**The Effect of Tumor Necrosis Factor alpha on Endothelin- 1 Production in Renal Tissue from Pregnant and Non-Pregnant Rats**

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Preeclampsia presents clinically as a triad of syndroms, hypertension, proteinuria, edema, and reduced maternal blood volume. It affects 5-10% of all pregnacies, and is a leading cause of perinatal morbitity and mortality. It has been strongly suggested that preeclamsia is associated with endothelial cell activation. It has been further suggested that ischemic placental tissue may contribute to this maternal endothelial activation via enhanced synthesis and release of cytokines such as Tumor Necrosis Factor alpha (TNF-α). This involement of TNF-α is further supported by reports of elevated circulating levels of TNF-α in women with preeclampsia.

As a consequence of endothelial cell activation, possibly mediated thru TNF-α, is the altered production of endothelin-1. Endothelin-l (ET-1) is a small peptide released from endothelial cells. It is a potent and long lasting vasoconstrictor especially of umbilical and uterine circulation. Additionally, ET-1 has also been shown to reduce renal blood flow because the renal vasculature is particularly responsive to vasoconstriction of ET-1. Endothelin-1 is associated with the development of proteinura in various forms of renal disease. Recent evidence suggests that elevated plasma Endothelin-1 levels in sheep and rats results in a syndrome similar to preeclampsia: hypertension, proteinuria, reduced maternal blood volume.

If taken all together, the information I just describe suggests a significant relationship between TNF-α, endothelial cell activation, ET-1 production and the development of a renal pathophysiology similar to what is seen in preeclampsia. Therefore my purpose this summer is to evaluate this relationship between TNF-α and Endothelin-1 in renal tissue. Then to determine if this relationship is different between pregnant and non-pregnant rats. (That this relationship may be different during pregnancy is supported by a number of reports that the vasculature become more sensitive to the effects of pro-inflamatory cytokins during pregnancy.)

My hypothesis is that TNF-α will stimulate ET-1 production in renal tissue, and this effect will be greater in tissue from pregnant rats as compared to non-pregnant rats. (Then this ET-1 will contribute to vasoconstriction and proteinuria seen in preeclampsia.)

To test the hypothesis an *in vivo* method was used. Four groups of rats were used: 1. Non pregant saline controls; 2. non pregnant TNF-α infusion; 3. Pregnant saline control; and 4. pregnant TNF-α infused. The jugular catheter was surgically implanted into the rat, and infused either saline or TNF-α. The rats were then sacrificed and kidneys removed. From each rat one kidney was used to isolated glomeruli, while the second kidney was used for renal cortical slices. Blood was also drawn at the time of sacrifice to obtain plasma samples. The isolated glomeruli, renal cortical slices, and plasma samples were then measure using an ELISA assay for ET-1.

The results of the experiment did not show an appreciable difference between controls and TNF-α infused rats. (more samples are being collected so data is not complete.) There was also no significant difference between pregant and non pregnant levels of ET-1.

The conclusion (from the limited data) is that TNF-α has no effect on ET-1 production in renal tissue and TNF-α does not exert an effect of ET-1 production in the the kidney of pregant rats.