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Review

Review: Potential druggable targets for the treatment of early onset preeclampsia

John W. Downing *, Curtis L. Baysinger, Raymond F. Johnson, Ray L. Paschall

Division of Obstetric Anesthesia, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, TN, USA

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ABSTRACT

Placental delivery is the only known cure for early onset preeclampsia, a major cause of maternal and neonatal morbidity and mortality worldwide. Prolonging pregnancy beyond 25 weeks without undue maternal risk favors fetal survival, improves neonatal outcome and saves money.

In vitro experiments using human placental tissue and *in vivo* studies employing "preeclamptic" animal models reveal the presence of likely druggable targets, especially within the maladapted intracellular nucleotide transduction pathways of preeclampsia.

This review focuses on some novel pharmacological treatment options targeting early onset severe preeclampsia. Human and animal derived experimental data support the possible roles of nitric oxide donors (glyceryltrinitrate), aspirin, dietary supplements (calcium, L-Arginine, anti-oxidant vitamins), phosphodiesterase-5 inhibitors, statins, carbon monoxide and most recently, hydrogen sulfide.

Extension of pregnancy or improvement of the disorder using means applicable in under resourced areas of the world would have a major positive impact on women's health globally. We therefore advocate the immediate launch of clinical trials testing simple innovative therapies in large obstetric units of developing countries such as South Africa or Brazil where preeclampsia is endemic and a regular killer of both mothers and offspring.

> "All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time" [1]. Austin Bradford Hill (1897–1991).

Introduction

The incidence (3–14%) of preeclampsia (PE), a major cause of maternal morbidity and mortality worldwide, is resource dependent [2]. Early onset PE (0.8% of <32 weeks pregnancies) generates significant fetal and neonatal wastage [3]. Expectant management garners minimal perinatal benefit and excessive maternal morbidity, prompting advisement of termination at <24 weeks [4]. In a "low-resource setting" no PE baby delivered <26 weeks lived [5].

Almost 20% of surviving extremely low birth weight (ELBW) infants manifests cerebral palsy (CP) at 18 months of age, 10% suffering impaired sight and/or hearing [6]. At 18 years 40% are disabled. Special education and medical costs for PE children delivered early (<26 weeks) rather than later (28–33 weeks) triples!

* Corresponding author. Address: Department of Anesthesiology & Division of Obstetric Anesthesia, Vanderbilt University School of Medicine, 4202 Vanderbilt University Hospital, 1211 22nd Avenue South, Nashville, TN 37232-7580, USA. Tel.: +1 615 322 8476(O), +1 615 370 8304(R); fax: +1 615 343 1732.

E-mail address: john.downing@vanderbilt.edu (J.W. Downing).

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Endothelial nitric oxide synthetase (eNOS) controls the reaction:

$$\text{LArginine}(\mathbf{Arg}) + \text{NADPH} + \text{H}^{+} + 2\text{O}_2 \blacktriangleright \text{Nitric Oxide}(\mathbf{NO}) + \text{LCitrulline} + \text{NADP}^{+}[7].$$

Within the Intra-Cellular Nucleotide (ICN) transduction pathway NO activates guanylate cyclase (sGC) converting guanine triphosphate (GTP) to cyclic gaunosine monophosphate (cGMP) that activates protein kinase G1 (PKG1) isozymes. Adenyl cyclase induces a parallel increase in cyclic adenosine monophosphate (cAMP). Both monophosphates relax uteroplacental and fetoplacental vasculature, inhibit platelet aggregation, prevent capillary leakage and are hydrolyzed by type specific phosphodiesterases (PDEs) [8–10]. ICN signaling cascade malfunctions impact PE's pathogenesis [8,11–15]. Pursuing druggable targets within the ICN system could ostensibly regulate PE – Fig. 1 – after Boerrigter and Burnett; Ahmed [16,17].

NO donors

Nitroglycerin (NTG) dilates fetoplacental vasculature *in vitro* and *in vivo* and decreases thrombin-fueled human endothelial cell *in vitro* expression of endothelin-1 (Et-1) [18]. NTG inhibits hypoxia/reoxygenation provoked human syncytiotrophoblast apoptosis and hypoxia-induced placental discharge of anti-angiogenic soluble fms-like tyrosine kinase (sFlt-1) and endoglin (sEng) [19,20]. Et-1, sFlt-1 and sEng are quintessential to PE pathophysiology [18–21].

GTN (5 mg) or placebo patches were randomly applied daily to women manifesting abnormal umbilical artery (Ua) Doppler waveforms at 24–26 weeks [22]. GTN did not perturb maternal hemodynamics or uterine artery (UA) and Ua Doppler parameters, but neither were the frequencies of PE, preterm delivery or IUGR reduced. In contrast NTG (50 mg) patches applied for 3 days decreased maternal blood pressure (MBP), lowered UA and Ua resistance (RI) and pulsatility (PI) indices, and successfully deferred delivery [23].

Conclusion

NO donors are useful for short term PE management. Maternal systemic hypotension and worsened placental perfusion are potential hazards.

Phosphodiesterase-5 (PDE5) inhibition

Hypothetically PDE5 inhibition for PE improves maternal and neonatal outcomes by boosting cGMP availability, inviting uteroplacental and fetoplacental vasorelaxation [8]. In the dual perfused, single isolated human placental cotyledon both the NO donor sodium nitroprusside (SNP) and UK 114542-27 (selective PDE5 inhibitor) relax pre-constricted fetoplacental arterioles [24–26]. PE attenuates bradykinin (BK) induced vasorelaxation of pre-constricted myometrial small arteries [27]. Pre-incubation with UK 343664 (another specific PDE5 inhibitor) enhanced BK induced vasorelaxation. Human Ua pre-constricted with 5-HT or histamine relax whenever cAMP/cGMP expression increases or breakdown decreases [9,10].

The ubiquitous PDE5 inhibitor sildenafil citrate (SC) dilated human chorionic plate arteries [10]. PDE5mRNA and protein were identified within arterial muscle and PDE5 detected within the fetoplacental circulation. Methylene blue (direct cGMP inhibitor) and Rp-8-Br-PET-cGMPS (cGMP-dependent protein kinase inhibitor) attenuated SC vasodilatation. The eNOS inhibitor *Nω*-nitro-L-arginine methyl ester (L-NAME) did not influence SC cGMP dependent vasorelaxation. In contrast SC augmented SNP generated vasodilatation. SC "prevented" PE induced human Ua endothelial dysfunction possibly through both NO/cGMP dependent and independent pathways [28]. Caution was advocated against SC obstetric use pending clarification of its effects on fetoplacental arteriolar resistance [10]. Contextually PDE5 inhibition reverses 5-HT and hypoxemic fetoplacental vasoconstriction (HFPV) [25,26].

Pro-angiogenic vascular (VEGF) and placental endothelial (PEGF) growth factors activate eNOS [29]. eNOS inhibition impedes NO-sGC-cGMP facilitation of pregnancy-induced "expansive" uterine circulatory remodeling and placental vasodilatation [30].

Only humans and gorillas are afflicted by PE making PE research difficult [31]. But murine and human placentae share architectural similarities [32]. L-NAME treated pregnant rats develop hypertension, proteinuria, glomerular capillary endotheliosis and intra-uterine growth restriction (IUGR) with increased fetal losses [21,33–35]. Vasopressor refractoriness, low platelets, reduced creatinine clearance, blood volume restriction, hemoconcentration and increased blood viscosity are described [34,35].

L-NAME decreased rat uterine artery diameter and distensability [36]. SC co-treatment restored litter size, fetal growth and placental vascular distension but did not lower MBP. SC may relax tonic spiral arteries to augment uteroplacental blood flow (UBF) and optimize trans-placental exchange. Others found that SC lowered MBP, modulated proteinuria, reduced fetal wastage ostensibly by increasing UBF, and reduced plasma sFlt-1 and sEng levels [21,37].

Neurologically intact IUGR infants delivered by PE mothers exhibited lower IQs at age three, the differences waning by age six [38,39]. Furthermore PE was allied with inferior cognitive advancement at age two in ELBW infants born before 32 weeks [40]. Cauli et al. therefore theorized that SC would reestablish cognizance in pups born of PE rodents [41]. Pregnant dams drank plain water or water medicated with L-NAME 50 mg/kg; SC 4 mg/kg; or L-NAME 50 mg/kg plus SC 4 mg/kg. Pup learning ability for a Y maze conditional discrimination task was impaired by L-NAME but not SC or L-NAME plus SC. Learning problems equated with cerebellum glutamate-NO-cGMP pathway dysfunction. SC restored learning capacity and cerebellar cGMP levels.

Chronic prenatal hypoxia induced by L-NAME in rats generated IUGR, increased pup mortality and accelerated apoptotic activity mainly in the subventricular and pallidum zones, changes evocative of CP [42]. Healthy pregnant rats given SC 10, 50 or 90 mg/kg daily from gestational day 4–20 manifested little change in MBP and delivered normal, healthy litters [43]. SC increased plasma cGMP. The highest dose decreased maternal sodium retention,