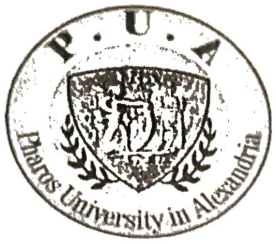

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Modulation by Endothelin and Thromboxane Signaling of Cardiovascular and Renal Damage in Preeclamptic Rats and Their Offspring

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In

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Abstract # 1

Prenatal Endothelin or Thromboxane Receptor Antagonism Surpasses Sympathoinhibition in Managing Cardiovascular and Renal Malfunctions in Preeclamptic Rats

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Current therapies for hypertension and end-organ damage caused by preeclampsia (PE) are limited and defective. Considering the importance of endothelin (ET) and thromboxane A2 (TXA2) signaling in PE pathophysiology, we tested the hypothesis that pharmacologic blockade of ETA or TXA2 receptors improves preeclamptic cardiovascular and renal insults. PE was induced by daily oral administration of L-NAME (50 mg/kg) to pregnant rats for 7 consecutive days starting from gestational day 14. The effects of co-exposure to atrasentan (ETA receptor blocker, 10 mg/kg/day) or terutroban (TXA2 receptor blocker, 10 mg/kg/day) on cardiovascular and renal anomalies induced by PE were assessed at gestational day 20 (GD20) and weaning time and compared to those evoked by α-methyldopa (10 mg/kg/day), the prototypic drug for PE management. Among all 3 drugs, terutroban was basically the most potent in ameliorating PE-evoked increments in blood pressure and decrements in urine sodium and creatinine clearance. The gene expression of ETA, but not TXA2, receptors was significantly increased in cardiac and renal tissues of PE rats both at GD20 and weaning and these effects disappeared after co-treatment with individual protective drugs. By contrast, ETB receptor expression was reduced in PE renal tissues and restored back to non-PE levels by atrasentan, but not α-methyldopa or terutroban. Signs of histopathological damage in cardiac and renal tissues of PE rats were indiscriminately improved by all therapies. Together, pharmacologic elimination of ETA or TXA2 receptors offers a relatively better prospect than α-methyldopa in controlling perinatal cardiovascular and renal complications sparked by PE.

KEY WORDS: Preeclampsia; end-organ damage; tissue inflammation; α-methyldopa; terutroban; atrasentan.

Abstract # 2

Modulation by Antenatal Therapies of Cardiovascular and Renal Programming in Male and Female Offspring of Preeclamptic Rats

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Morbidity and mortality risks are enhanced in preeclamptic (PE) mothers and their offspring. Here we asked if sexual dimorphism exists in (i) cardiovascular and renal damage evolved in offspring of PE mothers, and (ii) offspring responsiveness to antenatal therapies. PE was induced by administering NAME (50 mg/kg/day, oral gavage) to pregnant rats for 7 days starting from gestational day 14. Three therapies were co-administered with L-NAME, atrasentan (ETA receptor blocker), terutroban (TXA2 receptor blocker), or α-methyldopa (central sympatholytic drug). Cardiovascular and renal profiles were assessed in 3-month-old offspring. Compared with offspring of non-PE rats, PE offspring exhibited elevated systolic blood pressure and proteinuria and reduced heart rate and creatinine clearance (CrCl). Apart from a greater bradycardia in male offspring, similar PE effects were noted in male and female offspring. While terutroban, atrasentan, or α-methyldopa partially and similarly blunted the PE-evoked changes in CrCl and proteinuria, terutroban was the only drug that virtually abolished PE hypertension. Rises in inflammatory (TNFα) and oxidative (isoprostane) markers in cardiac and renal tissues of PE offspring were mostly and equally eliminated by all therapies in the two sexes, except for a greater dampening action of atrasentan, compared with α-methyldopa, on tissue TNFα in female offspring only. Histopathologically, antenatal terutroban or atrasentan was more effective than α-methyldopa in rectifying cardiac structural damage, myofiber separation and cytoplasmic alterations, in PE offspring. Overall, the repair by antenatal terutroban or atrasentan of cardiovascular and renal anomalies in PE offspring is mostly sex-independent and surpasses the protection offered by α-methyldopa, the conventional PE therapy.

KEY WORDS: Preeclampsia; fetal programming; end-organ damage; tissue inflammation; drug therapy.