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Pré-eclâmpsia e transportadores iônicos: uma revisão da literatura

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RESUMO

Introdução: A pré-eclâmpsia (PE) é atualmente uma das complicações mais comuns em obstetrícia, envolvendo de 3 a 5% de todas as gestações, e está entre as três principais causas de morbimortalidade materna e perinatal no mundo. A manifestação clínica se dá através da hipertensão gestacional após a 20° semana de gestação. Essa hipertensão deve estar acompanhada por proteinúria e/ou disfunções maternas de órgãos-alvo como, complicações neurológicas, edema pulmonar, trombose microvascular, insuficiência renal, lesão hepática, e/ou disfunção uteroplacentária. A fisiopatologia da PE é complexa e ainda não bem definida. Evidências crescentes sugerem que a regulação dos canais iônicos pode desempenhar um papel fundamental nas adaptações da circulação uterina durante a placentação. Na gestação, os canais iônicos têm papel importante na homeostase do meio materno-fetal, visto que auxiliam na passagem de nutrientes e outros compostos químicos entre a mãe e o feto, regulam a síntese e secreção de hormônios, auxiliam na migração de células trofoblásticas, controlam o transporte de elementos e regulam a contração e o relaxamento de células musculares lisas dos vasos sanguíneos. **Objetivos:** Elaborar uma revisão narrativa compilando os trabalhos que descrevem o envolvimento dos transportadores iônicos na pré-eclâmpsia. **Métodos:** Foram rastreados os trabalhos na literatura científica, na base de dados MEDLINE e EMBASE. Como critérios de inclusão foram utilizadas publicações em inglês com resumos disponíveis de janeiro de 2000 a abril de 2023, com os descritores “transportador de membrana”, “canais iônicos” e “pré-eclâmpsia”, com o uso de operadores booleanos. Foram selecionados os artigos de pesquisa original que descreviam algum método de estudo dos canais iônicos na PE, além de

artigos adicionais usados na construção da narrativa do texto, que descrevem características da pré-eclâmpsia e dos transportadores iônicos. Artigos duplicados na busca foram excluídos. **Resultados e Conclusões:** Foram arrolados 157 artigos científicos para elaboração da revisão narrativa, evidenciando o papel das principais famílias de transportadores iônicos entre tecido placentário, células primárias e tecido do cordão umbilical de todos os trimestres da gravidez de pacientes com PE, ensaios laboratoriais em células de cultivo, expressão de mRNA e experimentos em animais induzidos à PE. Em gestações complicadas, como em pacientes com PE, inúmeros estudos apontaram que, em condições prejudiciais, como na hipóxia e no estresse oxidativo, os canais iônicos são regulados negativamente e sua atividade é prejudicada. Assim, identificar as alterações em vias de sinalização dependentes de íons é imprescindível para compreender mais claramente a fisiopatologia da PE, visto que em caso de desregulação e/ou supressão de transportadores iônicos, a gravidez pode vir a apresentar complicações.

Palavras-chave: Pré-eclâmpsia. Canais iônicos. Placenta.

ABSTRACT

Introduction: Preeclampsia (PE) is currently one of the most common complications in obstetrics, complicating 3-5% of all pregnancies, and is among the top three causes of maternal and perinatal morbidity and mortality in the world. The clinical manifestation is through gestational hypertension after the 20th week of pregnancy. Such hypertension must be accompanied by proteinuria and/or maternal end-organ dysfunction such as neurological complications, pulmonary edema, microvascular thrombosis, renal failure, liver damage, and/or uteroplacental dysfunction. The pathophysiology of PE is complex and not yet well defined. Growing evidence suggests that ion channel regulation may play a key role in uterine circulation adaptations during placentation. During pregnancy, ion channels play an important role in the homeostasis of the maternal-fetal environment, as they help in the passage of nutrients and other chemical compounds between the mother and the fetus, regulate the synthesis and secretion of hormones, help in the migration of trophoblastic cells, they control the transport of elements and regulate the contraction and relaxation of smooth muscle cells in blood vessels. **Objectives:** To elaborate a narrative review compiling works that describe the involvement of ionic transporters in pre-eclampsia. **Methods:** We searched for all papers in the scientific literature, in the MEDLINE and EMBASE databases, restricting our query to publications in English with abstracts available from January 2000 to April 2023, with the descriptors “membrane transporter”, “ion channels” and “pre-eclampsia”, using Boolean operators. Original research articles that described some method of studying ion channels in PE were selected, as well as additional articles used in the construction of the text's narrative, which describe characteristics of preeclampsia and ion

transporters. Duplicate articles were excluded. **Results and Conclusions:** 157 scientific articles were used to prepare the narrative review, highlighting the role of the main families of ionic transporters between placental tissue, primary cells and umbilical cord tissue from all trimesters of pregnancy in patients with PE, laboratory tests on cells of cultivation, mRNA expression and experiments in animals induced to PE. In complicated pregnancies, such as in patients with PE, numerous studies have shown that, under harmful conditions, such as hypoxia and oxidative stress, ion channels are negatively regulated and their activity is impaired. Thus, identifying alterations in ion-dependent signaling pathways is essential to understand the pathophysiology of PE more clearly, since in the event of deregulation and/or suppression of ion transporters, pregnancy may become complicated.

Keywords: Pre-eclampsia. Ion channels. Placenta.

LISTA DE ABREVIATURAS

(H^+/K^+-ATPase): Hidrogênio-Potássio Adenosina trifosfatase

(H^+-ATPase): Hidrogênio Adenosina trifosfatase

(Na^+/K^-- ATPase): Sódio-Potássio Adenosina trifosfatase

AQP: Aquaporina

ATP: Trifosfato de adenosina

ATPase: Adenosina trifosfatase

Ca^{2+}: Cálcio

CACNA2D3: Subunidade auxiliar de canal fechado por tensão de cálcio alpha 2 delta 3

CIC: Canais de cloreto (do inglês, *chloride channels*)

Cl^-: Cloreto

CLICs: Canais iônicos intracelulares de cloreto (do inglês, *chloride intracelular ion channels*)

ENaC: Canais de sódio epiteliais (do inglês, *epithelial sodium channels*)

ER: Receptores de estrogênio (do inglês, estrogen receptors)

FIGO: Federação Internacional de Ginecologia e Obstetrícia

ICT: Canais e transportadores de íons (do inglês, *ion channels and transporters*)

K^+: Potássio

K2P: Canais de potássio de domínio de dois poros (do inglês, *two-pore domain*

potassium channels)

KCa: Canais de potássio ativados por cálcio

Kir: Canais de potássio retificadores internos

LH: Hormônio luteinizante (do inglês, *luteinizing hormone*)

Na^+: Sódio

PR: Receptor de progesterona (do inglês, *progesterone receptor*)

PE: Pré-eclâmpsia

ROCCs: Canais de cálcio operados por receptor (do inglês, *receptor-operated calcium channels*)

SAICs: Canais iônicos ativados por estiramento (do inglês, *stretch-activated calcium channel*)

SOCCs: Canais de cálcio operados por armazenamento (do inglês, *store- operated calcium channels*)

TRP: Potencial receptor transitório (do inglês, *transient receptor potential*)

VDAC: Canal aniônico dependente de voltagem (do inglês, *voltage-dependent anion channel*)

VGCCs: Canais de cálcio controlados por voltagem (do inglês, *voltage-gated calcium channels*)

VGKC: Canais de potássio dependentes de voltagem (do inglês, *voltage-gated potassium channel*)

VGSC: Canais de sódio dependentes de voltagem (do inglês, *voltage-gated sodium channel*)

SUMÁRIO

1 REFERENCIAL TEÓRICO

1.1 Pré-eclâmpsia

A pré-eclâmpsia (PE) é atualmente uma das complicações mais comuns em obstetrícia, ocorrendo em 3-5% de todas as gestações (1), e está entre as três principais causas de morbimortalidade materna e perinatal no mundo (2). Em relação a apresentação clínica, a Sociedade Internacional para o Estudo da Hipertensão na Gravidez (ISSHP), de 2021, define a PE como a hipertensão gestacional (PA sistólica elevada ≥140 mmHg e/ou PA diastólica ≥90 mmHg em 2 mensurações com intervalo de 4 horas em repouso ou PAS ≥160 mmHg ou PAD ≥110 mmHg em 1 ocasião) (3,4), de início recente, ou seja, após a 20° semana de gestação. Essa hipertensão gestacional deve estar acompanhada por uma ou mais das seguintes condições: proteinúria (≥ 30 mg/mmol de proteína urinária, relação creatinina em uma amostra de urina pontual (aleatória), ou relação albumina, creatinina ≥ 8 mg/mmol, ou ≥ 0,3 g/dL em uma coleta completa de urina de 24 horas ou ≥ 2 + por fita reagente se o teste confirmatório não estiver disponível), disfunções maternas de órgãos-alvo, como complicações neurológicas, edema pulmonar, complicações hematológicas por hemoconcentração relativa, neutrofilia relativa, trombose microvascular, hemólise e consumo de plaquetas (5), insuficiência renal, lesão hepática por inflamação periportal e lesão hepatocelular, e/ou disfunção uteroplacentária, como descolamento prematuro da placenta, desequilíbrio angiogênico e restrição do crescimento fetal (6).

A fisiopatologia da PE é complexa e ainda não bem definida. Atualmente, sabe-se que a PE envolve fatores de risco adquiridos, genéticos e imunológicos, e seu quadro clínico resolve-se, na maioria dos casos, após o parto (4). De modo

geral, há uma disfunção endotelial que prejudica o desenvolvimento da insensibilidade aos vasoconstritores necessários para manter a pressão arterial normal (7). Ademais, em relação à placentação, o remodelamento prejudicado das artérias espiraladas uterinas, bem como a invasão trofoblástica prejudicada, provocam uma queda na perfusão uteroplacentária e, consequentemente, hipóxia placentária. Essa hipóxia, afeta diferentes vias de sinalização celular, resultando em aumento de vasoconstritores, como tromboxano A1 e endotelinas, e em diminuição de vasodilatadores, como prostaciclina (PGI2), óxido nítrico e fator hiperpolarizante derivado do endotélio (EDHF), criando intensa vasoconstrição (8,9). Esses desarranjos, por fim, resultam em disfunção endotelial e atenuam a vasodilatação dependente do endotélio devido ao estresse oxidativo e, subsequentemente, a um estado inflamatório generalizado em comparação com a gravidez normal. Além disso, a placentação anormal promove liberação de marcadores antiangiogênicos que promovem disfunção endotelial, vasoconstrição e desregulação imunológica. Essa série de alterações afeta negativamente órgãos maternos, provocando as inúmeras condições clínicas já mencionadas acima (10,11).

A circulação feto-placentária medeia a troca de nutrientes e resíduos entre os sistemas materno e fetal e, assim, fornece oxigênio e nutrientes adequados para o desenvolvimento fetal normal (12). Essa capacidade de fornecimento nutricional, em uma gestação normal, se dá pela adaptação da circulação uterina à gravidez. Esse cenário é mediado, pelo menos em parte, pelo aumento da vasodilatação, diminuição do tônus vascular e remodelação vascular (13). Embora os mecanismos que contribuem para a diminuição do tônus vascular uterino e aumento significativo do fluxo sanguíneo uterino durante a gravidez não sejam completamente compreendidos, evidências crescentes sugerem que a regulação dos canais iônicos

pode desempenhar um papel fundamental nas adaptações da circulação uterina durante a placentação (13,14,15,16,17,18). Além disso, os mecanismos subjacentes à contração e relaxamento das células musculares lisas são dependentes das alterações do potencial de membrana, que, por sua vez, são afetados por alterações da condutância iônica via canais iônicos e transportadores. Assim, identificar as alterações em vias de sinalização dependentes de íons é imprescindível para compreender mais claramente a fisiopatologia de doenças gestacionais, como a PE, visto que em caso de desregulação e/ou supressão de transportadores iônicos, a gravidez pode vir a se tornar complicada.

Portanto, o objetivo deste estudo é realizar uma revisão narrativa da literatura, buscando a relação dos transportadores de membrana mais estudados em tecidos retirados de gestantes com a PE, como placenta, vilos e vasos umbilicais, visando encontrar a relevância funcional das alterações desses canais e seus impactos clínicos sugeridos. Logo, com o entendimento de diferentes estudos na área, será possível elucidar o papel dos canais iônicos na fisiopatologia da PE.

1.2 Canais iônicos

Etapas de processos fisiológicos como equilíbrio do pH, respostas imunes, secreção, contração muscular, regulação do volume e do ciclo celular e sinais elétricos (nervos, músculos e sinapses) são mediados pelo movimento de íons entre o fluido intracelular e extracelular (19). Canais e transportadores de íons (*ion channels and transporters*, ICT) são proteínas transmembrana que controlam estritamente o movimento de íons através da membrana celular, mantendo os gradientes iônicos das células. Desta forma, os ICTs auxiliam na natureza seletivamente permeável da membrana celular, funcionando como portas de entrada

para íons carregados que não podem se difundir livremente através das barreiras da membrana lipídica (20).

Os canais iônicos se caracterizam por serem excelentes translocadores, pois agem de forma rápida e possuem poros que permitem que íons específicos atravessem a membrana em favor de um gradiente eletroquímico. Alguns canais, ao exemplo dos que dependem da voltagem, têm a condição de responder a variações de potencial elétrico, abrindo ou fechando em resposta à magnitude do potencial de membrana. Canais iônicos também podem ser controlados por sinais químicos extracelulares (neurotransmissores) e intracelulares (segundo mensageiro) ou podem responder a estímulos mecânicos e térmicos. Em oposição a esses fatores, os transportadores (também chamados de bombas de íons) realizam movimentações de forma lenta e o movimento de íons ocorre ativamente contra o gradiente de concentração usando energia, tipicamente na forma de trifosfato de adenosina (ATP) (19,20).

1.2.1 Canais de Potássio

Os canais de potássio (K^+) são caracterizados por serem uma família complexa de canais iônicos e podem receber quatro divisões quanto as suas classes: (I) Canais de potássio dependentes de voltagem (VGKC), (II) Canais de potássio ativados por cálcio (KCa), (III) Canais de potássio retificadores internos (Kir) e (IV) Canais de potássio de domínio de dois poros (K2P) (20). Os níveis de K^+ podem desempenhar papel importante no controle do potencial de membrana, determinação e duração do potencial de ação, modulação da secreção de hormônios e equilíbrio dos sinais excitatórios nas células (21).

Alterações no ciclo celular em células que apresentam tumores são

relacionadas à perda de função ou expressão alterada de canais de K^+ em vários tipos de tumores (20). No caso de VGKC e KCa, o controle da proliferação de células tumorais pode ocorrer através da modulação do potencial de membrana (Vm), que por sua vez regula o fluxo transmembrana de cálcio (Ca^{2+}). Os níveis intracelulares de Ca^{2+} participam no controle dos checkpoints do ciclo celular, na proliferação normal e neoplásica (22).

1.2.2 Canais de Sódio

Há dualidade entre tipos diferentes de canais de sódio (Na^+): (I) canais de sódio dependentes de voltagem (*voltage-gated sodium channel*, VGSC) e (II) canais de sódio epitelial (*epitelial Na^+ channel*, ENaC). Presentes em epitélios absortivos (como túbulos torcidos distais dos rins, cólon, pulmão e ducto da glândula salivar), os ENaC têm relação com a absorção de Na^+ e desempenham papéis fundamentais na manutenção da homeostase do íon sódio, que está diretamente ligada à regulação do volume de líquido extracelular (23). Entretanto, os VGSC estão envolvidos na fase inicial do potencial de ação na maioria das células, sendo importantes na geração e propagação do potencial de ação (20).

Os VGSC apresentam em sua formação principal a glicoproteína de membrana integral de múltiplas extensões formadoras de poros (subunidade α) que pode ser associada a uma ou mais subunidades β reguladoras. As subunidades β são proteínas integrais de membrana que modulam a corrente de sódio e podem atuar como moléculas de adesão celular em termos de interação com moléculas da matriz extracelular, comunicação entre células adjacentes, regulação da migração celular, agregação celular e interação com o citoesqueleto (24). A expressão/função

aberrante de VGSCs está relacionada à migração celular, invasão e metástase tumoral (20).

1.2.3 Canais de Cloreto

O cloreto (Cl^-) se caracteriza por ser o ânion em maior quantidade nos espaços extra e intracelular e o transporte de Cl^- através da membrana plasmática está envolvido em vários processos fisiológicos, desde a homeostase até o controle do volume e regulação das células excitáveis (25). Os canais de cloreto (ClC) são uma família de canais aniônicos que medeiam o transporte de íons Cl^- através da célula. Eles podem desempenhar sua função ao atuarem por dependência de voltagem, desencadeados pelo cálcio, ou ativados por vários ligantes e segundos mensageiros e podem ser divididos em duas grandes classes: canais de Cl voltagem-dependentes da família ClC e a condutância transmembrana da fibrose cística regulador (CFTR) (26).

A desregulação dos canais de Cl^- foi detectada em uma grande diversidade de cânceres, relacionada à migração celular, invasão e metástase (25). O canal iônico intracelular de Cl (CLICs) é uma classe emergente de canais envolvida no desenvolvimento do câncer (27). O CFTR se expressa nas células epiteliais de vários tecidos e órgãos. Embora o CFTR defeituoso esteja bem descrito como associado à fibrose cística, a desregulação no CFTR pode promover ou suprimir a progressão do câncer (28).

1.2.4 Canais de Cálcio

O cálcio se destaca por ser um importante íon sinalizador e serve como

segundo mensageiro para vários processos celulares fundamentais, como controle do ciclo celular, migração e apoptose (29). A regulação dos níveis de Ca^{2+} intracelular envolve o fluxo de Ca^{2+} através da membrana plasmática e a liberação de estoques de Ca^{2+} intracelular no retículo endoplasmático e nas mitocôndrias (20).

Os canais de Ca^{2+} têm sua ativação realizada em grande parte em resposta à despolarização da membrana e, além disso, medeiam o influxo de cálcio em resposta a potenciais de ação e sinais despolarizantes (30). Os canais de cálcio recebem suas classificações de acordo com seu mecanismo de ativação: (I) Canais de cálcio controlados por voltagem (*voltage-gated calcium channels*, VGCCs), (II) canais de cálcio operados por receptor (*receptor-operated calcium channels*, ROCCs), (III) canais de cálcio operados por armazenamento (*store-operated calcium channels*, SOCCs), (IV) canais de potencial receptor transiente (*transient receptor potential*, TRPs), (V) canais iônicos sensíveis a ácido (*acid-sensitive ion channels*, ASICs) e (VI) canais iônicos ativados por estiramento (*stretch-activated ion channels*, SAICs) (31).

Tais canais se destacam por desempenhar importantes papéis na fisiologia humana e não é surpresa que disfunções dos canais de cálcio estejam associadas a proliferação, sobrevivência, angiogênese e migração de células tumorais (20, 31, 32,33).

1.2.5 Aquaporinas

Aquaporinas (AQP) se destacam por serem proteínas integrais de membrana que servem como canais e permitem a regulação do transporte de água essencial à homeostase em resposta a gradientes osmóticos criados pelo transporte ativo de

solutos. As isoformas de AQP identificadas em mamíferos se apresentam em diversos órgãos e tecidos e estão envolvidas em muitas funções biológicas. A expressão alterada de AQP está relacionada à carcinogênese em diversos tecidos, especialmente motilidade, invasividade e angiogênese (34, 35).

1.3 Canais iônicos e seu papel na pré-eclâmpsia

Os canais iônicos são proteínas formadoras de poros, que permitem o fluxo de íons através das membranas e tem como principal função a seletividade. Além disso, os canais iônicos têm a capacidade de mutação, conforme o meio exposto e o estímulo recebido. Eles podem ser divididos em vários subtipos, dependendo do tipo de íon transportado e da forma de sua ativação. Muitos canais iônicos são controlados por voltagem, outros são controlados por segundos mensageiros e outros ainda por mediadores intracelulares e/ou extracelulares (36).

Na gestação, os canais iônicos têm papel importante na homeostase do meio materno-fetal, visto que auxiliam na passagem de nutrientes e outros compostos químicos entre mãe e feto. Na placenta, por exemplo, eles têm funções imprescindíveis, como regulação de síntese e secreção de hormônios, migração de células trofoblásticas, controle do transporte de elementos e regulação da contração/ relaxamento de células musculares lisas dos vasos sanguíneos (37).

Em gestações complicadas, como em pacientes com PE, inúmeros estudos apontaram que, em condições prejudiciais, como na hipóxia e no estresse oxidativo, os canais iônicos são regulados negativamente e sua atividade é prejudicada (38, 39, 40). Portanto, o objetivo deste estudo é realizar uma revisão narrativa da literatura, buscando a relação dos transportadores de membrana mais estudados em

tecidos retirados de gestantes com PE, visando encontrar a relevância funcional das alterações nesses transportadores e suas sugestões impactos clínicos. Portanto, com o entendimento de diferentes estudos na área, será possível elucidar o papel dos transportadores de íons na fisiopatologia da EP.

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3 OBJETIVOS

3.1 Objetivo geral

Avaliar o papel dos transportadores iônicos na fisiopatologia da pré-eclâmpsia.

3.2 Objetivo específico

Abordar, na revisão, possíveis alterações na expressão e função com alterações em:

- tônus vascular;
- balanço hídrico;
- migração e invasão trofoblástica;
- proliferação celular.

4 ARTIGO CIENTÍFICO

“Preeclampsia and ionic transporters: a literature review”

Thaís Duarte Borges de Moura, Fernanda Bordignon Nunes, Bianca Dalla Vecchia Crestani, Thales Fernando Canabarro Araujo, Eduarda Luiza Hanauer, Helena von Eye Corleta and Gisele Branchini

Preeclampsia and ionic transporters: a literature review

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Abstract

Preeclampsia (PE) is currently one of the most common complications in obstetrics, involving 3-5% of all pregnancies, and is among the top three causes of maternal and perinatal morbidity and mortality in the world. The clinical manifestation is through gestational hypertension after the 20th week of pregnancy. Such hypertension must be accompanied by proteinuria and/or maternal end-organ dysfunction such as neurological complications, pulmonary edema, microvascular thrombosis, renal failure, liver damage, and/or uteroplacental dysfunction. The pathophysiology of PE is complex and not yet well defined. What is currently known is that PE involves acquired, genetic, and immunological risk factors. Overall, placentation is impaired due to insufficient remodeling of the uterine spiral arteries as well as impaired trophoblastic invasion. This pathological picture causes a drop in uteroplacental perfusion and, consequently, local hypoxia. Hypoxia, in the end, promotes endothelial dysfunction, vasoconstriction and immune dysregulation, resulting in the aforementioned clinical changes. Growing evidence suggests that ion transporter regulation may play a key role in uterine circulation adaptations during placentation. During pregnancy, ion transporters play an important role in the homeostasis of the maternal-fetal environment, as they help in the passage of nutrients and other chemical compounds between the mother and the fetus. Ion transporters also regulate the synthesis and secretion of hormones, help in the migration of trophoblastic cells, they control the transport of elements and regulate the contraction and relaxation of smooth muscle cells in blood vessels. In complicated pregnancies, such as in patients with PE, numerous studies have shown that, under harmful conditions, such as hypoxia and oxidative stress, ion transporters are negatively regulated and their activity is impaired. Thus, identifying alterations in ion-dependent signaling pathways is essential to understand the pathophysiology of PE more clearly, since in the event of deregulation and/or suppression of ion transporters, pregnancy may become complicated. Therefore, the aim of this study was to carry out a narrative review of the literature, seeking the relationship of the most studied membrane transporters in PE, aiming to find the functional relevance of changes in these transporters and their organic impacts. Therefore, with the understanding of different studies on the subject, it will be possible to elucidate the role of ion transporters in the pathophysiology of PE.

Introduction

Preeclampsia (PE) is currently one of the most common obstetric disease, involving 3-5% of all pregnancies [1], and is among the top three causes of maternal and perinatal morbidity and mortality worldwide [2]. Regarding clinical presentation, the International Society for the Study of Hypertension in Pregnancy (ISSHP) defines PE as gestational hypertension after the 20th week of gestation [3,4]. This gestational hypertension must be accompanied by one or more of the following conditions: proteinuria, maternal target organ dysfunction and/or uteroplacental dysfunction [5,6].

The pathophysiology of PE is complex and not yet well defined. Currently, it is known that PE involves acquired, genetic and immunological risk factors, and its clinical picture resolves after delivery [4]. There is usually endothelial dysfunction that compromises the vascular physiology necessary to maintain normal blood pressure [7]. Furthermore, regarding placentation, impaired remodeling of the uterine spiral arteries, as well as impaired trophoblastic invasion, cause a drop in uteroplacental perfusion and, consequently, placental hypoxia. This hypoxia affects cellular signaling pathways, resulting in an increase in vasoconstrictors, such as thromboxane A1 and endothelin, and a decrease in vasodilators, such as prostacyclin (PGI2), nitric oxide and endothelium-derived hyperpolarizing factor (EDHF), creating intense vasoconstriction (resulting in hypertension) [8,9]. These derangements ultimately result in endothelial dysfunction and attenuate endothelium-dependent vasodilation due to oxidative stress and subsequently a generalized inflammatory state compared to normal pregnancy. In addition, abnormal placentation promotes the release of antiangiogenic markers that promote endothelial dysfunction, vasoconstriction and immune dysregulation. This series of alterations adversely affects maternal organs, causing the numerous clinical conditions already mentioned above [10,11].

Feto-placental circulation mediates the exchange of nutrients and waste between the maternal and fetal systems and thus provides adequate oxygen and nutrients for normal fetal development [12]. This nutritional supply capacity, in a normal pregnancy, is due to the adaptation of the uterine circulation to the pregnancy. This scenario is mediated, at least in part, by increased vasodilation, decreased vascular tone, and vascular remodeling [13]. Although the mechanisms that contribute to decreased uterine vascular tone and significantly increased uterine blood flow during pregnancy are not completely understood, increasing evidence suggests that ion transporter regulation may play a key role in uterine circulation adaptations during pregnancy [13-18]. Furthermore, the mechanisms underlying the contraction and relaxation of smooth muscle cells are dependent on changes in membrane potential, which, in turn, are affected by changes in ionic conductance via ion transporters and transporters. Thus, identifying alterations in ion-dependent signaling pathways is essential to understand more clearly the pathophysiology of gestational diseases, such as PE, since in the event of deregulation and/or suppression of ion transporters, pregnancy may become complicated.

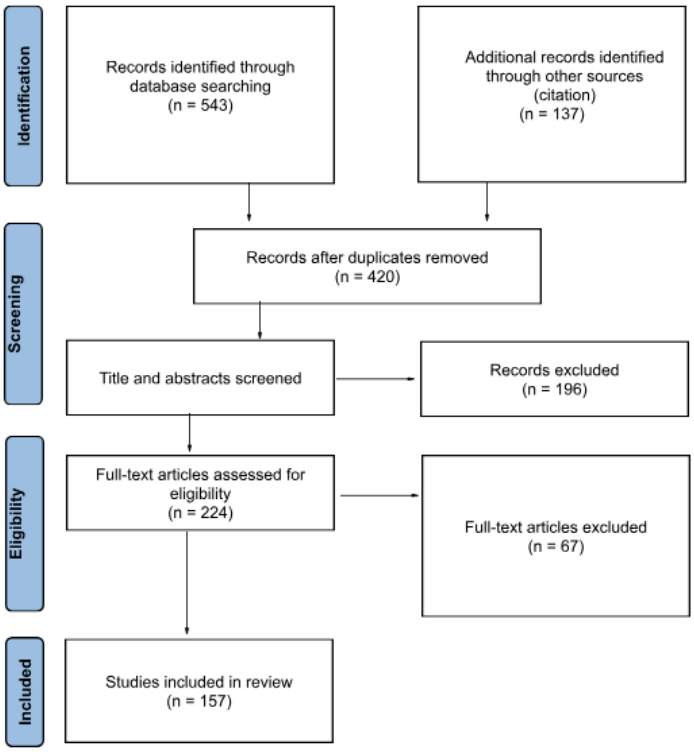
Therefore, the aim of this study is to carry out a narrative review of the literature, seeking the relationship of the most studied membrane transporters in tissues taken from pregnant women with PE, aiming to find the functional relevance of changes in these transporters and their suggested clinical impacts. Therefore, with the understanding of different studies in the area, it will be possible to elucidate the role of ion transporters in the pathophysiology of PE.

Scientific methodology

Regarding the methodology, two databases were searched, MEDLINE and EMBASE, restricting the consultation to publications in English with abstracts available from January 2000 to April 2023. The descriptors used were “pre-eclampsia and ion transporter”. After reading the title and abstract, studies were selected that evaluated ionic transporters between placental tissue, primary cells and umbilical cord tissue from all trimesters of pregnancy in patients with PE, as well as laboratory tests in cell culture, mRNA expression analysis and PE induction in animal experiments. Articles that did not address ionic transporters or that only addressed the ion or chemical element in isolation were excluded. Then, when examining the full text of the articles, studies that did not deal with membrane

transporters and receptors were excluded. Finally, data on the characteristics and results of the studies selected to compile this review were collected. The selection is shown in Figure 1.

Fig. 1. Flow diagram showing the study selection process.



Preeclampsia and ionic transporters

Ion transporters are pore-forming proteins that allow the flow of ions across membranes and have selectivity as their main function. In addition, ion transporters have the ability to mutate, depending on the environment exposed and the stimulus received. They can be divided into several subtypes, depending on the type of ion transported and the way of its activation. Many ion transporters are controlled by voltage, others are controlled by second messengers, and still others by intracellular and/or extracellular mediators [19].

During pregnancy, ion transporters play an important role in the homeostasis of the maternal-fetal environment, as they help in the passage of nutrients and other chemical compounds between mother and fetus. In the placenta, for example, they have essential functions, such as regulation of hormone synthesis and secretion, trophoblastic cell migration, control of element transport, and regulation of contraction/relaxation of smooth muscle cells in blood vessels [20].

In complicated pregnancies, such as in patients with PE, numerous studies have shown that, under harmful conditions, such as hypoxia and oxidative stress, ion transporters are negatively regulated and their activity is impaired [13,15,21]. Table 1 shows the compiled data on the expression of ionic transporters in preeclamptic pregnancies.

Table 1 - The distribution of membrane transporters in the human placenta, primary cells and umbilical vessels in patients with preeclampsia

Transporter Name	Gene Name	Location in PE studies	References
Potassium Transporters			
Internal Rectifying Potassium Channels (Kir)			

Kir 2.1	*KCNJ2*	Syncytiotrophoblasts, blood vessels	[13,22]
Calcium-activated Potassium Transporters (KCa)			
K Ca 1,1	*KCNMA1*	Blood veins	[15,23,24,25]
Voltage-gated Potassium Channels (Kv)			
Kv3.1	*KCNE5*	Syncytiotrophoblasts	[26]
Kv7.1	*KCNQ1*	Placental tissue	[26]
Kv7.3	*KCNQ3*	Syncytiotrophoblasts, blood vessels	[15,26]
ATP-sensitive Potassium Transporter (KATP)			
Kir6.1/SUR2B	-	Umbilical artery	[27]
Potassium Pump			
Na+/K+-ATPase	-	Trophoblast, syncytiotrophoblasts, placental artery, umbilical vessels	[28-35]
Epithelial Sodium Transporters (ENaC)			
ENaCα	*SCNN1A*	Cytotrophoblast, syncytiotrophoblasts	[36]
ENaCβ	*SCNN1B*	Syncytiotrophoblasts	[36,37]
ENaCγ	*SCNN1C*	Syncytiotrophoblasts	[36,38]
Sodium Pump			
Na+/H+-3	-	Syncytiotrophoblast	[39]
Na+/Mg2+	-	Cytotrophoblast	[40,41]
Voltage-gated Calcium Transporters (Cav)			
Cav 1,1	*CACNA1S*	Syncytiotrophoblasts	[42]
Cav 1,2	*CACNA1C*	Syncytiotrophoblasts	[34,42-44]
Cav 1,3	*CACNA1D*	Syncytiotrophoblasts	[43,44]
Calcium Pump			
Ca2+-ATPase	*PMCA1 ATP2B1*	Syncytiotrophoblast, trophoblast, smooth muscle cells, human umbilical vein endothelial cells	[45-51]
Ca2+-ATPase	*SERCA2, ATP2A2*	Syncytiotrophoblast	[45]
Transient Receiver Potential (TRP)			
TRPC Subfamily (Canonical)			
TRPC3	*TRPC3*	Cytotrophoblast, syncytiotrophoblasts	[52]
TRPC4	*TRPC4*	Cytotrophoblast, syncytiotrophoblasts	[52]
TRPC6	*TRPC6*	Syncytiotrophoblasts	[52,53]
TRPM Subfamily (Melastatin)			
TRPM6	*TRPM6*	Trophoblasts	[54-56]
TRPM7	*TRPM7*	Trophoblasts	[54,55]
TRPV Subfamily (Vanilloid)			
TRPV1	*TRPV1*	Cytotrophoblast, syncytiotrophoblasts	[57-60]

TRPV5	*TRPV5 (ECaC1, CaT2)*	Syncytiotrophoblasts	[61]
TRPV6	*TRPV6 (ECaC2, CaT1)*	Cytotrophoblast, syncytiotrophoblasts	[61-63]
Chloride Transporter			
CIC Family (CLC)			
CIC-3	*CLCN2*	Cytotrophoblast, syncytiotrophoblasts, trophoblast	[64]
Maxi chloride channel			
Maxi-Cl	-	Syncytiotrophoblasts	[65-68]
Aquaporins (AQP)			
AQP1	*AQP1*	Cytotrophoblast, blood vessels das villi	[69,70]
AQP2	*AQP2*	Syncytiotrophoblasts, trophoblasts	[59]
AQP3	*AQP3*	Cytotrophoblast, syncytiotrophoblasts, villi	[71-74]
AQP4	*AQP4*	Syncytiotrophoblasts, villi, endothelial cells	[75]
AQP9	*AQP9*	Cytotrophoblast, syncytiotrophoblasts, villi	[76-79]
Nicotine Acetylcholine Receptors (nAChR) - Subunits			
nAchRα2	*CHRNA2*	Syncytiotrophoblasts, villi	[20,80]
nAchRα3	*CHRNA3*	Syncytiotrophoblasts, blood vessels	[81,80]
nAchRα4	*CHRNA4*	Syncytiotrophoblasts, blood vessels	[81,80]
nAchRα5	*CHRNA5*	Syncytiotrophoblasts, blood vessels	[81,80]
nAchRα6	*CHRNA6*	-	[81]
nAchRα7	*CHRNA7*	Cytotrophoblast, syncytiotrophoblast, villi, blood vessels	[80-85]
nAchRα9	*CHRNA9*	Syncytiotrophoblasts, villi, blood vessels	[81,80]
nAchRα10	*CHRNA10*	Syncytiotrophoblasts, blood vessels	[81]
nAchRβ1	*CHRNB1*	Villi	[81,80]
nAchRβ2	*CHRNB2*	Villi	[81,80]
nAchRβ4	*CHRNB4*	-	[81]
nAchRδ	*CHRND*	Villi	[81,80]
nAchRε	*CHRN*	-	[81]
GABA-type Receptors			
GABA A	*GABRP*	Trophoblasts	[86]
P2X Receptors			
P2X4	*P2RX4*	Cytotrophoblast, blood vessels	[87,88]
P2X7	*P2RX7*	Cytotrophoblast, blood vessels	[87,89]
Ryanodine receptors (RyRs)			
RyR1	*RYR1*	Cytotrophoblast, syncytiotrophoblasts	[90,91]
RyR2	*RYR2*	Syncytiotrophoblasts	[91]

RyR3	*RYR3*	Cytotrophoblast, syncytiotrophoblasts	[90,91]
Inositol 1,4,5-Triphosphate Receptors (IP3R)			
IP3R1	*ITPR1*	Syncytiotrophoblast	[90,91]
IP3R2	*ITPR2*	Syncytiotrophoblast	[90,91]
IP3R3	*ITPR3*	Syncytiotrophoblast	[90,91]

CaV, voltage-gated calcium channel; CLC, chloride channel; K2P, two-pore domain potassium channel; KCa, calcium-activated potassium channel; Kir, inwardly rectifying potassium channel; nAchR, nicotinic acetylcholine receptor; NaV, voltage-gated sodium channel; P2X, purinergic receptor P2X; 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.

1. Potassium Transporters

Potassium transporters are widely distributed in all cells of the human body and are related to several physiological functions, such as control of membrane potential, determination and duration of action potential, volume regulation and hormone secretion [92]. The four subfamilies of potassium channels currently studied in PE are the internal rectifying potassium channels, Kir; potassium channels activated by Ca(2+), KCa; potassium channels four segments transmembrane-2 pores, K2P; and voltage-gated potassium channels, Kv. In addition to these, it is worth mentioning the ATP-sensitive potassium channels and the Na+/K+-ATPase pump [27,28].

1.1 Internal rectifying potassium channels (Kir)

The family of internal rectifying potassium channels (Kir) comprises many subtypes of channels (Kir2.0, Kir 2.1–4 and Kir 6.0-2, Kir2.1) that are involved in maintaining the resting potential in different cells, in particular predominantly expressed in the smooth muscle of small diameter resistance vessels rather than in larger arteries [13]. In particular, there are many reports on the relationship between changes in this type of canal and pathologies during pregnancy [22]. One research group evaluated ion channels in the placenta, both normal and in pathological conditions, such as PE and intrauterine growth restriction. They observed an altered distribution of Kir2.1, Kv2.1 and K2p 3.1 channels in PE placentas between the apical and basolateral domains, which could impact transport across the placenta [22]. Kir channels are activated by membrane hyperpolarization, so an inward current of potassium is observed to restore the resting membrane potential. Kir channels provide the dominant conductance of potassium ions near the resting membrane potential and can modulate basal vascular tone as well as promote vasodilation in response to hypoxia [13]. Currently, our - group is carrying out a study on the expression of potassium and calcium channels in PE placentas, and we found greater expression of the Kir2.1 channel in PE placenta samples compared to placentas from normotensive pregnant women, while Kir3.4 and Kir6.4 showed lower expression in placenta PE (Leoterio et al., unpublished data). A proposed mechanism of hypoxia-mediated increase in uterine vascular tone during pregnancy is the inhibition of Kir channels through protein kinase C (PKC) [13]. Thus, the lower expression of Kir channels in the PE placenta could also be involved in the increased uterine vascular tone seen in this gestational disease.

1.2 Calcium-activated potassium channels (KCa)

Another class of potassium channels is the calcium-activated potassium (KCa) channels. Today, eight human calcium-activated channels are known: KCa1.1 (large conductance, BKCa or Maxi-K), KCa2.1 (small conductance, SK1), KCa2.2 (small conductance, SK2), KCa2.3 (small conductance, SK2). small conductance, SK3), KCa3.1 (intermediate/small conductance, IKCa or SK4), KCa4.1, KCa4.2 and KCa5.1 [93].

It is important to emphasize that KCa are involved in angiogenesis, since the blockade of these channels inhibits the secretion of vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) by endothelial cells and may be related to poor blood vessel formation and insufficient

remodeling of spiral arteries [94].
IKCa and SKCa are the main components of endothelium-dependent hyperpolarization factors (EDHFs) and are involved in the regulation of vascular tone, mainly in resistance vessels, through membrane hyperpolarization and, consequently, leading to vasodilation [95]. Furthermore, a study in mice showed that the KCa2.3 channel modulates placental vascular development and fetal health through VEGF signaling [96]. Thus, dysfunction of KCa channels may be related to malformation of blood vessels and insufficient remodeling of spiral arteries, promoting the occurrence and development of PE. Previous studies have shown a downregulation of IKCa and SKCa in placental chorionic plaque arteries in PE patients [17], in cultures of human umbilical vein endothelial cells with plasma from PE patients [97] and in endothelial cells of the uterine microvasculature via pathways mediated by superoxide [97-99]. However, in our studies, we did not observe differences in immunohistochemical expression of KCa3.1 (IK or SK4) in PE or normal placenta samples (Leoterio et al., unpublished data).
Worton et al. (2021) used kynurenine as a vasodilation promoting factor, and observed vasorelaxant effects on KCa1.1 channels located in vascular smooth muscle and are relatively selective for maternal arteries, with no direct relaxing effect on placental arteries [23]. Another study from 2020 points out that (−)-carveol acts on voltage-operated calcium channels and partially modulates KCa1.1 channels, thus promoting a vasorelaxant effect on the contractility of smooth muscle cells of human umbilical arteries [24]. Thus, a dysfunction of KCa1.1 channels may be related to vasoconstriction of maternal blood vessels, which would contribute to an increase in blood pressure in PE and, consequently, in cells of umbilical vessels.
Reinforcing this last point, studies suggest that increased oxidative stress in preeclamptic human primary umbilical vein endothelial cells may downregulate the NO system by suppressing KCa1.1 and SKCa channels [25]. As well as decreasing expression KCa1.1 can induce pathological remodeling, increase the resistance of and inhibit the reactivity of chorionic plaque arteries to NO [16]. Therefore, placental hypoxia, resulting from poor placentation, can produce direct effects not only on the uterine spiral arteries, but also on the vessels of the umbilical cord.

1.3 Four-segment transmembrane-2-pore potassium channels (K2P)

Two-pore potassium channels (K2P) play a role in determining the resting membrane potential and generate leakage currents [100]. Interestingly, these channels are subject to local regulation by physical and chemical factors in the vicinity that include pH, oxygen tension and lipids [100]. These channels are still poorly studied in maternal-fetal membranes, but they have already been identified in myometrial cells and placental vessels [100-102]. However, there are no studies linking these channels with preeclampsia. Further studies are essential, as hypoxia and alterations in the local pH may be factors that alter the expression of these channels and, consequently, alter the membrane potential of placental cells, impairing the entry of other ions.

1.4 Voltage-gated potassium channels (Kv)

Voltage-gated potassium channels (Kv) are a family of channels that have a wide variety of subunits and are present in different types of tissues. These channels can be expressed as pore-forming subunits (Kvα) and in association with accessory subunits, such as the association with sulfonylurea receptors (SUR) forming ATP-sensitive potassium channels (KATP). In muscle cells of blood vessels, they present a heterogeneous pattern of expression depending on the size of the vessel and the vascular bed, helping to tone these vessels. Considering Kvα, Kv family members can be grouped into 12 different subfamilies (Kv1-12). Members of the Kv7 channel family, for example, contribute to blood vessel muscle cell hyperpolarization and vascular tone in various vascular beds [7]. Kv have already been identified in syncytiotrophoblasts, placental chorionic plate resistance arteries and in placental blood vessels [103-110].
In PE, these channels have been studied in chorionic plaque arteries and placental tissue [15,26]. Wei et al. (2018) analyzed the expression and function of Kv7 channels (encoded by the KCNQ1–5 genes)

and found that mRNA for KCNQ3 was specifically up-regulated, whereas those for KCNQ4 and KCNQ5 were down-regulated in female chorionic plate arteries. with PE compared to normotensive women [15].
This reinforced Mistry et al. (2011) that showed an increase in the mRNA expression of KCNQ3 and KCNE5 in PE with localization restricted mainly to the syncytiotrophoblast. KCNQ4 and KCNE1 isoforms were suppressed in placentas of women with PE. KCNQ1 expression was increased and KCNQ5 decreased in the PE group [26]. Therefore, the inadequate differential expression of isoforms can lead to altered cell proliferation and, consequently, negatively regulate blood vessel tension in women with PE.

1.5 ATP-sensitive potassium channels (KATP)

ATP-sensitive potassium channels (KATP) are a group of channels composed of an internal rectifying potassium channel (Kir) structural unit and a sulfonylurea receptor (SUR) regulatory unit. They are composed of Kir6.1, Kir6.2, SUR1, SUR2A and SUR2B. Kir6.1 and SUR2B channels are widely distributed in vascular smooth muscle cells. KATPs have numerous functions such as controlling membrane potential, regulating smooth muscle cell proliferation, modulating vascular remodeling, and controlling vascular smooth muscle function [27]. KATP have already been identified in the syncytiotrophoblast and in placental blood vessels [111,112].
Regarding PE, a recent Yin et al. (2021) evaluated the expression of Kir6.1 and SUR2B units of KATP in human umbilical arteries of PE patients with severe features of early and late onset compared to normotensive patients. They observed that SUR2B expression levels in pregnant women with severe PE were lower than in normotensive pregnant women and that, compared with late-onset severe PE, SUR2B expression levels were lower in the umbilical arteries of women with severe PE from early onset [27]. That is, SUR2B under expression is more significant in early-onset severe PE. This suggests that the expression of the SUR2B unit may be related not only to the occurrence and development of severe PE, but also that the timing of occurrence of severe PE may be related to reduced SUR2B extension of the KATP channel. This is important, as one of the functions of these channels is to control the function of vascular smooth muscle, a lower expression of this subunit can cause inhibition of the potassium channel and, consequently, produce vasoconstriction.

1.6 Potassium pump

The Na+/K+-ATPase pump consists of a transmembrane protein that uses energy to transport sodium and potassium ions. It is present in all cells of the body and is made up of two alpha (α) subunits, two beta (β) subunits, and two gamma (γ) subunits. The binding sites for sodium, potassium, ATP and all substances that can stimulate or inhibit the functioning of this structure are located in the α subunits.
In placentation, this pump plays an essential role in trophoblastic invasion. Uterine luminal sodium is taken up by endometrial epithelial cells via ENaC and is transported into the blood via Na+/K+-ATPase, forcing water uptake from the lumen into the blood due to Na+ gradients. Reduction of uterine fluid is essential for close opposition between trophoblast and luminal epithelial cells for successful implantation [28].
Furthermore, reduced activity of the Na+/K+-ATPase pump is widely reported in PE and may be caused by a reversible oxidative modification, possibly caused by phosphorylation of the α1 subunit of the Na+/K+-ATPase molecule [30]. Abad et al. (2015) also reported that PE does not alter placental expression of the β1 subunit, but causes a large decrease in Na+/K+-ATPase activity, possibly caused by lipid peroxidation of the membrane in which the molecule is incorporated [29]. Even more recently, Brownfoot et al. (2021) reported a high level of glutathionylation of the β1 pump subunit in placentas of PE patients, possibly caused by excessive and persistent oxidative stress in the placenta in PE [33], [32]. Regardless of the cause, these studies point to a decrease in pump activity in PE placentas, which can trigger dysfunction throughout pregnancy.
In the last two years, studies report the role of marinobufagenin with Na+/K+-ATPase in PE. Marinobufagenin is a bufadienolide inhibitor of the alpha-1 subunit of Na/K-ATPase [34]. The

development of PE is associated with an increase in the production of marinobufagenin, which possibly not only decreases the function directly of the Na+/K+-ATPase pump, but also, through the Fli1-dependent mechanism (Friend leukemia integration 1 transcription factor), stimulates the synthesis of collagen in the umbilical arteries and ultimately leads to impaired vasorelaxation and the development of vascular stiffness, present in PE [31,34].

2. Sodium transporters

Sodium transporters are integral membrane proteins that form ion channels, conducting sodium ions across a cell's membrane. They belong to the superfamily of cation channels and can be classified according to a voltage change, called voltage-gated sodium channels, or according to their ligand, called ligand-activated sodium channels. In addition, there are sodium pumps, which exchange ions in cell membranes, and epithelial sodium channels [36-41].
Currently, despite being widely studied in tissues of the nervous system, the expression of voltage-gated sodium channels in maternal-fetal tissues remains little explored.

2.1 Epithelial sodium channels (ENaC)

The epithelial sodium channel (ENaC) is an ion channel expressed in cells of the reproductive tract. It is composed of three structurally related subunits, α, β and γ. Its main function is the transepithelial transport of sodium. ENaC is expressed in placental trophoblast cells and may mediate the invasiveness of trophoblast cells [113].
Endometrial vascular permeability increases at the site of attachment, mediated by cyclooxygenase (COX)-derived prostaglandins [114]. Continuous increase in prostaglandin expression is necessary for decidualization [115,116]. Activation of ENaC induces COX-2, necessary for implantation. The upregulation of COX-2 in ENaC appears to be mediated by activation-dependent calcium influx of ENaC [117]. Cyclic AMP Response Element Binding Protein (CREB) phosphorylation is reported to be responsible for COX-2 transcription. Interestingly, CREB is a transcription factor known to regulate prostaglandin production [118].
In 2012 a reduced expression of ENaC in term placentas in preeclampsia compared to normal pregnancy was demonstrated, suggesting that ENaC may play a role in the pathogenesis of preeclampsia [119]. Wang et al. (2013) detected a decreased epithelial sodium channel expression in placenta with preeclampsia compared to normal pregnancy [36]. This ENaC dysfunction may affect normal trophoblast invasion and migration in the placenta, reinforcing previous findings. Furthermore, inhibition of the ENaCα subunit was found to inhibit migration of a human trophoblast cell line, indicating a role for ENaC in trophoblast cell migration and placentation [38].

2.2 Sodium pumps

Na+/H+ pumps (NHEs) are a widely expressed family of proteins that mediate the exchange of extracellular Na+ for intracellular H+ and are related to various functions such as transepithelial transport, cell volume balance, and cell proliferation [39]. These functions are compromised in PE pregnancies. However, little is known about these bombs in PE. Dietrich et al. (2013) analyzed the NHE-3 isoform in syncytiotrophoblast cells. NHE-3 expression was significantly lower in PE than in normal placentas, both in mRNA and protein levels, especially in the cytoplasm of syncytiotrophoblastic cells. This decrease in NHE-3 expression may be associated with a lower intracellular pH, which may impair placental functions [39].
The Na+/Mg2+ pump is an important homeostatic mechanism in cytotrophoblasts. The fact that the Na+/Mg2+ pump is deficient in the preeclamptic placenta may contribute to the hypomagnesemia and vasoconstriction observed in these patients [40]. Standley et al. (2002) used JEG-3 cells (JEG-3 cytotrophoblastic human choriocarcinoma cells) to assess the functional Na+/Mg2+ pump. It was observed that this pump maintains low [Mg2+]i in cytotrophoblastic cells. [Mg 2+]i is acutely regulated by [Mg]o. As placental trophoblasts are sites of maternal-fetal ion exchange and [Mg]o is altered in

preeclampsia, disorders or alterations of this pump may contribute to pregnancy complications [41].

3. Calcium Transporters

Calcium transporters are the most widely distributed type of ion transporter in the placenta, especially in syncytiotrophoblast cells [120,121]. In the placenta, expression of various functions of cell signaling, secretion of proteins and hormones [121]. In placental blood vessels, these channels are involved in the regulation of fetoplacental vasoconstriction [61]. They are divided into two major groups, voltage-gated calcium channels and ligand-gated calcium channels.

3.1 Voltage-gated calcium channels (Cav)

Several types of calcium channels have been identified in studies on human placenta at different stages of placentation [120,121]. After fertilization and attachment of the blastocyst to the receptive endometrial epithelium, trophoblasts should be able to adopt an invasive phenotype (cross the basement membrane of the endometrial epithelium and invade the endometrial stroma) and subsequently induce vascular remodeling, two essential steps for placental growth [122]. Although still debated, calcium channels appear to contribute to mechanisms in the early stages of pregnancy. Calcium modulation is involved in key cellular mechanisms pertinent to blastocyst adhesion/implantation, including excitation, exocytosis, migration, cell proliferation, and cell death [28]. It is important to note that intracellular calcium is also required for transcription factors to regulate gene expression [123].

Calcium transport in the human placenta occurs mainly through calcium channels present in syncytiotrophoblasts [121], where Cav1.1, Cav1.2 and Cav1.3 voltage-gated L-type calcium channel isoforms were detected. In syncytiotrophoblasts, these ion channels play a role in cell signaling and hormone secretion [61,42]. In placental blood vessels, voltage-gated L-type Ca channels are primarily involved in the regulation of fetoplacental vasoconstriction [124].

In PE, Tang et al. (2018) compared the effect of magnesium sulfate on placental and non-placental vessels. It was observed that placental vessels responded weakly to magnesium sulfate compared to non-placental vessels. This difference was related to weaker activity of the calcium channel and lower contractility of smooth muscle cells, consequently, lower vasodilation [44]. These characteristics are important for understanding the action of magnesium sulfate used in the treatment of PE.

3.2 Calcium pumps

Intracellular and plasma membrane calcium transport ATPases play an essential role in cell homeostasis, such as excitation-contraction and stimulus-secretion coupling, which serve physiological processes. There are three different types of calcium pumps in mammalian tissues: the sarcoplasmic reticulum calcium ATPases (SERCAs), which sequester calcium from within the endoplasmic or sarcoplasmic reticulum; plasma membrane calcium ATPases (PMCAs), which expel calcium from the cell; and the secretory pathway of calcium ATPases (SPCA), located in the Golgi apparatus and maintain cellular magnesium balance [125].

PMCAs are ATP-driven calmodulin-dependent pumps. PMCAs release calcium ions from the cell and may thus contribute to the regulation of global and subcellular free intracellular calcium concentrations [126]. Furthermore, PMCAs also have important roles as support proteins in signal transduction [127]. In humans, PMCAs belong to a family of four different genes (ATP2B1–4) that encode PMCA1–4 proteins. PMCA1 and 4 proteins are expressed in different parts of the body, such as in the human reproductive system [128]. SERCAs, on the other hand, are calcium pumps involved in replenishing the cytosol to endoplasmic reticulum calcium stores. In humans, SERCAs belong to a family of three different genes (ATP2A1–3) that encode SERCA1–3 proteins [125]. In humans, changes in placental calcium metabolism, including changes in PMCA or SERCA expression, have been observed in the placentas of pregnancies with PE [91].

PMCA activity, in human trophoblast and syncytiotrophoblast, is reduced in women with preeclampsia

[29,46]. This decrease may be related to the low renewal rate of this protein in the plasma membranes of patients with preeclampsia. Furthermore, decreased activity of this protein was also evidenced in myometrial cells [47]. In uterine biopsies from PE patients, an increased level of thiobarbituric acid reactive substances (TBARS) was observed, which may result in an increase in cytosolic calcium concentration in vascular smooth muscle cells of preeclamptic women [48]. In the syncytiotrophoblast, Borrego et al. (2006) suggested that the decrease in PMCA activity is a consequence of the increased level of lipid peroxidation presented by these membranes [49,50]. This is because hypoxia, by increasing the calcium content of syncytiotrophoblast plasma membranes, stimulates its level of lipid peroxidation which, in turn, inhibits its PMCA activity [129]. A scenario that is similar to placental hypoxia in PE. Recently, a study evaluated the relationship between microRNA (miR)-27b-3p and the ATP2B1 regulation pathway, the gene that encodes the PMCA1 protein. It was observed that, when using serum from patients with hypertension, there was endothelial dysfunction in inducing trophoblast invasion. This suggests that miR-27b-3p may be considered a molecular risk factor in the pathogenesis and development of preeclampsia [51].

Unlike research with PMCA and PE, few studies relate this disease with the expression of SERCAs. Cha et al. (2019) covered the behavior of SERCA-2 against magnesium sulfate levels in antepartum administration in patients with PE. It was observed that SERCA-2 expression was increased in the presence of PE and antepartum administration of magnesium sulfate. This indicates that magnesium sulfate treatment may be associated with SERCA-2 expression [45].

No study was found relating the secretory pathway of calcium ATPases (SPCA), located in the Golgi apparatus, with PE.

4. Transient receptor potential (TRP)

Transient receptor potential (TRP) ion channels are named after the discovery of the channels in Drosophila. TRPs are activated by extracellular and intracellular stimuli and play a multitude of physiological and pathological roles. There are seven subfamilies of TRPs, including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin), and TRPN (Drosophila NOMPC) in mammals [130]. TRP (Transient Receptor Potential) channel proteins are widely expressed in female reproductive organs and are supposedly related to placental development, transport across the fetal-maternal barrier and plate work [120]. So far, syncytiotrophoblast in term placentas is known to have storage-operated Ca 2+ entry and to express TRPC3, TRPC4, and TRPC6 proteins [52]. In an experiment with mice, the deficiency in TRPC6 channel expression was related to altered amounts of Zn and Fe in tissues of the placenta, liver, kidney and brain. Furthermore, in that study, it was linked to reduced litter sizes, placental structural changes, and altered levels of placental development markers. In PE, elevated amounts of TRPC6 proteins were observed in human placenta, suggesting a potential compensatory role for this protein with other ion influx/efflux pathways [53]. More studies need to be carried out to unravel the reason for the increased expression of this channel in the human placenta.

The melastatin subfamily member transient potential 7 (TRPM7) and its homologue TRPM6 are ion channels permeable to divalent cations (Mg^{2+} , Ca^{2+} and Zn^{2+}) and an α-kinase. They have been implicated in a variety of cellular functions and are critically associated with intracellular signaling, including receptor tyrosine kinase mediated pathways. TRPM6 is mainly expressed in epithelial cells of the kidney and gastrointestinal system, whereas TRPM7 is expressed generally in diverse tissues [54]. In a study examining placentas from women with PE compared to placentas from normotensive women, preeclamptic placentas showed reduced expression of TRPM6 and TRPM7 [55], which was associated with altered cellular magnesium homeostasis. These phenomena were associated with decreased placental vascular endothelial growth factor (VEGF) expression in PE, effects normalized by magnesium sulfate treatment [131].

The endocannabinoid system is a signaling system comprising endocannabinoids (endogenous lipids), cannabinoid receptors (CB1, CB2 and transient receptor potential vanilloid 1 (TRPV1)) and the enzymes involved in their metabolism [58]. Lombó et al. (2022) showed that although there is an increase in TRPV1 protein mRNA levels in the placentas of PE patients [60], there was no change in

TRPV1 expression levels in preeclamptic placentas [58]. Concerning the TRPV6 receptor, a study from 2013 demonstrated a direct correlation between this channel and maternal-fetal calcium transportation [62]. In cases of PE, oxidative stress not only impaired calcium metabolism but also elevated TRPV6 expression. This increase in the expression of calcium transport proteins under conditions of placental hypoxia may indicate a physiological adaptation to maintain the equilibrium between maternal and fetal calcium demand during pregnancy [62].
TRPC1, TRPC5, TRPM2, TRPM4, TRPV4 and TRPV5 receptors, although found in placental tissue [20], still remain unknown when related to PE. There are still no studies relating the expression and importance of the TRPA, TRPP, TRPML and TRPN subfamilies in the human placenta of preeclamptic patients.

5. Chloride Transporters

Evidences indicates that chloride plays an essential role in the membrane potential to form an electrochemical gradient for maternal-fetal solute transport through the syncytiotrophoblast [65].
The intracellular chloride channel (CLIC) constitutes a subgroup of proteins of the glutathione-S-transferase superfamily (GSTs). In humans, they are divided into six members (CLIC1, CLIC2, CLIC3, CLIC4, CLIC5, CLIC6), and are present in normal placenta and fetal membranes, as in other tissues [132]. These channels regulate chloride ion concentration, stabilize cell membrane potential, regulate cell volume, and aid in cellular apoptotic processes [64,133,134].
In placentas form PE patients a increased expression of CLIC3 may contribute to facilitating chloride ion movement within the placenta and regulating cell proliferation, differentiation, and apoptosis [64]. However, more studies need to be done at the electrophysiological level to better analyze the function of this channel.
The Maxi-Cl channel is responsible for most of the studies on high conductance maxi-anion channels (MACs) [135]. Maxi-Cl is permeable to ATP and other small signaling molecules serving as an electrogenic pathway in cell-to-cell signal transduction. This channel has been detected in human placenta and vascular endothelium, among other tissues [136]. Maxi-Cl is an efficient pathway for chloride entry into the cell. It is involved in the regulation of cell volume, fluid secretion, apoptosis and cargo transfer. However, in the placenta and other cells, the molecular biology of Maxi-chloride channels is not completely clear [65].
In PE, placental processes can be affected by changes in the Maxi-Cl channels. Modifications in the functionality of this type of channel can affect biological processes such as volume regulation, generation of membrane potential or transport of nutrients such as the amino acid Taurine [66,67]. Riquelme (2009) suggested that the Maxi-chloride channel in preeclampsia loses regulation, remaining open regardless of voltage [65]. In PE, this channel remains permeable to Taurine. As the concentration of taurine in the placenta is higher than in maternal blood, it is possible that there is an efflux of taurine through these channels [65]. Taurine deficits can lead to uterine growth restriction and impaired perinatal development [68].

6. Aquaporins (AQP)

Aquaporins (AQPs) are water transporters that allow the rapid passive movement of water across a membrane. Aquaporins are divided into groups. The classic AQPs (AQP 0, 1, 2, 4, 5, 6 and 8), selectively permeable to water; aquaglyceroporins (AQP 3, 7, 9 and 10), transport water, non-polar solutes and also gases and metabolites; heterodox aquaporins (AQP 11 and 12) do not have clearly identified functions [76]. In the female reproductive system, they are expressed during the implantation process, both in the uterus and in fetal cells, in particular, in placental trophoblasts, chorionic villi and fetal membrane [76]. In the placenta, as water transporters, they have a role as a regulator of maternal-fetal fluid flow [137].
In placentas from patients with PE, AQP1 has a significantly inverse correlation between amniotic fluid index and placental levels, playing an important role in regulating maternal-fetal fluid balance [69]. In addition, in a model with mice in a clinical state similar to PE in pretreatment with low-dose aspirin, a

reduction in the expression of the AQP1 protein and a decrease in placental lesions, such as narrowing of the uterine spiral arteries, edema and calcifications was demonstrated [70]. Thus, this transporter may be involved not only in placental water balance, but also in other pathways of placentation.

Increased expression of AQP2 during the middle secretion phase (implantation period) was found in human glandular and luminal epithelial cells. AQP2 is expressed more in placental tissues of patients with PE than in normal pregnancies and is correlated with lower levels of human chorionic gonadotropin (HCG) in preeclamptic pregnancy [59]. AQP3 was less expressed in placental tissue from patients with late-onset PE compared to normal pregnancy, suggesting that it is an adaptive response of the placenta to reduce trophoblast apoptosis. Whereas in fetal membranes, AQP3 expression was significantly higher, which could be a phenomenon of excessive adaptive reaction and/or a type of feedback regulation in response to dysfunctional fluid exchange between the fetal membrane and amniotic fluid in patients [71,72]. In early-onset PE, a previous study showed that inhibition of AQP3 protein expression mitigated placental apoptosis reactions [73]. Furthermore, AQP3 has been associated with the development of hypertension after pregnancy, which may be related to risk factors such as metabolic syndrome and oxidative stress [74].

In a recent study, AQP4 protein expression was weakly detectable in patients with preeclampsia, but its mRNA was elevated compared to non-pathological placentas. In biochemical assays, hypoxia increased AQP4 mRNA but reduced AQP4 protein expression in human placental cells, thus suggesting that oxygen may regulate AQP4 expression. This is likely because the potential damage to syncytiotrophoblast membranes produced by intermittent hypoxia may contribute to creating an unfavorable environment for the insertion of AQP4 into the plasma membrane in the placental phase, increasing its lysosomal degradation [75]. In preeclamptic pregnancy, abnormal expression of AQP4, attributable to fluctuations in oxygen tension within the placenta, may play a key role in causing this gestational disorder.

Studies have shown that AQP9 expression is significantly increased in preeclamptic placentas. However, the increased oxidative stress seen in preeclampsia may impair AQP9's lactate transporter function. The same study showed that AQP9 is expressed not only in syncytiotrophoblast apical membrane [137], but in trophoblast mitochondria. Thus, AQP9 may mediate not only entry of metabolites such as lactic acid into the cytosol but also into mitochondria [76]. Consequently, its lack of functionality in preeclamptic placentas may impair the survival of trophoblastic cells, altering their invasion in early pregnancy. This molecule may thus serve as a crucial biomarker in early-onset preeclampsia [76,78]. Castro et al. (2011) proposed that in placentas with PE, insulin signaling mechanisms may be altered in the human placenta, producing an overexpression of AQP9 that does not correlate with an increase in its functionality [79].

Aquaporins AQP5, AQP8 and AQP11, although found in placental tissue [20], still remain unknown when related to PE.

7. Other ionic transporters

Nicotinic acetylcholine receptors (nAChRs) are part of the Cys-loop family of ligand-gated ion channels. The receptor is formed as a pentamer, with five subunits arranged around a central pore that is permeable to cations after binding of an agonist such as acetylcholine (ACh) or nicotine. Seventeen nAChR subunits have been characterized and two types of nAChRs are known; muscular type and neuronal type [92]. The β1 nAChR subunit is traditionally characterized as a muscle-like subunit. These receptors have already been described in the placenta in previous studies [138-140] and their relationship with smoking [138,141,142].

In PE, the expression of several nAChR subunits is dysregulated. Several studies have analyzed the α7nAChR subunit [82-85]. This subunit is widely expressed in placental tissue and may be related to poor oxygen supply and complications for the fetus, as blood vessels in the PE placenta have thickened lining [82]. Furthermore, this protein subunit appears to be expressed in patients with PE with severe features compared with PE without severity [83].

More recent studies evaluate other nAChR subunits in the placenta, aiming to identify its expression

and correlate it with the clinical picture in PE. MacHaalani et al. (2015) found that α2, α7, α9, β1, β2, and δ nAChR subunits are increased in preeclamptic placenta, even in the absence of smoking by pregnant women [81]. However, in the presence of smoking, these results are divergent. The changes were restricted to the villi and were specific for the α9, β1 and β2 subunits. Cigarette smoking appears to have a protective effect for the β2 subunit and an additive effect for the α9 and β1 subunits within cells of the nucleus villi rather than the trophoblast layer [80]. Furthermore, the literature speculates a possible protective effect of smoking on the development of PE, since the α9 nAChR subunit may be correlated with the estrogen receptor (17β-estradiol) [93].

Of the subunits studied so far, only the α7 subunit has been altered at the protein level, so it is still the most studied as a likely target in the development of PE. This is further supported by the role of α7 in inflammation, which is impaired function in the preeclamptic placenta. However, studies relating this subunit to the expression of sFlt-1 and sEng were unable to show significant alterations, possibly because the study used a cell line of human umbilical vein endothelial cells as a model of maternal vascular endothelium [143]. Further studies should replicate this experiment in other cell lines to confirm the effects of the α7 subunit on inflammation, apoptosis and vascular tone. Therefore, the precise role of the α7 subunit in PE remains to be determined, as well as whether it is indeed the subunit responsible for the protective effects of smoking [81].

The main role of gamma-aminobutyric acid (GABA) is as an inhibitory neurotransmitter in the mature central nervous system at type A GABA receptors (GABA A). The GABA A receptor is made up of five subunits that form a chloride ion channel. The GABA A receptor π subunit (GABRP) has been identified in cytotrophoblasts and syncytiotrophoblasts of human and mouse placentas [86,144,145]. GABRP subunit expression is increased in the placentas of patients with PE. In trophoblast cells of the HTR-8/SVneo lineage, GABRP has been shown to promote apoptosis and inhibit trophoblast cell invasion [86]. Therefore, this increase in π subunit expression in preeclamptic placentas may be directly linked to poor trophoblastic invasion at the beginning of placentation, characteristic of PE. More studies are needed to explore this relationship.

Purinergic P2X receptors are ATP-activated ion channels. Studies report that P2X4, P2X7 subunits modulate the intracellular concentration of ionic calcium and potassium efflux in cytotrophoblasts [87], [88]. The P2X4 subunit is a nitrated protein in placenta and is increased in placenta PE [88]. The role of these receptors in controlling placental electrolyte transport has not yet been studied in detail.

The ryanodine receptors (RyRs) are a family of high conductance channel proteins that release ionic calcium from intracellular stores such as the sarcoplasmic and endoplasmic reticulum. In mammals there are three types of RyRs: RyR1, RyR2 and RyR3. RyR1 is abundant in skeletal muscle, coupling the cell's action potentials to the release of ionic calcium from the sarcoplasmic reticulum and subsequent activation of the contractile apparatus. RyR2 is found at the highest levels in the heart, where it is blocked by extracellular calcium influx. And RyR3 is widely distributed, particularly in the brain and smooth muscle. In the placenta, these three types of channels have been identified in cytotrophoblast and syncytiotrophoblast cells, demonstrating a major role in fetal-placental calcium homeostasis [90]. In PE, the mRNA expressions of these channels were 75% lower compared to the healthy pregnancy group [90,91]. The reduced expression suggests impairment in calcium extrusion from the endoplasmic reticulum and, consequently, in intracellular calcium homeostasis [90,146]. In addition to this function, type 1 and 3 RyRs may play a role in trophoblast migration during embryo formation [146]. Another group of receptors important in calcium homeostasis are the inositol 1,4,5-triphosphate receptors (IP3R). These receptors act as a second messenger in intracellular calcium signaling through the extracellular signaling cascade of tyrosine kinase and G protein-coupled receptors. IP3 binds to its receptor (IP3R) and calcium will be released from the endoplasmic reticulum [90]. In PE, the mRNA expressions of these channels were 60% lower compared to the healthy pregnancy group [90,91]. Furthermore, it is possible that this receptor is related to mitochondrial fission and health in human placental mesenchymal cells under conditions of pathological hypoxia in PE [147].

Recently, Zhao et al. (2023) covered placental ion channels. In this review, the expression of ion channels in human placental tissue and primary cells was addressed [20]. However, there was a need to cover other tissues, such as the umbilical cord vessels, and relate them to PE, since this disease is

one of the causes of maternal-fetal morbidity and mortality and affects the dynamics of many ion channels and membrane receptors. It is worth mentioning that in this review we highlight different membrane transporters, including pumps. Figure 2 represents a compiled summary of the channels studied so far and the main functions changed in the places where these channels operate.

Currently, ion channels are increasingly being the target of randomized clinical trials, especially transporters involving calcium ions. Nifedipine, a calcium channel blocker drug, has been studied since the 1990s, when its relationship to lowering blood pressure and improving renal function without affecting blood flow in the umbilical artery in cases of preeclampsia was highlighted [148,149]. Recently, studies have correlated the effectiveness of nifedipine compared to other drugs to safely reduce blood pressure to target levels in patients with pre-eclampsia [150,151]. Another drug being studied is nicardipine, an L-type voltage-dependent calcium channel blocker. This drug is used in the treatment of patients with PE [152]. Today, a phase 3 clinical trial is evaluating the efficacy of nicardipine compared to urapidil in patients with PE [153].

Diltiazem, an L-type calcium channel antagonist, was effective in controlling arterial hypertension in the postpartum period of patients with PE [154]. Nimodipine, another L-type calcium channel blocker, is rapidly absorbed after oral administration and has important maternal and fetal cerebral vasodilator activity. It is an effective and easy-to-administer antihypertensive agent when used in patients with preeclampsia [155].

Magnesium sulfate is a competitive antagonist with action on the L-type calcium channel, it is an effective drug for the treatment and prophylaxis in the prevention of PE [156]. Currently, a new protocol for the use of magnesium sulfate is being developed, aiming to evaluate the effects of comparatives of three magnesium sulfate administration regimens when used in the care of women with severe preeclampsia [157].

Among the most studied ion channels in pregnancy today are transient receptor potential channels (TRPs), nicotine acetylcholine receptors (nAchR) and aquaporins. However, ion channels are still little studied in placental tissue in patients with PE. For example, the literature still does not have any studies involving channels of the zinc-activated channel (ZAC), Piezo channels and store-operated calcium channel (SOCC), as well as other subfamilies of channels already reported. Our study group is currently investigating the SOCC mechanism in placental samples and placental bed biopsies.

Conclusion

A large number of membrane ion transporters are distributed in placental tissue, primary cells and umbilical cord tissue. It is known that these transporters have important functions, especially in the regulation of hormone synthesis and secretion, in the maintenance of trophoblast homeostasis, in the control of nutrient transport between mother and fetus, and in vascular contraction and relaxation. Studies demonstrated that in harmful conditions, such as hypoxia present in patients with PE, ion transporters are negatively regulated and their activity is impaired.

Potassium transporters are associated with vascular tone, as they regulate vasodilation in resistance vessels by membrane hyperpolarization in response to hypoxia. Furthermore, potassium transporters are involved in angiogenesis, since their blockade inhibits the secretion of VEGF and IGF by endothelial cells. Inadequate expression negatively regulates placental vessel tension and angiogenesis, as occurs in PE. These transporters can are a target for future treatments, as they are related to the initial phase of placentation.

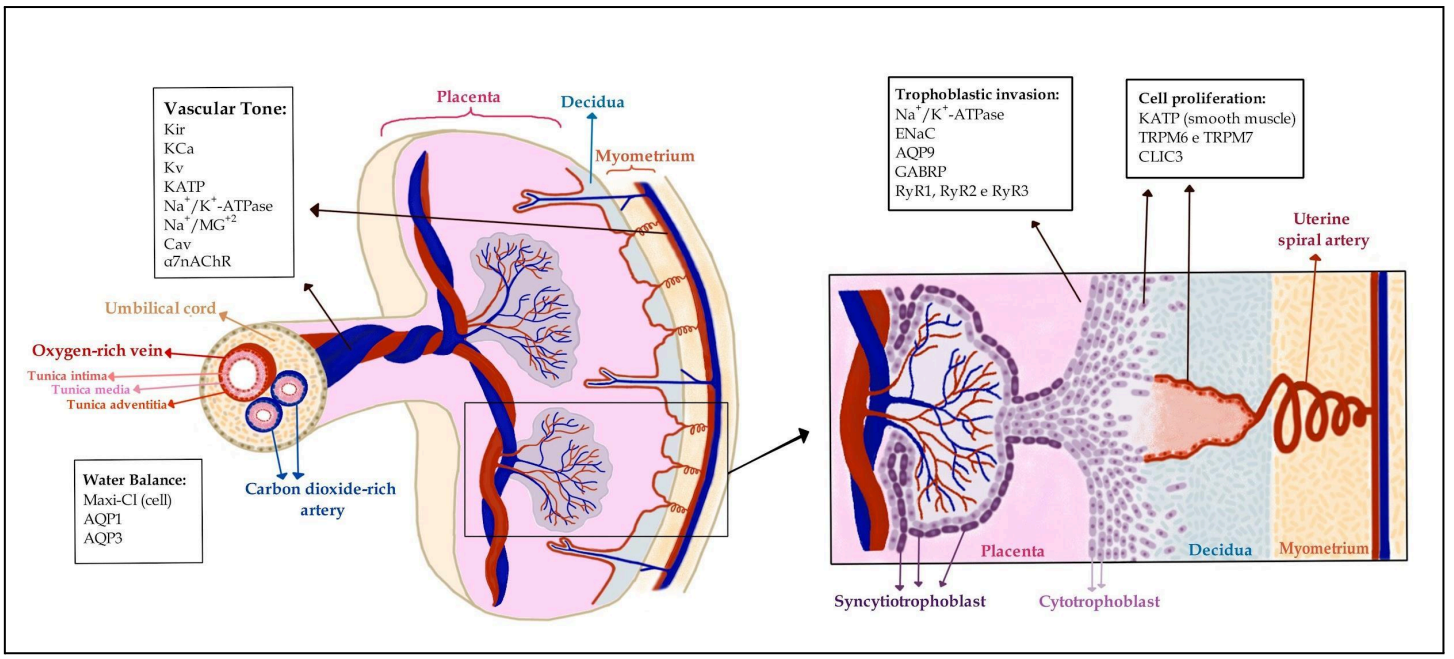
Sodium transporters, although little studied in the placenta of patients with PE, are represented by an essential group in implantation placenta: the ENaC. This channel absorbs luminal sodium and transports it to the blood via a pump, forcing water absorption due to the Na+ gradient. Thus, it promotes a suitable environment for trophoblast implantation and invasion. This channel is underexpressed in the PE placenta. As the onset of the PE problem begins with abnormal placentation, investigating therapeutic ways to stimulate ENaC expression will be important for proper implantation of the placenta.

Calcium transporters, as well as SERCAs, should be studied together with TRPV, since the underexpression of Cav and overexpression of SERCAs (subtypes 1,2, and 3) may be related to the

increase in TRPV6 expression, which could be a physiological adaptation in balance between maternal and fetal demand for calcium. Finally, the nAChR is an excellent group of ionic transporters to study, as smoking appears to have a protective effect on some subunits. So, identifying or developing an agonist with characteristics similar to nicotine could be a therapeutic and/or protective target in the development of PE.

Therefore, an analysis of the main current findings on the role of ionic transporters in the development and progression of PE was necessary. Further investigations are still needed, such as those already suggested, focused on maternal-fetal tissues to elucidate the pathophysiology of PE.

Fig. 2. Graphical representation of ion transporter altered in EP and its main implications. The key points of PE development and progression in which altered expression and/or function of ion channels and transporters are the processes related to the maintenance of vascular tone, trophoblastic invasion, cell proliferation and water balance.



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5 CONCLUSÕES

Um grande número de transportadores iônicos de membrana está distribuído em tecido placentário, células primárias e tecido do cordão umbilical. Sabe-se que esses transportadores possuem importantes funções, em especial, na regulação da síntese e secreção de hormônios, na manutenção da homeostase dos trofoblastos, no controle do transporte de nutrientes entre mãe e feto e na contração e relaxamento vascular. Em gestações complicadas, como em pacientes com PE, inúmeros estudos apontaram que em casos de condições prejudiciais, como na hipóxia, os canais iônicos são regulados negativamente e sua atividade é prejudicada. Por isso, analisar os principais achados atuais nesse contexto clínico se fez necessário.

Porém, mais do que apenas descrever seu envolvimento na fisiopatologia da PE, é necessário buscar novas formas de terapia que possam fazer uso destas proteínas como alvo farmacológico, que sejam eficazes e seguras para o paciente. Embora existam poucos ensaios clínicos até o momento que validem o uso de canais iônicos como marcadores moleculares ou alvos terapêuticos na PE, os dados apresentados destacam o papel dos canais iônicos na fisiopatologia da PE com uma abordagem terapêutica promissora a ser investigada, com ênfase nos receptores de nicotina acetilcolina (nAchR), os TRPs (TRPP2, TRPV5 e TRPV6), as aquaporinas (3, 8 e 9) e conexina 43.

6 CONSIDERAÇÕES FINAIS

Este trabalho de mestrado foi desenvolvido durante os anos de 2022 e 2023 em alternativa ao projeto de pesquisa inicialmente proposto, cujo título era “Avaliação do papel dos canais de cálcio operados por estoque na fisiopatologia da pré-eclâmpsia”. Isto se deveu ao contexto pandêmico enfrentado durante os anos de 2021 e 2022. Pelo fato de o projeto original envolver recrutamento de pacientes e técnicas experimentais de cultivo celular, com a suspensão das atividades de laboratórios de pesquisa nos meses iniciais da pandemia, e com a impossibilidade de recrutamento de paciente durante boa parte do ano de 2021, optou-se por modificar o foco do estudo, desenvolvendo-se um trabalho de revisão envolvendo o objeto de estudo inicial, a pré-eclâmpsia. A temática de fisiopatologia de canais iônicos foi inserida em virtude de ser um tema de estudo de outras pesquisas do Grupo de Biofísica Celular, Molecular e Computacional, definindo-se, assim, o tema da revisão narrativa. Optamos por uma revisão narrativa com o intuito de elaborar um trabalho que abordasse de uma forma abrangente os mais diversos estudos que descrevessem algum aspecto da fisiologia dos transportadores iônicos relacionada à pré-eclâmpsia. Esse compilado de informações proporcionou um embasamento teórico robusto a respeito do tema, abrindo uma perspectiva de elaboração de uma revisão sistemática relacionando o uso de bloqueadores de canais em mulheres com risco de desenvolver pré-eclâmpsia.