The timing and source of endothelin expression in ischemia/reperfusion-induced fetal growth restriction in the rat

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Background: Ischemia/reperfusion (I/R) of one rat uterine horn produces fetal and placental growth restriction in both horns. This suggests the involvement of circulating factors in the development of fetal growth restriction (FGR). We have shown, using endothelin (ET) antagonism, that the vasoconstrictor ET is central to this process. I/R-induced placental tissue damage and resultant FGR were both prevented by ET antagonism. The source and timing of the ET expression relative to the I/R insult has not been determined.

Objective: To investigate the timing and tissue source of endothelin expression following unilateral uterine I/R in the rat.

Methods: Unilateral occlusion of uterine and ovarian arteries for 30 min, or sham operation, was performed on timed-pregnant Sprague-Dawley rats (225-250 grams) on gestation day 17 (term=22 days), under combined ketamine/xylazine/acepromazine (40, 8, and 1.3 mg/kg, respectively) anesthesia. Uterine wall, uterine placental bed, and placenta were collected at 3 h, 6 h, 1 day, and 4 days post-I/R, from a separate group of 8-10 rats at each time for each treatment (I/R and sham). Following total RNA isolation, RT-PCR for preproET-1 was performed, normalized to rRNA, and the results were compared among groups by ANOVA with $p<0.05$ considered statistically significant. Results are presented as mean ± SE.

Results: RT-PCR revealed a significant increase in ET-1 expression in uterine wall at 3 h following I/R (ratio of preproET-1 mRNA/rRNA: $2.4 \times 10^{-5} \pm 1.8 \times 10^{-6}$ and $3.3 \times 10^{-5} \pm 2.1 \times 10^{-6}$, sham vs I/R respectively, $p<0.01$). There was no difference in ET-1 expression between the ipsilateral (ischemic) uterine horn and the contralateral horn. Though mean values tended to be slightly greater in other tissues and at other times, no statistically significant differences were evident at the longer times in any of the tissues examined.

Conclusions: Endothelin expression increases in the uterus in response to I/R. This increased ET-1 expression is observed early following the I/R insult. The effect of the excess ET-1 at this early time is sufficient to result in significant FGR at term, a condition which can be ameliorated by ET_A antagonists administered immediately following I/R.