

Preeclampsia treatment for mothers also benefits offspring

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Therapeutic role of intrapartum PDE-5 inhibition on blood pressure and renal injury in offspring of preeclamptic rats

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Introduction

- Preeclampsia is a serious complication in pregnancy characterized by increased blood pressure and proteinuria after 20 weeks gestation that is detrimental to both the mother and the fetus. Up to 10% of pregnancies are complicated by preeclampsia.
- Offspring of preeclamptic pregnancies have increased blood pressure (BP) during childhood and nearly double the risk of stroke later in life. These offspring also carry increased risk for cardiovascular, metabolic, and kidney diseases.
- The Barker hypothesis proposes that the adverse intrauterine environment created by preeclampsia programs fetal tissues and organs to develop high BP from early childhood.
- Our laboratory has previously characterized the Dahl salt sensitive rat (Dahl S), a known genetic model of hypertension and kidney disease, as a spontaneous model of superimposed preeclampsia.
- Animal models of hypertension have demonstrated the ability of various therapies such as nitric oxide (NO) donors to program hypertension. Sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor, prolongs the NO-cGMP signaling cascade and improves the maternal syndrome of preeclampsia; however, determination of optimal timing, effectiveness, and safety during perinatal use have yet to be reported.

Hypothesis

Use of a PDE-5 inhibitor during preeclamptic pregnancy improves long-term BP and renal injury in the offspring.

Protocol

Female Dahl S rats on a 0.5% salt diet, a previously characterized spontaneous model of superimposed preeclampsia, were mated and treated orally with sildenafil (50 mg/kg/day), labetalol (currently used to manage hypertension in preeclamptic patients; 10 mg/kg/day), or vehicle from gestational day 10 to delivery. Dams were placed on normal salt chow at delivery throughout weaning at four weeks of age (n=6 per treatment).

At seven weeks of age, male and female offspring were acclimated to cages for four days before tail cuff BP measurement on day five. The process was repeated at 10-12 weeks of age for analysis of the time-dependent change in systolic BP (n=4/group). At 3 months of age, rats were anesthetized, and blood and kidneys were collected.

Kidney sections were fixed in 10% formalin, paraffin embedded, sectioned, and stained with Masson's Trichrome stain. Tubulointerstitial scarring was measured in 4 µm kidney sections stained with Masson's Trichrome (Neon SB microscope with DS-P11.5 Meg Color C digital camera and Ne-Elemis image-analysis software version 3.0) (n=3/group).

Urine was collected via 24-hour metabolic cage for measurement of urinary protein (Bradford assay) and KM-1 (QuikChem HAD System). Blood urea nitrogen (BUN) was measured in plasma collected during tissue harvest on the Vet Ace Chemistry Analyzer at the UMMC core lab. (n=2-4/group).

Figure 1: Systolic blood pressure measurements at 7 and ~11 weeks of age in male and female offspring of preeclamptic pregnancies. Systolic BP increased significantly in male Dahl S offspring of untreated mothers as expected; however, the offspring from sildenafil treated dams exhibited a decrease in SBP (M-CON: +35±0.4 mmHg; M-SLD: -11±5 mmHg). This protective effect was not elicited by treatment with labetalol (+15±9 mmHg). Female offspring demonstrated a similar trend (F-CON: +14 mmHg; F-SLD: -4±9 mmHg; F-LAB: +5±4 mmHg). Data presented are mean±SEM. *p<0.05 vs CON.

Figure 2: Quantification of tubulointerstitial fibrosis and kidney injury marker 1 (KM-1) in male and female offspring of preeclamptic pregnancies. Tubulointerstitial scarring is increased in male Dahl S offspring of untreated mothers as compared with offspring of sildenafil treated dams (Area: CON: 9±0.8%; SLD: 5±0.6%), but no changes were observed in kidney sections from female rats. KM-1 excretion was significantly decreased in female offspring of SLD-treated mothers (CON: 23.1±2.1 ng/day; SLD: 13.6±1.4 ng/day) indicating a reduction in tubular injury though no difference was seen in male offspring. Data presented are mean±SEM. *p<0.05 vs CON.

Figure 3: Proteinuria and BUN measurements at 3 months of age in male and female offspring of preeclamptic pregnancies. While no significant difference is observed in proteinuria between CON and SLD groups, female SLD offspring exhibit significantly less protein excretion than their male littermates (M-SLD: 138±18 mg/day; F-SLD: 53±7 mg/day). Female SLD offspring also exhibit significantly lower levels of BUN compared to the CON female group (F-CON: 22±1 mg/dL; F-SLD: 16±1 mg/dL). Data presented are mean±SEM. *p<0.05 vs CON.

Conclusions and Future Directions

- The pregnant Dahl S rat fed a normal salt diet is a spontaneous model of preeclampsia that mimics many characteristics of the human disease.
- Our current findings demonstrate that the long-term increase in blood pressure seen in offspring of untreated preeclamptic mothers is attenuated by use of intrapartum sildenafil therapy. We also show that renal injury at three months of age is reduced in male offspring of preeclamptic mothers treated with sildenafil.
- These preliminary data, combined with our recently published studies, suggest that sildenafil during preeclamptic pregnancy may improve fetal outcomes through improvement of uteroplacental blood flow, preservation of nitric oxide signaling pathways.
- Our findings support the hypothesis that a PDE-5 inhibitor during preeclamptic pregnancy may improve long-term BP and renal injury in the offspring.
- These results also highlight significant effects of intrapartum treatment on male apparent renal injury and BP versus kidney function in female offspring.
- We are currently completing a full study to determine the effects of intrapartum PDE-5 inhibition on the lifespan of these offspring.

Acknowledgements

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Hannah Turbeville performed research that showed treating preeclampsia with sildenafil citrate (Viagra) may help protect the cardiovascular health of the offspring. Credit: Hannah Turbeville, University of Mississippi Medical Center

An estimated six to 15 million people in the U.S. are children born of a pregnancy complicated by preeclampsia. New research performed in rats reveals that treating preeclampsia with sildenafil citrate (Viagra) may help protect the cardiovascular health of the offspring.

Preeclampsia occurs when women with otherwise normal [blood pressure](#) experience elevated [blood](#) pressure during pregnancy. Children of women with preeclampsia during pregnancy have higher blood pressure during childhood and almost double the risk of stroke later in life.

"The ultimate goal of our work is to improve the long-term health of women and children affected by preeclampsia," said Hannah Turbeville, a [doctoral student](#) at the University of Mississippi Medical Center, who conducted the new study. "There are limited guidelines for addressing the [health risks](#) to these groups, and we hope not only to bring attention to these risks but also to propel research forward that will inform preventative interventions."

Turbeville will present the new research at the American Physiological Society's annual meeting during the [2019 Experimental Biology meeting](#) to be held April 6-9 in Orlando, Fla.

In previous work, the researchers found that sildenafil citrate, which lowers blood pressure by acting on the nitric oxide pathway, can treat preeclampsia in a rat model of the condition while also decreasing blood pressure in offspring. In the new work, they wanted to determine how sildenafil citrate affects the offspring's response to stressors that normally increase blood pressure.

To mimic human preeclampsia as much as possible, the researchers used a rat model that develops the condition without a procedure or drug.

They then exposed the offspring to a stressor that increases blood pressure. The researchers observed smaller increases in blood pressure for male offspring of rats treated with sildenafil citrate compared to those that did not receive treatment or received a more commonly used blood pressure medication. The [protective effect](#) was not apparent in female offspring.

"Our studies demonstrate the potential for targeted therapy of the nitric oxide pathway to improve the body's response to stressors in the later lives of children of women who experienced [preeclampsia](#)," said Turbeville. "This pathway plays an important role in improving blood flow and lowering blood pressure."

The researchers are working to better understand the gender-specific response to sildenafil citrate. They are also exploring whether the improved response to stressors leads to decreased risk of chronic diseases such as high blood [pressure](#) and chronic kidney disease when these offspring become adults.

Provided by Experimental Biology

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