali TY, Pipkin FB, Khan RN. The effect of pH and ion channel modulators on human placental arteries. *PLoS One* 2014; **9**:1–21.
40. Decher N, Maier M, Dittrich W, Gassenhuber J, Brüggemann A, Busch AE, Steinmeyer K. Characterization of TASK-4, a novel member of the pH-sensitive, two-pore domain potassium channel family. *FEBS Lett* 2001; **492**:84–89.
41. Kang D, Mariash E, Kim D. Functional expression of TRESK-2, a new member of the tandem-pore K + channel family. *J Biol Chem* 2004; **279**:28063–28070.
42. Luo Y, Kumar P, Mendelson CR. Estrogen-related receptor γ (ERRγ) regulates oxygen-dependent expression of voltage-gated potassium (K+) channels and tissue kallikrein during human trophoblast differentiation. *Mol Endocrinol* 2013; **27**:940–952.
43. Mistry HD, McCallum LA, Kurlak LO, Greenwood IA, Pipkin FB, Tribe RM. Novel expression and regulation of voltage-dependent potassium channels in placentas from women with preeclampsia. *Hypertension* 2011; **58**:497–504.
44. Mistry HD, Kurlak LO, Whitley GS, Cartwright JE, Broughton Pipkin F, Tribe RM. Expression of voltage-dependent potassium channels in first trimester human placentae. *Placenta* 2014; **35**: 337–340.
45. Su K, Kyaw H, Fan P, Zeng Z, Shell BK, Carter KC, Li Y. Isolation, characterization, and mapping of two human potassium channels. *Biochem Biophys Res Commun* 1997; **241**:675–681.
46. Mills TA, Greenwood SL, Devlin G, Shweikh Y, Robinson M, Cowley E, Hayward CE, Cottrell EC, Tropea T, Brereton MF, Dalby-Brown W, Wareing M. Activation of KV7 channels stimulates vasodilatation of human placental chorionic plate arteries. *Placenta* 2015; **36**:638–644.
47. Wei X, Zhang Y, Yin B, Wen J, Cheng J, Fu X. The expression and function of KCNQ potassium channels in human chorionic plate arteries from women with normal pregnancies and pre-eclampsia. *PLoS One* 2018; **13**:1–16.
48. Fyfe GK, Panicker S, Jones RL, Wareing M. Expression of an electrically silent voltage-gated potassium channel in the human placenta. *J Obstet Gynaecol* 2012; **32**:624–629.
49. Zheng L, Lindsay A, McSweeney K, Aplin J, Forbes K, Smith S, Tunwell R, Mackrill JJ. Ryanodine receptor calcium release channels in trophoblasts and their role in cell migration. *Biochim Biophys Acta Mol Cell Res* 2022; **1869**:119139.
50. Clarson LH, Roberts VHJ, Hamark B, Elliott AC, Powell T. Store-operated Ca2+ entry in first trimester and term human placenta. *J Physiol* 2003; **550**:515–528.
51. Fonfria E, Murdock PR, Cusdin FS, Benham CD, Kelsell RE, McNulty S. Tissue distribution profiles of the human TRPM cation channel family. *J Recept Signal Transduct* 2006; **26**: 159–178.
52. Ong ACM, Ward CJ, Butler RJ, Biddolph S, Bowker C, Torra R, Pei Y, Harris PC. Coordinate expression of the autosomal dominant polycystic kidney disease proteins, polycystin-2 and polycystin-1, in normal and cystic tissue. *Am J Pathol* 1999; **154**: 1721–1729.

53. Lez-Perrett SG, Batelli M, Kim K, Essafi M, Timpanaro G, Moltabetti N, Reisin IL, Amin Arnaout M, Cantiello HF. Voltage dependence and pH regulation of human polycystin-2-mediated cation channel activity. *J Biol Chem* 2002; **277**:24959–24966.
54. González-Perrett S, Kim K, Ibarra C, Damiano AE, Zotta E, Batelli M, Harris PC, Reisin IL, Arnaout MA, Cantiello HF. Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca2+− permeable nonselective cation channel. *Proc Natl Acad Sci U S A* 2001; **98**: 1182–1187.
55. Montalbetti N, Li Q, Wu Y, Chen XZ, Cantiello HF. Polycystin-2 cation channel function in the human syncytiotrophoblast is regulated by microtubular structures. *J Physiol* 2007; **579**: 717–728.
56. Montalbetti N, Li Q, Timpanaro GA, González-Perrett S, Dai XQ, Chen XZ, Cantiello HF. Cytoskeletal regulation of calcium-permeable cation channels in the human syncytiotrophoblast: Role of gelsolin. *J Physiol* 2005; **566**:309–325.
57. Nomura H, Turco AE, Pei Y, Kalaydjieva L, Schiavello T, Weremowicz S, Ji W, Morton CC, Meisler M, Reeders ST, Zhou J. Identification of PKDL, a novel polycystic kidney disease 2-like gene whose murine homologue is deleted in mice with kidney and retinal defects. *J Biol Chem* 1998; **273**:25967–25973.
58. Montalbetti N, Cantero MR, Dalghi MG, Cantiello HF. Reactive oxygen species inhibit polycystin-2 (TRPP2) cation channel activity in term human syncytiotrophoblast. *Placenta* 2008; **29**: 510–518.
59. Puttnam R, Davis BR, Pressel SL, Whelton PK, Cushman WC, Louis GT, Margolis KL, Oparil S, Williamson J, Ghosh A, Einhorn PT, Barzilay JI *et al.* Association of 3 different antihypertensive medications with hip and pelvic fracture risk in older adults secondary analysis of a randomized clinical trial. *JAMA Intern Med* 2017; **177**:67–76.
60. Costa MA, Fonseca BM, Keating E, Teixeira NA, Correia-Da-Silva G. Transient receptor potential vanilloid 1 is expressed in human cytotrophoblasts: Induction of cell apoptosis and impairment of syncytialization. *Int J Biochem Cell Biol* 2014; **57**: 177–185.
61. Martínez N, Abán CE, Leguizamón GF, Damiano AE, Farina MG. TPRV-1 expression in human preeclamptic placenta. *Placenta* 2016; **40**:25–28.
62. Zhang Y, Liang P, Yang L, Shan KZ, Feng L, Chen Y, Liedtke W, Coyne CB, Yang H. Functional coupling between TRPV4 channel and TMEM16F modulates human trophoblast fusion. *Elife* 2022; **11**:e78840.
63. Moreau R, Hamel A, Daoud G, Simoneau L, Lafond J. Expression of calcium channels along the differentiation of cultured trophoblast cells from human term placenta. *Biol Reprod* 2002; **67**:1473–1479.
64. Moreau R, Daoud G, Bernatchez R, Simoneau L, Masse A, Lafond J. Calcium uptake and calcium transporter expression by trophoblast cells from human term placenta. *Biochim Biophys Acta Biomembr* 2002; **1564**:325–332.
65. Bernucci L, Henríquez M, Díaz P, Riquelme G. Diverse calcium channel types are present in the human placental syncytiotrophoblast basal membrane. *Placenta* 2006; **27**:1082–1095.
66. Stumpf T, Zhang Q, Hirnet D, Lewandrowski U, Sickmann A, Wissenbach U, Dörr J, Lohr C, Deitmer JW, Fecher-Trost C. The human TRPV6 channel protein is associated with cyclophilin B in human placenta. *J Biol Chem* 2008; **283**:18086–18098.
67. Cejudo-Roman A, Pinto FM, Subirán N, Ravina CG, Fernández-Sánchez M, Pérez-Hernández N, Pérez R, Pacheco A, Irazusta J, Candenas L. The voltage-gated sodium channel Nav1.8 is expressed in human sperm. *PLoS One* 2013; **8**:1–13.
68. Escobar J, Gormaz M, Arduini A, Gosens K, Martinez A, Perales A, Escrig R, Tormos E, Roselló M, Orellana C, Vento M. Expression of aquaporins early in human pregnancy. *Early Hum Dev* 2012; **88**:589–594.
69. Zhu XQ, Jiang SS, Zhu XJ, Zou SW, Wang YH, Hu YC. Expression of aquaporin 1 and aquaporin 3 in fetal membranes and placenta in human term pregnancies with oligohydramnios. *Placenta* 2009; **30**:670–676.
70. Shao H, Pan S, Lan Y, Chen X, Dai D, Peng L, Hua Y. Tanshinone IIA increased amniotic fluid volume through down-regulating placental AQPs expression via inhibiting the activity of GSK-3β. *Cell Tissue Res* 2022; **389**:547–558.
71. Ding H, Ding Z, Zhao M, Ji B, Lei J, Chen J, Li M, Li M, Chen Y, Gao Q. Correlation of amniotic fluid index and placental aquaporin 1 levels in terms of preeclampsia. *Placenta* 2022; **117**: 169–178.
72. Zhao Y, Lin L, Lai A. Expression and significance of aquaporin-2 and serum hormones in placenta of patients with preeclampsia. *J Obstet Gynaecol* 2018; **38**:42–48.
73. Damiano A, Zotta E, Goldstein J, Reisin I, Ibarra C. Water channel proteins AQP3 and AQP9 are present in syncytiotrophoblast of human term placenta. *Placenta* 2001; **22**:776–781.
74. Wang S, Amidi F, Beall M, Gui L, Ross MG. Aquaporin 3 expression in human fetal membranes and its up-regulation by cyclic adenosine monophosphate in amnion epithelial cell culture. *J Soc Gynecol Investig* 2006; **13**:181–185.
75. Szpilbarg N, Castro-Parodi M, Reppetti J, Repetto M, Maskin B, Martinez N, Damiano AE. Placental programmed cell death: Insights into the role of aquaporins. *Mol Hum Reprod* 2015; **22**: 46–56.
76. Zhou J, Zhang D, Bai J, Li Z, Chen Y. Altered expressions of AQP3 and ADP are closely related with the risk of preeclampsia occurrence. *Gynecol Obstet Invest* 2020; **85**:362–370.
77. Mobasheri A, Wray S, Marples D. Distribution of AQP2 and AQP3 water channels in human tissue microarrays. *J Mol Histol* 2005; **36**:1–14.
78. De Falco M, Cobellis L, Torella M, Acone G, Varano L, Sellitti A, Ragucci A, Coppola G, Cassandro R, Laforgia V, Varano L, De Luca A. Down-regulation of aquaporin 4 in human placenta throughout pregnancy. *In Vivo* 2007; **21**:813–818.
79. Szpilbarg N, Seyahian A, Di PM, Castro-Parodi M, Martinez N, Farina M, Damiano AE. Oxygen regulation of aquaporin-4 in human placenta. *Reprod Biomed Online* 2018; **37**:601–612.
80. Jiang SS, Zhu XJ, Di DS, Wang JJ, Jiang LL, Jiang WX, Zhu XQ. Expression and localization of aquaporins 8 and 9 in term placenta with oligohydramnios. *Reprod Sci* 2012; **19**:1276–1284.
81. Wang S, Chen J, Beall M, Zhou W, Ross MG. Expression of aquaporin 9 in human chorioamniotic membranes and placenta. *Am J Obstet Gynecol* 2004; **191**:2160–2167.
82. Li SH, Yin HB, Ren MR, Wu MJ, Huang XL, Li JJ, Luan YP, Wu YL. TRPV5 and TRPV6 are expressed in placenta and bone tissues during pregnancy in mice. *Biotech Histochem* 2019; **94**: 244–251.
83. Zhu X, Jiang S, Hu Y, Zheng X, Zou S, Wang Y, Zhu X. The expression of aquaporin 8 and aquaporin 9 in fetal membranes and placenta in term pregnancies complicated by idiopathic polyhydramnios. *Early Hum Dev* 2010; **86**:657–663.
84. Vilariño-García T, Pérez-Pérez A, Dietrich V, Guadix P, Dueñas JL, Varone CL, Damiano AE, Sánchez-Margalet V. Leptin upregulates aquaporin 9 expression in human placenta in vitro. *Gynecol Endocrinol* 2018; **34**:175–177.
85. Medina Y, Acosta L, Reppetti J, Corominas A, Bustamante J, Szpilbarg N, Damiano AE. Lactic acid transport mediated by aquaporin-9: Implications on the pathophysiology of preeclampsia. *Front Physiol* 2021; **12**:774095.
86. Parodi MC, Farin M, Dietrich V, Abán C, Szpilbarg N, Zotta E, Damiano AE. Evidence for insulin-mediated control of AQP9 expression in human placenta. *Placenta* 2011; **32**:1050–1056.
87. Marino GI, Castro-Parodi M, Dietrich V, Damiano AE. High levels of human chorionic gonadotropin (hCG) correlate with increased aquaporin-9 (AQP9) expression in explants from human preeclamptic placenta. *Reprod Sci* 2010; **17**:444–453.

88. Vilariño-García T, Pérez-Pérez A, Dietrich V, Fernández-Sánchez M, Guadix P, Dueñas JL, Varone CL, Damiano AE, Sánchez-Margalet V. Increased expression of aquaporin 9 in trophoblast from gestational diabetic patients. *Horm Metab Res* 2016; **48**: 535–539.
89. Berryman M, Bretscher A. Identification of a novel member of the chloride intracellular channel gene family (CLIC5) that associates with the actin cytoskeleton of placental microvilli. *Mol Biol Cell* 2000; **11**:1509–1521.
90. Murthi P, Stevenson JL, Money TT, Borg AJ, Brennecke SP, Gude NM. Placental CLIC3 is increased in fetal growth restriction and pre-eclampsia affected human pregnancies. *Placenta* 2012; **33**: 741–744.
91. Money TT, King RG, Wong MH, Stevenson JL, Kalionis B, Erwich JJHM, Huisman MA, Timmer A, Hiden U, Desoye G, Gude NM. Expression and cellular localisation of chloride intracellular channel 3 in human placenta and fetal membranes. *Placenta* 2007; **28**:429–436.
92. Bremer S, Hoof T, Wilke M, Busche R, Scholte B, Riordan JR, Maass G, Tümmler B. Quantitative expression patterns of multidrug-resistance P-glycoprotein (MDR1) and differentially spliced cystic-fibrosis transmembrane-conductance regulator mRNA transcripts in human epithelia. *Eur J Biochem* 1992; **206**:137–149.
93. Mylona P, Glazier JD, Greenwood SL, Sides MK, Sibley CP. Expression of the cystic fibrosis (CF) and multidrug resistance (MDR1) genes during development and differentiation in the human placenta. *Mol Hum Reprod* 1996; **2**:693–698.
94. Castro-Parodi M, Levi L, Dietrich V, Zotta E, Damiano AE. CFTR may modulate AQP9 functionality in preeclamptic placentas. *Placenta* 2009; **30**:642–648.
95. Faller DP, Egan DA, Ryan MP. Evidence for location of the CFTR in human placental apical membrane vesicles. *Am J Physiol Cell Physiol* 1995; **269**:C148–C155.
96. Riquelme G, Parra M. Regulation of human placental chloride channel by arachidonic acid and other cis unsaturated fatty acids. *Am J Obstet Gynecol* 1999; **180**:469–475.
97. Xiao X, Tang Y, Wooff Y, Su C, Kang M, O'Carroll SJ, Chen Q, Chamley L. Upregulation of pannexin-1 hemichannels explains the apparent death of the syncytiotrophoblast during human placental explant culture. *Placenta* 2020; **94**:1–12.
98. Al-Lamki RS, Skepper JN, Burton GJ. Are human placental bed giant cells merely aggregates of small mononuclear trophoblast cells? An ultrastructural and immunocytochemical study. *Hum Reprod* 1999; **14**:496–504.
99. Nishimura T, Dunk C, Lu Y, Feng X, Gellhaus A, Winterhager E, Rossant J, Lye SJ. Gap junctions are required for trophoblast proliferation in early human placental development. *Placenta* 2004; **25**:595–607.
100. Winterhager E, Von Ostau C, Gerke M, Gruemmer R, Traub O, Kaufmann P. Connexin expression patterns in human trophoblast cells during placental development. *Placenta* 1999; **20**:627–638.
101. Lang I, Schweizer A, Hiden U, Ghaffari-Tabrizi N, Hagendorfer G, Bilban M, Pabst MA, Korgun ET, Dohr G, Desoye G. Human fetal placental endothelial cells have a mature arterial and a juvenile venous phenotype with adipogenic and osteogenic differentiation potential. *Differentiation* 2008; **76**:1031–1043.
102. Goffin F, Munaut C, Malassiné A, Evain-Brion D, Frankenne F, Fridman V, Dubois M, Uzan S, Merviel P, Foidart JM. Evidence of a limited contribution of feto-maternal interactions to trophoblast differentiation along the invasive pathway. *Tissue Antigen* 2003; **62**:104–116.
103. Cronier L, Guibourdenche J, Niger C, Malassiné A. Oestradiol stimulates morphological and functional differentiation of human villous cytotrophoblast. *Placenta* 1999; **20**:669–676.
104. Dukic AR, Gerbaud P, Guibourdenche J, Thiede B, Taskén K, Pidoux G. Ezrin-anchored PKA phosphorylates serine 369 and 373 on connexin 43 to enhance gap junction assembly, communication, and cell fusion. *Biochem J* 2018; **475**:455–476.
105. Jinping Z, Leijia Z, Xuehong L, Fuqun Z. Expression of Cx43 and Pax3 proteins in the human placental villi and decidua during early pregnancy. *Biomed Mater Eng* 2014; **24**:3841–3847.
106. Segond N, Degrelle SA, Berndt S, Clouqueur E, Rouault C, Saubamea B, Dessen P, Fong KSK, Csiszar K, Badet J, Evain-Brion D, Fournier T. Transcriptome analysis of PPARγ target genes reveals the involvement of lysyl oxidase in human placental cytotrophoblast invasion. *PLoS One* 2013; **8**:e79413.
107. He X, Chen Q. Reduced expressions of connexin 43 and VEGF in the first-trimester tissues from women with recurrent pregnancy loss. *Reprod Biol Endocrinol* 2016; **14**:1–7.
108. Pidoux G, Gerbaud P, Gnidehou S, Grynberg M, Geneau G, Guibourdenche J, Carette D, Cronier L, Evain-Brion D, Malassiné A, Frendo JL. ZO-1 is involved in trophoblastic cell differentiation in human placenta. *Am J Physiol Cell Physiol* 2010; **298**: 1517–1526.
109. McDonald EA, Wolfe MW. Adiponectin attenuation of endocrine function within human term trophoblast cells. *Endocrinology* 2009; **150**:4358–4365.
110. Cronier L, Defamie N, Dupays L, Théveniau-Ruissy M, Goffin F, Pointis G, Malassiné A. Connexin expression and gap junctional intercellular communication in human first trimester trophoblast. *Mol Hum Reprod* 2002; **8**:1005–1013.
111. Cronier L, Frendo JL, Defamie N, Pidoux G, Bertin G, Guibourdenche J, Pointis G, Malassiné A. Requirement of gap junctional intercellular communication for human villous trophoblast differentiation. *Biol Reprod* 2003; **69**:1472–1480.
112. El-Khalik SRA, Ibrahim RR, Ghafar MTA, Shatat D, El-Deeb OS. Novel insights into the SLC7A11-mediated ferroptosis signaling pathways in preeclampsia patients: identifying pannexin 1 and toll-like receptor 4 as innovative prospective diagnostic biomarkers. *J Assist Reprod Genet* 2022; **39**:1115–1124.
113. Morley LC, Shi J, Gaunt HJ, Hyman AJ, Webster PJ, Williams C, Forbes K, Walker JJ, Simpson NAB, Beech DJ. Piezo1 channels are mechanosensors in human fetoplacental endothelial cells. *Mol Hum Reprod* 2018; **24**:510–520.
114. Horinouchi T, Higashi T, Higa T, Terada K, Mai Y, Aoyagi H, Hatate C, Nepal P, Horiguchi M, Harada T, Miwa S. Different binding property of STIM1 and its novel splice variant STIM1L to Orai1, TRPC3, and TRPC6 channels. *Biochem Biophys Res Commun* 2012; **428**:252–258.
115. Sabirov RZ, Islam MR, Okada T, Merzlyak PG, Kurbannazarova RS, Tsiferova NA, Okada Y. The atp-releasing maxi-cl channel: Its identity, molecular partners, and physiological/pathophysiological implications. *Life* 2021; **11**:1–19.
116. Dörr J, Fecher-Trost C. TRP channels in female reproductive organs and placenta. *Adv Exp Med Biol* 2011; **704**:909–928.
117. Belkacemi L, Bédard I, Simoneau L, Lafond J. Calcium channels, transporters and exchangers in placenta. *Cell Calcium* 2005; **37**: 1–8.
118. Jakoubek V, Bíbová J, Hampl V. Voltage-gated calcium channels mediate hypoxic vasoconstriction in the human placenta. *Placenta* 2006; **27**:1030–1033.
119. Suzuki Y, Watanabe M, Saito CT, Tominaga M. Expression of the TRPM6 in mouse placental trophoblasts; potential role in maternal–fetal calcium transport. *J Physiol Sci* 2017; **67**:151–162.
120. Riquelme G. Apical maxi-chloride channel from human placenta: 12 years after the first electrophysiological recordings. *Biol Res* 2006; **39**:437–445.
121. Vallejos C, Riquelme G. The maxi-chloride channel in human syncytiotrophoblast: A pathway for taurine efflux in placental volume regulation? *Placenta* 2007; **28**:1182–1191.
122. Wareing M. Oxygen sensitivity, potassium channels, and regulation of placental vascular tone. *Microcirculation* 2014; **21**:58–66.
123. Williams JLR, Fyfe GK, Sibley CP, Baker PN, Greenwood SL. K+ channel inhibition modulates the biochemical and morphological differentiation of human placental cytotrophoblast cells in vitro. *Am J Physiol Regul Integr Comp Physiol* 2008; **295**: 1204–1213.

124. Díaz P, Sibley CP, Greenwood SL. Oxygen-sensitive K+ channels modulate human chorionic gonadotropin secretion from human placental trophoblast. *PLoS One* 2016; **11**:1–15.
125. Kiernan MF, Barrie A, Szkolar J, Mills TA, Wareing M. Functional evidence for oxygen-sensitive voltage-gated potassium channels in human placental vasculature. *Placenta* 2010; **31**:553–555.
126. Jewsbury S, Baker PN, Wareing M. Relaxation of human placental arteries and veins by ATP-sensitive potassium channel openers. *Eur J Clin Invest* 2007; **37**:65–72.
127. Warrington JP, Coleman K, Skaggs C, Hosick PA, George EM, Stec DE, Ryan MJ, Granger JP, Drummond HA. Heme oxygenase-1 promotes migration and β-epithelial Na+ channel expression in cytotrophoblasts and ischemic placentas. *Am J Physiol Regul Integr Comp Physiol* 2014; **306**:641–646.
128. Del Mónaco SM, Marino GI, Assef YA, Damiano AE, Kotsias BA. Cell migration in BeWo cells and the role of epithelial sodium channels. *J Membr Biol* 2009; **232**:1–13.
129. Ducza E, Csányi A, Gáspár R. Aquaporins during pregnancy: their function and significance. *Int J Mol Sci* 2017; **18**:2593.
130. Kordowitzki P, Kranc W, Bryl R, Kempisty B, Skowronska A, Skowronski MT. The relevance of aquaporins for the physiology, pathology, and aging of the female reproductive system in mammals. *Cell* 2020; **9**:1–25.
131. Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. *Early Hum Dev* 2007; **83**:699–706.
132. Banderali G, Martelli A, Landi M, Moretti F, Betti F, Radaelli G, Lassandro C, Verduci E. Short and long term health effects of parental tobacco smoking during pregnancy and lactation: a descriptive review. *J Transl Med* 2015; **13**:1–7.
133. Bao J, Liu Y, Yang J, Gao Q, Shi SQ, Garfield RE, Liu H. Nicotine inhibits LPS-induced cytokine production and leukocyte infiltration in rat placenta. *Placenta* 2016; **39**:77–83.
134. Chen J, Qiu M, Huang Z, Chen J, Zhou C, Han F, Qu Y, Wang S, Zhuang J, Li X. Nicotine suppresses the invasiveness of human trophoblasts by downregulation of CXCL12 expression through the alpha-7 subunit of the nicotinic acetylcholine receptor. *Reprod Sci* 2020; **27**:916–924.
135. Zhou J, Liu F, Yu L, Xu D, Li B, Zhang G, Huang W, Li L, Zhang Y, Zhang W, Wang H. nAChRs-ERK1/2-Egr-1 signaling participates in the developmental toxicity of nicotine by epigenetically down-regulating placental 11β-HSD2. *Toxicol Appl Pharmacol* 2018; **344**:1–12.
136. Dowling O, Rochelson B, Way K, Al-Abed Y, Metz CN. Nicotine inhibits cytokine production by placenta cells via NFκB: Potential role in pregnancy-induced hypertension. *Mol Med* 2007; **13**:576–583.
137. Holloway AC, Salomon A, Soares MJ, Garnier V, Raha S, Sergent F, Nicholson CJ, Feige JJ, Benharouga M, Alfaidy N. Characterization of the adverse effects of nicotine on placental development: in vivo and in vitro studies. *Am J Physiol Endocrinol Metab* 2014; **306**:E443–E456.
138. Wong MK, Holloway AC, Hardy DB. Nicotine directly induces endoplasmic reticulum stress response in rat placental trophoblast giant cells. *Toxicol Sci* 2016; **151**:23–34.
139. Zhu Y, Tan YQ, Leung LK. Aflatoxin B1 disrupts transient receptor potential channel activity and increases COX-2 expression in JEG-3 placental cells. *Chem Biol Interact* 2016; **260**:84–90.
140. Zhu Y, Yao X, Leung LK. Zeranol induces COX-2 expression through TRPC-3 activation in the placental cells JEG-3. *Toxicol Vitr* 2016; **35**:17–23.
141. Lee JH, Ahn C, Kang HY, Hong EJ, Hyun SH, Choi KC, Jeung EB. Effects of octylphenol and bisphenol A on the metal cation transporter channels of mouse placentas. *Int J Environ Res Public Health* 2016; **13**:1–13.
142. Yuan M, Hu M, Lou Y, Wang Q, Mao L, Zhan Q, Jin F. Environmentally relevant levels of bisphenol A affect uterine decidualization and embryo implantation through the estrogen receptor/serum and glucocorticoid-regulated kinase 1/epithelial sodium ion channel α-subunit pathway in a mouse model. *Fertil Steril* 2018; **109**:735–744.e1.
143. Tewari N, Kalkunte S, Murray DW, Sharma S. The water channel aquaporin 1 is a novel molecular target of polychlorinated biphenyls for in utero anomalies. *J Biol Chem* 2009; **284**:15224–15232.
144. Marino GI, Assef YA, Kotsias BA. The migratory capacity of human trophoblastic BeWo cells: Effects of aldosterone and the epithelial sodium channel. *J Membr Biol* 2013; **246**:243–255.
145. Sharma SC, Rao AJ. Effect of calcium ion channel antagonists on chorionic gonadotropin secretion. *Biochem Mol Biol Int* 1997; **43**:1101–1106.
146. Henriquez M, Riquelme G. 17β-Estradiol and tamoxifen regulate a maxi-chloride channel from human placenta. *J Membr Biol* 2003; **191**:59–68.
147. Stasenko S, Bradford EM, Piasek M, Henson MC, Varnai VM, Jurasović J, Kušec V. Metals in human placenta: focus on the effects of cadmium on steroid hormones and leptin. *J Appl Toxicol* 2010; **30**:242–253.
148. Kovacs G, Montalbetti N, Franz MC, Graeter S, Simonin A, Hediger MA. Human TRPV5 and TRPV6: key players in cadmium and zinc toxicity. *Cell Calcium* 2013; **54**:276–286.
149. Khattar V, Wang L, Bin PJ. Calcium selective channel TRPV6: Structure, function, and implications in health and disease. *Gene* 2022; **817**:146192.
150. Nelson W, Adu-Gyamfi EA, Czika A, Wang YX, Bin DY. Bisphenol A-induced mechanistic impairment of decidualization. *Mol Reprod Dev* 2020; **87**:837–842.
151. Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, Chevrier C, Eggesbø M, Guxens M, Krämer U, Legler J, Martínez D *et al.* Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European Birth Cohorts. *Environ Health Perspect* 2012; **162**:162–170.
152. Svensson BG, Hallberg T, Nilsson A, Schütz A, Hagmar L. Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. *Int Arch Occup Environ Health* 1994; **65**:351–358.
153. Grandjean P, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B, Debes F, Murata K, Simonsen H, Ellefsen P, Budtz-Jorgensen E, Keiding N *et al.* Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol Teratol* 2001; **23**:305–317.
154. Aralla M, Mobasheri A, Groppetti D, Cremonesi F, Arrighi S. Expression of aquaporin water channels in canine fetal adnexa in respect to the regulation of amniotic fluid production and absorption. *Placenta* 2012; **33**:502–510.
155. Stenhouse C, Halloran KM, Hoskins EC, Newton MG, Moses RM, Seo H, Dunlap KA, Satterfield MC, Gaddy D, Johnson GA, Wu G, Suva LJ *et al.* Effects of exogenous progesterone on the expression of mineral regulatory molecules by ovine endometrium and placentomes. *Biol Reprod* 2022; **106**:1126–1142.