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INVITED REVIEW

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The role of α2-adrenergic receptors in hypertensive preeclampsia: A hypothesis

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Abstract

Preeclampsia, a major disorder of human pregnancy, manifests as persistent hypertension and proteinuria presenting after 20 weeks of pregnancy. Multiple systemic symptoms might be associated with preeclampsia including thrombocytopenia, liver impairment, pulmonary edema, and cerebral disturbances. However, vascular dysfunction remains the core pathological driver of preeclampsia. Defective placental implantation followed by dysfunctional placental spiral artery development promotes a hypoxic environment. Massive endothelial dysfunction characterized by reduced vasodilation, augmented vasoconstriction, and increased vascular permeability and inflammation ensues. Interestingly, the same signaling and inflammatory pathways implicated in preeclampsia appear to be shared with other vascular disorders involving alteration of α_2-AR function. The role of α_2-ARs in the regulation of microcirculatory function has long been recognized, thus raising the question of whether they are involved in the pathogenesis of vascular dysfunction in preeclampsia. Here, we review possible interplay between signaling and inflammatory pathways common to preeclampsia and α_2-AR function/regulation. We speculate on the potential contribution of these receptors to the observed phenotype and the potential role for their pharmacological modulators as therapeutic interventions with preeclampsia.

1 | PREECLAMPSIA: A VASCULAR DISORDER WITH ADRENERGIC PARALLELS

PE is a major disease of human pregnancy, which typically presents around 20 weeks of gestation and is marked by a persistent hypertension and proteinuria.[1] PE affects around 3%-8% of women worldwide[2] and is associated with significant maternal and perinatal morbidity and mortality, particularly in those patients with early onset of PE.[3] PE is a more severe form of hypertensive disease that presents with at least one other systemic symptom. It is defined by the presence of de novo maternal hypertension (>140/90 mm Hg systolic/diastolic blood pressure) with proteinuria (>300 mg/24 h) or new-onset thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or visual or cerebral disturbances.[2] In severe cases, the mother may also develop comorbidities such as hepatic alterations, cerebral edema, disseminated vascular coagulation, and eclampsia.[4] For the fetus, the main complications associated with PE include intrauterine growth restriction leading

Abbreviations: 6-keto-PGF1, 6-ketoprostaglandin F1α; ACh, acetylcholine; ACTH, adrenocorticotrophic hormone; EC, endothelial cell; ERK, extracellular signal regulated kinase; FAK, focal adhesion kinase; GIRK, G protein-coupled inwardly rectifying potassium channels; GSH, glutathione; HPA, hypothalamic-pituitary-adrenal; HUVEC, human umbilical vein endothelial cell; NF-κB, nuclear factor-κB; NOS, nitric oxide synthases; NOX, nicotinamide adenine dinucleotide phosphate oxidase; PE, preeclampsia; PKC, protein kinase C; PKG, protein kinase G; RNS, reactive nitrogen species; ROCK, Rho-dependent kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, Tumor necrosis factor-α; TxA_2, thromboxane; UA, uterine artery; VSMC, vascular smooth muscle cells; α_2-ARs, α_2-adrenoceptors.

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to low birthweight, prematurity, and fetal death. After the onset of symptoms, progressive worsening may potentially lead to fetal and maternal mortality.[5] To date, there is no cure for PE and, in severe cases, the only effective treatment for PE is premature labor induction carrying inherent risks for premature neonates.[6]

Over the last decade, substantial progress has been made in understanding the pathophysiology of PE.[7] Taylor and Roberts posited that a dysfunctional placenta releases "toxic" factors into the maternal circulation that are responsible for the clinical manifestations of the disease.[8,9] This pathophysiology originates from a defect of placental implantation into the maternal uterine wall, characterized by insufficient trophoblast invasion, incomplete placental spiral artery remodeling, and subsequent decreased placental perfusion.[10] Accordingly, PE is considered primarily to be a vascular disorder with massive endothelial dysfunction and disturbed endothelial prostanoid balance, oxidative stress, and inflammation.[5]

On the other hand, α_2-ARs have long been recognized as determinants of microvascular reactivity[11,12] producing vasoconstriction independent of other adrenergic receptors.[13] They have been implicated in disorders with a vascular component including scleroderma[14] and Reynaud's disease.[15] Despite being regulated by the very factors that contribute to the pathophysiology of PE, experimental or clinical evidence linking α_2-ARs to the development of PE has not been forthcoming. In this review, we will speculate about the role of α_2-ARs in the pathophysiology of PE. We will introduce potential mechanisms and dissect possible signaling pathways that can be utilized by α_2-AR modulators to improve symptoms, disease progression, and clinical outcome.

2 | PATHOPHYSIOLOGY OF PRE-ECLAMPSIA

2.1 | Placentation: healthy and abnormal/reduced placental perfusion

The preeclamptic placenta is characterized by markedly reduced invasion of the uterine wall and reduced remodeling of the maternal vasculature.[16-18] Healthy placental invasion is characterized by extensive remodeling of the maternal uterine spiral arteries transforming from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion.[16,19,20] During the first trimester of gestation in humans, the intervillous space remains physiologically hypoxic because extravillous trophoblast cells plug maternal spiral arteries preventing maternal red blood cells from passing into this space. Twelve to fourteen weeks into normal gestation, placental extravillous trophoblasts colonize the maternal spiral arteries as far as the proximal third of the myometrium leading to vasodilation increasing blood flow and raising oxygen supply, thus reversing the previous hypoxic environment.[4] This requires extensive angiogenesis[21] involving the differentiation of cytotrophoblasts from an epithelial phenotype to an endothelial phenotype with an ability to invade the uterus and engraft maternal blood vessels.[22] In PE, research has shown a defective angiogenic process, mainly to due to failure cytotrophoblasts to differentiate, which is tightly regulated by antiangiogenic factors.[23] Specifically, persistent placental hypoxia promotes hypoxia-inducible factor-1 alpha release, which promotes transforming growth factor-β3 expression. TGF-β3 is an inhibitor of trophoblast differentiation[24] and subsequently favors a noninvasive trophoblast phenotype, further aggravating hypoxia.[25]

2.2 | Oxidative stress

As a result of irregular arterial blood flow, repeated ischemia/reperfusion episodes are generated. This leads to the production of ROS and RNS, which cause eventual oxidative damage.[26] Oxidative stress plays a major role in the initiation of placental and endothelial dysfunction, being the two major features of PE. Different cellular compartments and enzymes can contribute to the production of ROS and RNS. Enzymes include NOS, NOX, xanthine oxidases, and the mitochondrial electron transport chain.[4] Oxidative stress can also result from a lack of enzymatic and nonenzymatic antioxidants. Enzymatic antioxidants include SOD, hemeoxygenase, catalase, GSH peroxidase, and thioredoxin. SOD catalyzes the reduction of superoxide radicals into O_2 and H_2O_2, which is then broken down into H_2O and O_2 by catalase. Using GSH as a cofactor, GSH peroxidase plays a critical role in the reduction of hydrogen and lipid peroxides. Nonenzymatic antioxidants include GSH, vitamins C and E, nicotinamide adenine dinucleotide, and nicotinamide adenine dinucleotide phosphate.[27]

2.3 | Inflammation and endothelial dysfunction

The preeclamptic placenta stimulates the production and secretion of pro-inflammatory cytokines, the activation of NF-κB, and release of vasoactive compounds.[28] Upon activation in PE, NF-κB acts on promoter regions of genes involved in the inflammatory response including COX-2, the inducible form of cyclooxygenase expressed in monocytes, and plays an important role in inflammatory diseases.[29] It catalyzes the production of prostaglandins and TxA_2 that mediate inflammation. TxA_2 is also a potent vasoconstrictor.[30] Activation of ECs by inflammatory substances and ROS leads to a dysfunctional phenotype characterized by loss of structural properties of their membranes and plasma leakage from the vessel lumen to the interstitial space. TNF-α, which is induced by ROS, and thrombin have been demonstrated to be responsible for increased endothelial permeability.[31] TNF-α can also directly induce oxidative damage through the activation of NOX, or stimulation of mitochondrial oxidative stress.[32] NOX activation can lead to the production of superoxide anions that can scavenge NO and subsequently impair endothelial-dependent dilation.[33] NOX2 expression increased in HUVECs exposed to preeclamptic women serum.[34] Moreover, oxidative stress can also lead to downregulation of endothelial calcium-activated potassium channels, which contribute significantly to endothelium-dependent relaxation.

3 | ADRENOCEPTORS SIGNALING

Adrenergic receptors are a heterogeneous group of hormone/neurotransmitter G protein-coupled receptors that have been divided into three major types, the α_1-, α_2-, and β-adrenoceptors, based on their affinities for agonists and antagonists, their coupling to signaling pathways, and their amino acid sequences.[35,36] These adrenoceptors mediate central and peripheral actions of the natural adrenergic amines, adrenaline and noradrenaline.[37] It is well established that three subtypes of α_2-ARs exist, the $\alpha_{2A/D}$, α_{2B}, and α_{2C} subtype. The α_2-AR subtypes couple to $G_{i/o}$ resulting in inhibition of adenylyl cyclase and a decrease in cAMP formation, as well as other signal transduction pathways, since many of the physiological effects of α_2 activation cannot be explained only by decreases in cAMP formation.[37,38] For example, activation of α_2-ARs may inhibit endothelin-1 formation in the cerebral vasculature,[39] stimulate inward rectifying K^+ currents,[40] or activate phospholipase C, leading to smooth muscle contraction.[41,42] Additionally, the α_{2A} subtype may interact with G_s, leading to stimulation of adenylyl cyclase activity.[43] In vivo, α_2-AR agonists elicit a wide range of effects including hypotension and bradycardia, analgesia, hypothermia, and sedation.[37,44]

3.1 | Role of α2-ARs in Microcirculation

The α_2-ARs are widely distributed in the cardiovascular system and mediate different physiological effects.[45] For example, activation of the presynaptic α_2-ARs decreases sympathetic outflow and activity, thereby leading to a decrease in blood pressure.[46] On the other hand, activation of smooth muscle α_2-ARs induces contraction.[47] α_2-ARs are also functionally expressed on the vascular endothelium, and isolated arteries from various vascular beds (coronary, renal, and mesenteric), have shown relaxation upon activation of these receptors.[48-50]

α_{2A}-ARs actions, being primarily presynaptic, typically represent the pharmacological functions of nonselective α_2-agonists, including bradycardia and hypotension. In contrast to the α_{2A}-AR, the α_{2B}-AR has been shown to be involved in the vascular hypertensive effect of α_2-AR agonists and is required for the development of the placental vasculature.[51] α_{2B}-AR acts primarily as a "postsynaptic receptor" outside of the central nervous system.[52,53] The α_{2C}-AR is critical for suppression of epinephrine release from the adrenal chromaffin cells [54] and plays a role in the modulation of hypothermia.[55] While the α_{2A}- and α_{2B}-AR subtypes are enriched on cell surface at steady state, the α_{2C}-AR is distributed between the surface and intracellular compartments.[55]

An important physiological effect mediated by α_{2C}-ARs is thermosensitivity in cutaneous blood vessels.[56] In cutaneous arteries of the mouse tail, α_2-AR constriction at 37°C is mediated by α_{2A}-ARs. However, after moderate cooling, cAMP-Rap1A signaling activates RhoA to induce α_{2c}-adrenoceptor translocation from their typical retention site in the Golgi compartment to the surface of microvascular smooth muscle cells. Once on cell surface, α_{2C}-ARs can respond to receptor agonists, such as norepinephrine and mediate vasoconstriction.[57]

3.2 | Localization in placenta

Previous binding studies have demonstrated the presence of α_2-ARs in the human placenta.[58,59] Immunostaining showed immunoreactivity for all α_2-AR subtypes.[60] It has been suggested that α_2-ARs are equally activated owing to a similar p-ERK staining in all the α_2-AR-positive sections.[60] However, this remains anecdotal evidence that warrants further investigation before a causative link can be established. Interestingly, placentas from women with severe PE showed higher extravillous trophoblast staining for the α_{2C}-AR. Another study reported that the α_{2A}- and α_{2B}-ARs were present in human placenta with an approximate ratios of 60% and 40%, respectively.[61] This study also found that α_2-AR is lower at term compared to the first trimester. This contrasts with the pattern of increasing β-AR density in placenta at term. This shift in respective adrenergic receptor density may be important for regulation of placental vascular tone.[61] Collectively, these data indicate that α_2-ARs may play a role in the pathogenesis of severe PE.

4 | INFLAMMATION POTENTIALLY LINKS α_2-AR FUNCTION TO PATHOGENESIS OF PE

4.1 | COX enzymes and preeclampsia

PE is characterized by an imbalance between two COX products,[62,63] manifested by increased production of vasoconstrictor TXA_2 in the placenta coupled to decreased endothelial-derived production of its functional antagonist prostacyclin.[64] Oxidative stress is likely to be the causative agent.[65] Studies demonstrated that both COX-1 and COX-2 isoform activities could be observed in placenta and placental vascular bed from healthy and PE term pregnancies.[66] Yet, results of investigating their role in PE were inconsistent. One study showed that the expression of COX-1, rather than COX-2, was increased in PE.[66] Yet on the other hand, ECs of vessels isolated from PE pregnancies exhibited higher expression of COX-2.[67] The amount of 6-keto-PGF1 released from PE ECs is significantly less than that produced from ECs of normal pregnancy.[67] 6-keto-PGF1 is a physiologically active and stable metabolite of prostacyclin, found in nearly all mammalian tissue and is a powerful vasodilator as well as an inhibitor of platelet aggregation. Taken together, it can be deduced that COX-2 may be involved in the pathogenesis of preeclampsia,[67] especially that it may play a role in the decreased bioavailability of 6-keto-PGF1.

4.2 | COX enzymes, α2-AR, the HPA axis, and peripheral inflammation

Although there is controversy regarding the relative levels of COX enzymes in the setting of PE, it is well established that prostaglandins, produced by these enzymes, play a role in stimulating the HPA

axis, and that this stimulation often occurs via adrenergic activation.[68,69] Activation of HPA is known to result in increased blood levels of mineralocorticoids, catecholamines, and glucocorticoids, all of which mediate subsequent VSMC contraction.[70] As such, α_2-ARs might interact with COX products to contribute to vasoconstriction and hypertension by central and peripheral mechanisms potentially contributing to the pathogenesis of preeclampsia. In rat brain, mRNA of both COX isoenzymes is expressed constitutively with COX-2 being the predominant isoform.[71] Central α_2-AR stimulation by clonidine-induced ACTH and corticosterone secretion, which was blocked by either COX-1 or COX-2 inhibitors.[72] It would be interesting to investigate whether PE is associated with HPA hyperactivity and whether this is associated with increased COX-2 metabolites and α_2-AR activity. This is particularly important since cortisol increases vascular resistance and contractile sensitivity by potentiating the responsiveness of VSM cells to epinephrine and norepinephrine [73] and that chronically elevated cortisol levels are intimately associated with elevated blood pressure.[74] Significantly, this cortisol-evoked enhancement of adrenergic pressor effect was shown to be mainly mediated by α_2-AR activity.[75] It is noteworthy that cortisol levels were elevated in umbilical cord blood from preeclamptic women.[76] These data highlight a possible dual central/peripheral role of α_2-AR in mediating the effects of stressors, inflammatory and otherwise, leading to HPA activation, corticosterone secretion, and subsequent vasoconstriction. These effects are summarized in Figure 1.

In the context of peripheral inflammation, while COX-2 inhibition was shown to attenuate neutrophil-endothelium interaction, a key step in inflammation-evoked endothelial dysfunction in PE,[77] a similar role for α_2-AR modulation in this process cannot be discounted. Indeed, an anti-inflammatory role for α_2-AR agonists, evident by decreased endothelial-leukocyte interaction, has been reported.[78] α_2-AR agonists caused an increase in the resistance of ECs to neutrophil extravasation, through inhibition of TNF-α-decreased expression of adhesion molecules.[78] Of course, more studies are needed to investigate the anti-inflammatory effect of α_2-ARs in placental preeclamptic tissues and animal models. However, the current literature makes it tempting to speculate for a novel role of α_2-AR in modulating inflammation, especially in the context of pathophysiology or therapeutics of PE. A schematic representation of the anti-inflammatory role of α_2-ARs stimulation is provided in Figure 2.

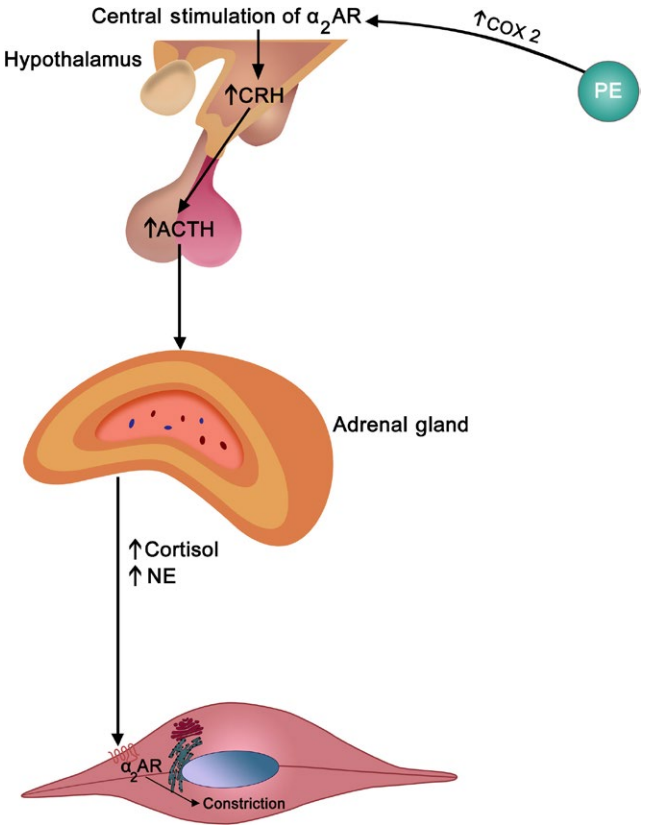

FIGURE 1 Central and peripheral contribution of α_2-AR activity to the hypertensive effect of inflammation in PE. Increased COX activity might trigger HPA axis activation mediated by central α_2-AR stimulation. Increased cortisol and NE secretion will follow. Cortisol increases α_{2C}-AR expression on VSMCs further aggravating the NE-mediated vasoconstriction and hypertension

5 | IMPAIRED VASODILATION IN PE COULD BE RELATED TO DECREASED α_2-AR SIGNALING

5.1 | Nitric oxide and preeclampsia

NO is a principal vasodilator released by ECs and diffuses to the underlying VSMC layer triggering vasorelaxation.[49,79] Because of its potency in mediating vasorelaxation, several studies aimed at understanding the role of NO in the isolated UA of PE animal models[80,81] and in human placental vessels.[82] However, these studies have revealed inconsistent results with controversy regarding the presence or absence of NO-induced vasodilation in PE.

Studies showed that, when treated with ACh, UAs from a transgenic preeclamptic rat model relaxed less than those from normal rats.[81,83] Yet, other studies deduced that reduced NO production cannot account for increased vasoconstriction of preeclamptic uterine vessels, due to the notion that decidual ECs from preeclamptic pregnancies did not produce less NO than cells from normal pregnancies.[84] Interestingly, a recent study showed that the placental vasculature lacks its own endogenous endothelium-derived NO.[82] In contrast to human nonplacental vessels,[85-87] ACh showed no vasodilatory effect on human placental vessels. This was also consistent with results from sheep and rat vessels examined in the very study. Collectively, these results suggest that the vasorelaxant effects stimulated by endothelial NO system in isolated placental vessels may be very weak.

It is important to note, however, that NO still plays a role in the vasodilation of the placental vasculature. Indeed, endothelium-independent vasodilation, expressed as the vasodilatory response to the NO donor SNP, although reduced, was still present in preeclamptic placental vessels.[80,82] This indicated that it might be the smooth muscle portion of the NO-dependent vasodilatory

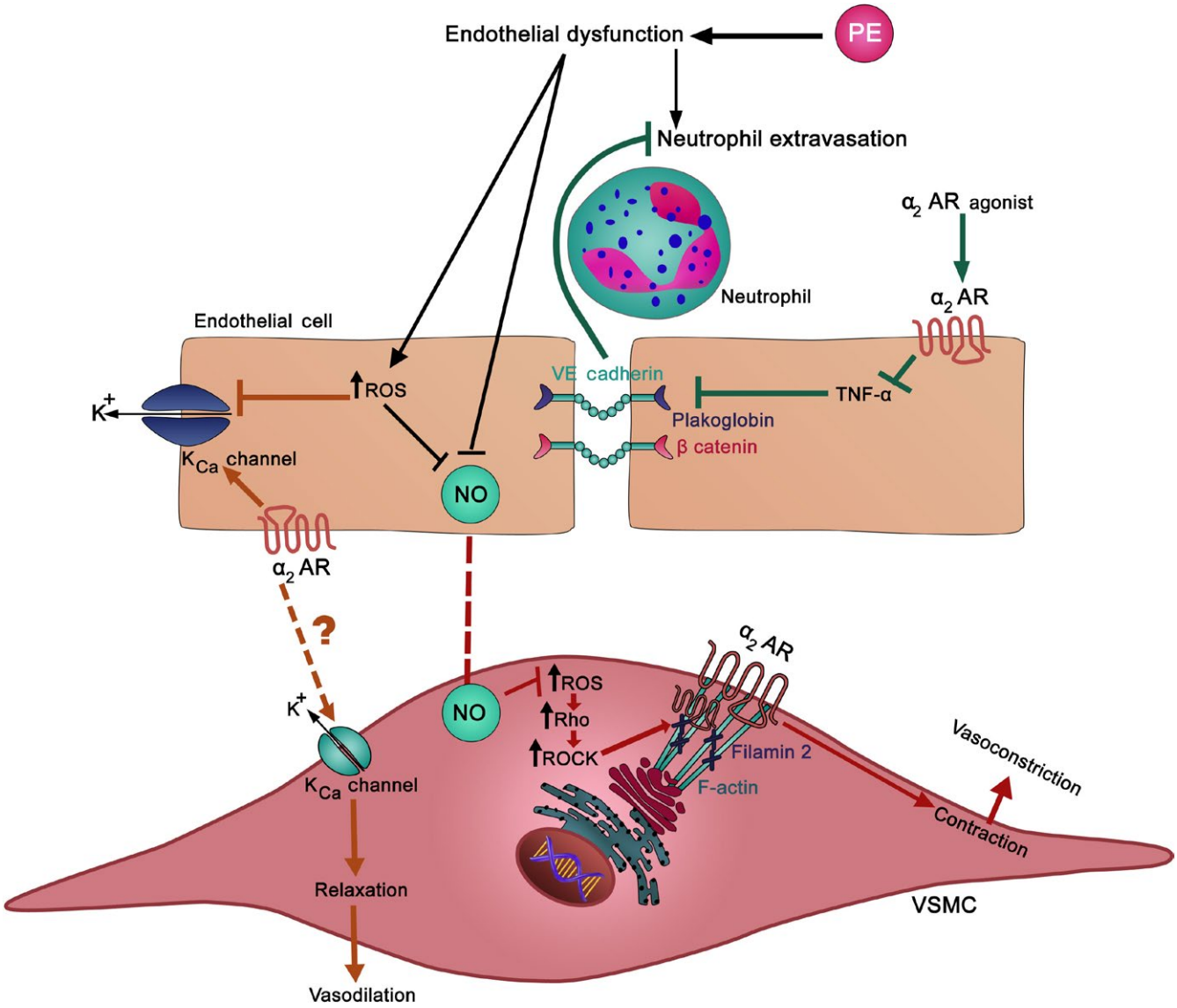

FIGURE 2 Targeting α_2-AR signaling might offer a viable target for interference with endothelial dysfunction in PE. Activation of endothelial α_2-ARs serves multiple potential roles. Reduction of TNF-α-mediated increase in adhesion molecule expression could contribute to neutrophil extravasation and decrease endothelial inflammation in PE. From a functional perspective, activation of endothelial α_2-ARs might improve endothelium-dependent vasodilation through activation of K_{Ca} channels. Direct VSMC effects via α_2-AR-mediated VSMC K-channel activation cannot be discounted as well. Finally, an improved vascular status could potentially improve VSMC response to NO leading to reduced RhoA/ROCK activity and reduced α_{2C}-AR recruitment to the VSMC membrane

pathway that is altered in preeclamptic vessels. In fact, preeclamptic placental vessels exhibited decreased cGMP production, sGC activity, and CUCYA3 (subunit of sGC) expression.[82] There is notably lower levels of L-arginine concentration, NO production, or eNOS enzymatic activity, as well as lower expression of NOS enzymes (eNOS and iNOS, but not nNOS) in human placental vessels compared to placental tissue in both normal pregnancies and preeclamptic pregnancies.[82] This suggests that the NO that is present may stem from placental tissue, and not placental vessels. Altogether, what we presented so far challenges the conventional theory on placental ischemia-initiated endothelial dysfunction and NO reduction in PE, and that altered vascular functions may originate in VSMCs rather than ECs. These findings raise important questions on what mediates placental vasorelaxation if endothelial NO contribution is very weak. As such, an alternative explanation for the dysfunctional endothelial-mediated vasodilation in PE might be required. Significantly, a study investigating the interaction between the NO and α_2-AR-mediated endothelium-dependent vasorelaxation in mesenteric arterial segments from mice lacking eNOS demonstrated an inhibitory role of NO on the α_2-AR-mediated relaxation and that cGMP may be involved in this mechanism.[45] Thus, it becomes prudent to examine this vasorelaxation in PE, a setting with weak production/response to NO. An increased role for α_2-AR modulators as vasodilators in PE could be argued; and hence, alteration in α_2-ARs expression/function might underlie the VSMC deficit leading to impaired vasodilation. However, this remains to be established.

On the other hand, it is noteworthy that other studies have pointed out a role for NO in vasorelaxant action of clonidine through the activation of the l-arginine-NO-cyclic GMP cascade.[49,88-90] However, a distinction must be made between mechanisms involving α_2-AR-induced relaxation in large conduit arteries vs small resistance arterioles, which might be vastly different.[45]

5.2 | K^+ channels and α_2-ARs in preeclampsia

Indeed, previous studies suggested a role for NO-independent mechanisms for uterine and placental vessels dilation. UA preparations showed residual ACh-evoked dilation upon treatment with L-NAME[80] that was abrogated with K^+ channel inhibitors.[91,92] Therefore, whether NO-independent mechanisms are unaltered or play a compensatory role in PE may provide an exciting insight into the pathology of this disease. Activation of α_2-ARs has been linked to activation of Ca^{2+}-activated (K_{Ca}) [93] and GIRK K^+ channels.[94] Indeed, in VSMCs from placental vessels, SNP evoked an increase in whole-cell K^+ currents that was comparable to nonplacental VSMCs, and that effect was weaker in placental VSMCs from preeclamptic pregnancies.[82] Moreover, endothelial K_{Ca} channels are downregulated by serum factors as a result of ROS generation in PE, which may contribute to the pathogenesis.[95] Whereas Kir 3.1, the subunit contributing to the GIRK channel function, was implicated in renal microvascular dysfunction in diabetic rat models,[96] its contribution to the placental vessel function under physiological conditions or in PE has not been examined. Thus, the alteration of α_2-AR function and/or interaction with K_{Ca} and GIRK channels in the endothelial and/or VSMC layer in PE could potentially underlie the arteriolar vasodilation and is certainly worth systematic investigation. The proposed role of α_2-ARs in a K-channel-mediated vasodilatory effect is included in Figure 2.

6 | RHOA/ROCK SIGNALING, PLACENTATION, AND α_2-AR-MEDIATED VASOCONSTRICTION

6.1 | ROCK in trophoblast differentiation, apoptosis, and invasion

Trophoblast differentiation, invasion into the maternal decidual stroma, and formation of anchoring villi are an indispensable physiological process of early human placental development.[97] Ensuing vascular changes that would ensure an adequate blood supply to the growing fetus are equally critical.[97] These activities are regulated by numerous growth factors as well as extracellular matrix proteins and adhesion molecules that are expressed at the fetal-maternal interface.[97] Signaling cascades/proteins such as the GTPase RhoA, ROCK, $ERK_{1/2}$, FAK, PI3K, Akt/protein kinase B, and mTOR, as well as TGF-β-dependent SMAD factors all appear to be involved.[97]

Of particular and contextual significance is the RhoA/ROCK signaling pathway that plays an important role in the regulation of trophoblast differentiation, apoptosis, and invasion.[97,98] Furthermore, RhoA and ROCK are expressed in human trophoblast where they are involved in trophoblast migration.[99] Indeed, genetic ablation of ROCK in mice resulted in intrauterine growth retardation and fetal death, both of which are common complications of PE.[100] Additionally, increased placental apoptosis and microvilli shedding have both been shown to occur in PE.[101] It is thought that this shedding may provoke an inflammatory response in the mother, contributing to the endothelial dysfunction seen in preeclampsia.[102] Oshiro et al[103] demonstrated that the downstream effectors of ROCK may play an important role in the formation of microvilli-like structures. Others have also reported that the increase in ROCK expression is mainly localized in syncytiotrophoblast cells of the villous tissue.[104] This suggests that the increased expression of ROCK could be viewed as a compensatory response to microvilli shedding. These findings may have profound implications for PE where vasoconstriction and ROCK elevation are implicated. This signaling pathway may contribute to the severity of abnormal placentation and subsequent vasoconstriction and hypertension seen in PE. As discussed below, ROCK plays a considerable role in unmasking α_{2C}-AR vasoconstrictor function. This might drive the speculation of a contributing role for this receptor in the various elements modulated by ROCK in PE pathophysiology, especially as pertains to vasoconstriction. However, this remains to be established.

6.2 | ROCK and α2C-ARs translocation and expression

The role of RhoA/ROCK activation in arterial constriction is well established. RhoA also appears to mediate effects of various cues. For instance, stressors such as moderate or physiological cooling to 28°C induce a rapid increase in mitochondrial ROS in VSMCs, leading to RhoA-ROCK activation. This ROS-induced Rho activation causes reorganization of the actin cytoskeleton, which then evokes the translocation of α_{2C}-ARs from the *trans*-Golgi to the cell surface.[56] Without this translocation, α_{2C}-ARs would remain intracellularly trapped and would thus be unable to respond to their physiological agonists nor impart any effect on vasoconstriction.[57,105] Importantly, when VSMCs isolated from human dermal arterioles are treated with Rho or ROCK inhibitors, no receptor translocation or actin dynamics are seen.[106] This clearly argues for a critical and rather indispensable role for Rho-ROCK in the recompartmentalization of vascular α_{2C}-ARs. As such, the interplay between ROS and ROCK in α_{2C}-AR expression and function, along with heightened arteriolar constriction, is established. Importantly, evidence shows that ROS production is increased in PE and promotes vasoconstriction by activating PKC and RhoA/ROCK signaling pathways.[107] The latter potentially culminates in increased spatial and functional rescue of α_{2C}-AR.

One of the key modulators of Rho activation is NO. NO leads to increased intracellular accumulation of cGMP, which in turn induces VSMC relaxation by activating the cGMP-dependent PKG.[108,109] The potent vasodilator action of the cGMP/PKG pathway is explained through a decrease in cytosolic Ca^{2+},[110] and "Ca^{2+}desensitization" by stimulation of myosin light chain phosphatase activity.[111,112]

Importantly, NO has been shown to impart an inhibitory control on Rho/ROCK signaling in multiple studies.[113,114]

In the context of PE, reduced VSMC sensitivity to NO might favor RhoA stimulation. This activation would in turn lead to α_{2C}-ARs translocation to the VSMC surface, thus promoting vascular hypercontractility. Indeed, when its expression in the placenta of normotensive women was compared to that of preeclamptic patients, immunohistochemistry and Western blotting analysis showed that ROCK expression is significantly higher in PE.[104] This implies an association between ROCK and PE, especially in light of ROCK's role in α_{2C}-AR-mediated constriction of small-sized arteries.

It is important to note that one study reported a lower expression of RhoA in umbilical arteries of PE women compared to normal pregnant women, whereas ROCK I and ROCK II mRNA levels were similar.[115] While this might appear contradictory to what we propose, a closer look at this study revealed that the lower expression of RhoA was at mRNA and not the protein level. As such, it might still be possible that increased translational efficiency would lead to equivalent protein levels of RhoA, independently of the mRNA levels. Furthermore, the downregulation of RhoA mRNA levels in umbilical arteries from pregnancies complicated by PE may serve as a protective mechanism to counteract the diminished perfusion associated with the pathophysiology, especially that this reduced mRNA levels were reported very late during pregnancy where constrictive cues would be rather dramatically augmented.

Collectively, it is very interesting to speculate that specific modulators of α_{2C}-AR activity may be useful as therapeutic agents for remedying alterations of RhoA/ROCK signaling that is seen in PE. These agents may be important mediators in compensating the endothelium impairment as well as the decreased responsiveness to NO and increase in ROS seen in PE that in turn increases RhoA/ROCK signaling and perpetuate their downstream effects.

7 | CONCLUDING REMARKS

PE remains a major affliction of pregnancy with significant negative maternal and fetal outcomes. At its core, PE is a vascular disorder involving inflammation, impaired endothelial function, and augmented vasoconstriction. Although no direct evidence correlate PE with altered α_2-AR function, a multitude of shared regulatory pathways link them together. α_2-AR mediate central and peripheral vascular responses to stressful maternal stimuli, regulate inflammatory pathways implicated in PE, specifically target vasodilatory mechanisms relevant in PE, and are affected by signaling cascades triggered along PE pathogenesis. As it stands, the available evidence is rather circumstantial and does not establish a causal relationship one way or the other. Certainly, the pathways described could support a scenario where α_2-AR dysfunction might precipitate the inflammatory and functional changes seen in PE, yet the opposite situation cannot be ruled out. As such, systematic investigation of the involvement of subtype-specific α_2-AR function/dysfunction in PE is warranted. Examination of the consequences of intervention with α_2-AR modulators could shed light on the causal sequence of events in PE. Selective modulation of different α_2-AR subtypes might prove effective as a therapeutic intervention with PE. Whether through reduction of central activation of HPA and increased peripheral sensitivity to vasoconstriction; or through enhancement of peripheral anti-inflammatory effects and vasodilation, selective positive and negative modulators of α_2-AR activity might prove useful therapeutic tools in this disorder.

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