Hypertension in Response to Soluble FMS-Like Tyrosine Kinase-1 During Pregnancy: Role of Endothelin-1
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While soluble fms-like tyrosine kinase-1 (sFlt-1), an endogenous antagonist of vascular endothelial growth factor and placental growth factor has been implicated in the pathogenesis of hypertension during preeclampsia (PE), the mechanisms whereby enhanced sFlt-1 production leads to endothelial dysfunction and hypertension remain unclear. Both sFlt-1 and endothelin-1 production are elevated in women with PE and in placental ischemic animal models of PE, however, the importance of endothelin-1 and sFlt-1 interactions in control of blood pressure during pregnancy is unknown. The purpose of this study was to determine the role of endothelin-1 in mediating sFlt-1-induced hypertension in pregnant rats. To achieve this goal, sFlt-1 (1 ng/kg/d for 5 days) was infused into normal pregnant rats (NP) and pregnant rats orally treated with a selective endothelin type A receptor antagonist, ABT 627 (5 mg/kg/day for 5 days). Plasma concentration of sFlt-1 increased from 735_34 pg/ml in NP rats to 2498_645 pg/ml, (p_0.04) with infusion of sFlt-1. Mean arterial pressure increased from 100_1 mmHg in NP rats to 122_3 mm Hg, (p_0.0001) in sFlt-1 infused rats. Utilizing real-time PCR we found a three-fold increase in preproendothelin mRNA expression in the renal cortices of sFlt-1 induced-hypertensive pregnant rats. In addition, chronic ETAblockade completely abolished the blood pressure response to sFlt-1 in pregnant rats (104_3 vs100_1 mmHg, p_0.0001), while the ETA receptor antagonist had no effect on arterial pressure in NP rats (105_2 vs 100_1mm Hg). In conclusion, this study demonstrates that endothelin-1, via endothelin type A receptor activation, plays an important role in mediating the hypertension in response to excess sFlt-1 during pregnancy.