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Emerging drugs for preeclampsia – the endothelium as a target

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Abstract

Preeclampsia, the development of new onset hypertension and proteinuria during pregnancy, affects ~ 3 – 8% of all pregnancies and is a leading cause of maternal and perinatal morbidity and mortality. Despite the potentially devastating effects of this disease on the mother and the baby and the recent advances in understanding some of the pathological mechanisms responsible for the progression of preeclampsia, there are still few therapies available to manage the disease. The maternal syndrome of preeclampsia is characterized by systemic endothelial dysfunction; therefore, agents that improve endothelial function may hold promise to alleviate the symptoms of preeclampsia, delay the necessity for preterm delivery and improve neonatal outcomes. This brief review will focus on two therapies that are already approved for use in the US for other indications: PDE-5 inhibition to preserve nitric oxide – cGMP signaling to promote vasodilation and inhibition of the endothelin type A receptor to reduce vascular contraction.

Keywords

endothelin-1; hypertension; PDE-5; pregnancy; sildenafil

1. Introduction

Preeclampsia, a hypertensive disorder of pregnancy characterized by new onset hypertension after gestational week 20, is a leading cause of maternal and perinatal morbidity and death worldwide, affecting ~ 3 – 8% of all pregnancies in the US [1–3]. Despite the severity and incidence of this disease, the mechanisms of the pathogenesis of preeclampsia remain unclear, and treatment options are limited due to teratogenic effects of many standard antihypertensive medications. Current therapy for the management of preeclampsia includes antihypertensives such as methyldopa, labetalol and nifedipine and magnesium sulfate for prevention of eclamptic seizures [4]; however, these treatments have limited efficacy, and the only ‘cure’ for preeclampsia is the delivery of the placenta, resulting in iatrogenic

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Declaration of interest

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preterm births in many cases. There is a vital need for the discovery of new therapeutic options for women with preeclampsia that ameliorate the maternal symptoms and are safe for the growing fetus.

2. Role of endothelial dysfunction in the pathogenesis of preeclampsia

Although the initial causes of the development of preeclampsia remain unknown, it is thought that, in some cases of the disease, abnormal placentation due to insufficient trophoblast invasion and failure of spiral artery remodeling lead to inadequate blood flow to the placenta and a continuing cycle of repeated ischemia-reperfusion injury [5,6]. The resulting hypoxic environment within the placenta stimulates oxidative stress and the release of placental factors such as soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin, agonistic autoantibodies to the angiotensin type 1 receptor (AT1-AA) and inflammatory cytokines [7]. These factors, along with the presence of additional maternal risk factors for preeclampsia, contribute to a generalized systemic vascular endothelial dysfunction and result in increased systemic vascular resistance and hypertension [5].

In normal, healthy pregnancy, maternal systemic endothelial function is enhanced with increased nitric oxide (NO) production and a resistance to vasoconstrictors. However, in women with preeclampsia, reduced NO production results in reduced endothelium-dependent dilation, and the vasculature is hyper-responsive to vasoconstrictive stimuli, increasing vascular resistance (for detailed reviews, please see Refs. [5,8]). Two factors implicated in the endothelial dysfunction of preeclampsia are reduced NO-cGMP signaling and increased activation of the endothelin-1 (ET-1) system. Therefore, therapeutic agents that target these pathways are the focus of current clinical and basic research studies to determine if they can be used safely and effectively in women with preeclampsia. This review focuses on the use of PDE-5 inhibitors to preserve NO-cGMP signaling and endothelin receptor antagonists to inhibit the actions of ET-1. These agents are already approved for the treatment of pulmonary artery hypertension, and PDE-5 inhibitors are also used for the treatment of erectile dysfunction.

3. Role of NO deficiency and use of PDE-5 inhibitors in preeclampsia

Decreased NO activity is a characteristic feature in animal models of preeclampsia, and women with preeclampsia have reduced levels of NO metabolites in blood and amniotic fluid. Furthermore, systemic inhibition of NO synthase in pregnant rats results in a preeclamptic phenotype, indicating the crucial role of NO in maintaining cardiovascular health in pregnancy [7]. Therapies to preserve NO signaling could be beneficial to promote vasodilation, reduce blood pressure and potentially enhance uteroplacental perfusion in women with preeclampsia. PDE-5 inhibitors, such as sildenafil citrate, prolong the effects of NO signaling by inhibiting the breakdown of the second messenger of NO, cGMP. In addition to causing systemic vasodilation to reduce the hypertension associated with preeclampsia, PDE-5 inhibitors may also help with improving the reduced placental perfusion that is thought to be the cause of the maternal syndrome. Sildenafil has been shown to improve endothelial dysfunction in myometrial vessels of women who have

pregnancies complicated by intrauterine growth restriction and increase dilation of chorionic plate arteries obtained from women with healthy pregnancies [9,10].

Studies in animal models provide preclinical evidence to support the use of sildenafil in women with preeclampsia. In animal models of preeclampsia (the reduced uterine perfusion pressure [RUPP] rat model, the suramin-treated rat and the catechol-*O*-methyl transferase knockout mouse), beneficial effects of sildenafil included reduced blood pressure, improved fetal growth, enhanced endothelial function and normalized umbilical artery Doppler waveforms [11–13]. Furthermore, both clinical and preclinical studies suggest that sildenafil is safe during pregnancy as no adverse effects on maternal or fetal safety were observed in preeclamptic patients or in healthy Sprague Dawley rats [14,15].

Case reports support the use of sildenafil as an effective treatment for improving fetal growth in isolated cases of preeclampsia or fetal growth restriction [16,17]. However, in an initial clinical trial in a small cohort of women, sildenafil was not able to prolong pregnancy although there was a trend for improved fetal growth and decreased maternal blood pressure. The lack of efficacy in this trial may be due to lack of early intervention or insufficient drug concentrations due to the slow dosing regimen required to ensure patient safety in this initial study [14]. We look forward to the results of the ongoing STRIDER trial [18] that will determine if sildenafil improves fetal outcomes in fetuses with early onset severe growth restriction and hope that similar trials for the treatment of preeclampsia will be planned soon.

4. Role of ET-1 activation and use of endothelin receptor antagonists in preeclampsia

ET-1 is synthesized primarily in endothelial cells but also by the syncytiotrophoblast within the placenta. ET-1 promotes cell proliferation and differentiation and hormone production and modulates vascular tone. Increases in ET-1 production and release have been demonstrated in response to hypoxia, oxidative stress, TGF-β, IL-1β, sFlt-1, TNF-α and AT1-AA, factors commonly associated with the pathophysiological state of preeclampsia. ET-1 elicits its actions through two cell-surface G-protein-coupled receptors, ET-1 type A (ET_A), located primarily on vascular smooth muscle cells, and type B (ET_B) receptors, located on endothelial, vascular smooth muscle and epithelial cells. Signaling through the ET_A receptor results in cell proliferation and vasoconstriction, whereas activation of the ET_B receptors mediates vasodilation and natriuresis via NO and prostacyclin [19,20].

Several lines of evidence suggest a pathogenic role for ET-1 in preeclampsia. Reports from human studies show women with preeclampsia have a twofold to threefold increase in circulating ET-1 levels particularly in patients suffering from hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, although this is not a universal finding. However, recently, Verdonk *et al.* noted a positive correlation with plasma ET-1, sFlt-1 and mean arterial pressure, suggesting that high anti-angiogenic states, such as in preeclampsia, are associated with ET-1 activation and pathogenesis of the disease [21]. Data from the RUPP animal model of preeclampsia, in which uteroplacental blood flow is reduced, demonstrate raised mean arterial pressure and preproendothelin mRNA expression within

the kidney. More revealing data come from experimental animal models in which circulating maternal factors thought to play a role in the pathogenesis of preeclampsia were overexpressed. To this end, sFlt-1, TNF-α or AT1-AA infused into pregnant rats to mimic levels seen in human preeclampsia or HELLP syndrome yielded elevations in mean arterial pressure and increased preproendothelin levels. Cumulatively, these studies suggest a role for ET-1 as the final common pathway in the development of endothelial dysfunction and hypertension in preeclampsia [22,23].

Currently, ET receptor antagonists are used in the treatment of numerous cardiovascular diseases including systemic and pulmonary hypertension, congestive heart failure, myocardial infarction, vascular restenosis and atherosclerosis, renal failure, cancer and cerebrovascular disease. Indeed, administration of ET_A receptor blockers to numerous hypertensive pregnant animals models (RUPP, sFlt-1 infusion, TNF-α infusion, AT1-AA infusion models) has proven beneficial to reduce maternal hypertension [3]. However, although blockade of the endothelin system during the preeclamptic state presents as a beneficial pharmacological intervention, investigations yield results that are not favorable to fetal development [24]. Studies performed in genetically modified animals revealed ET-1 as essential for normal embryonic development. Animals lacking both ET-1 and the ET_A receptor develop cardiovascular and/or craniofacial malformations, whereas knockout of the ET_B receptor renders a phenotype similar to human megacolon (Hirschsprung's disease). However, endothelin receptor antagonists may still be a potential therapeutic target for the treatment of preeclampsia. Most studies have focused on administration of ET-1 receptor antagonists early in gestation, although it may be possible that later pharmacological intervention may prove efficacious and safe for the fetus. A more promising venture should be aimed toward the development of ET_A receptor blockers that would not cross the maternal–fetal interface. To this end, a group of small peptide inhibitors of the ET_A receptor have been developed. However, due to their peptidic nature, the clinical potential is hindered as they are rapidly hydrolyzed in the systemic circulation and gastrointestinal tract. An orally active, non-peptide, highly ET_A-selective receptor antagonist has been developed; however, no studies to date have investigated the efficacy or teratogenic effects in the setting of pregnancy or preeclampsia [25].

5. Expert opinion

Although there has been progress in understanding the mechanisms responsible for the pathogenesis of preeclampsia, effective therapeutic options for women suffering from this disease are still not available. We propose that agents that improve endothelial function and directly target the systemic vascular dysfunction of preeclampsia hold promise as potential new therapies to alleviate the maternal symptoms of preeclampsia to prolong pregnancy in severe preeclampsia. We propose that the available evidence from experimental animal studies supporting the use of PDE-5 inhibitors and endothelin receptor antagonists for the treatment of preeclampsia warrants further investigation of these agents to determine if such therapeutics will be beneficial in the heterogeneous and complex human disease and safe for the mother and baby.

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