Endothelin receptor A antagonism prevents fetal growth restriction in pregnant eNOS$^{-/-}$ mice

Kehuan Luo[1], Larry G Thaete[1], Xiao-Wu Qu[1], Mark G Neerhof[1,2]. [1]NorthShore University HealthSystem, Obstetrics & Gynecology, United States, [2]University of Chicago, Obstetrics & Gynecology, United States.

Background: Homozygous mating pairs of the NO-deficient endothelial nitric oxide synthase (eNOS) gene knockout mouse (eNOS$^{-/-}$) produce growth-restricted pups. Nitric oxide inhibits the production of the vasoconstrictor endothelin (ET). The reduced NO resulting from knockout of the eNOS gene stimulates the production of ET. Endothelin has been implicated in the pathophysiology of fetal growth restriction (FGR) in several animal models as well as in humans.

Objective: To evaluate the contribution of ET to the pathophysiology of FGR in maternal eNOS-deficient mice.

Methods: Virgin homozygous (eNOS$^{-/-}$) female mice (18-23 grams) were mated with eNOS$^{-/-}$ males (B6.129P2-Nos3^{tm1Unc}). On gestation days 13-19, ET_A antagonist (ABT-546, 20 mg/kg/day, Abbott Laboratories), or vehicle, was administered subcutaneously to homozygous eNOS$^{-/-}$ dams via an osmotic pump (implanted under 2-3% isoflurane anesthesia). Homozygous matings of eNOS$^{+/+}$ mice served as controls; n=16-19 maternal mice per experimental group. The mice were euthanized on day 19. Fetal and placental weights were documented and were compared among NO-deficient and control mice. Results are presented as means ± SE and were tested by ANOVA with $p<0.05$ considered statistically significant.

Results: Fetal weights from vehicle-treated eNOS$^{-/-}$ mice were significantly reduced compared with those from normal (eNOS$^{+/+}$) controls (0.97±0.02 vs. 1.11±0.03, $p<0.001$). Fetal weights from ET_A antagonist-treated eNOS$^{-/-}$ females were not significantly different from normal (eNOS$^{+/+}$) controls (1.07±0.02 vs. 1.11±0.03, $p>0.05$) and were significantly greater in comparison to those from vehicle-treated eNOS$^{-/-}$ controls (1.07±0.02 vs. 0.97±0.02, $p<0.05$).

Conclusions: Endothelin, acting via the ET_A receptor plays a prominent role in the pathophysiology of FGR in pregnant eNOS$^{-/-}$ mice. Maternally administered ET_A antagonism prevents FGR in this model.

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