

Title: Intrauterine growth restriction enhances hypertension and markers of vascular remodeling in adult rat offspring fed a high fat diet

Tom Miller, Blair Dodson, Yueqin Yang, Baifeng Yu, Erin Zinkhan, MD.

Background: Intrauterine growth restriction (IUGR) and fetal exposure to a maternal high fat diet (HFD) independently predispose to offspring hypertension in a sex-specific manner. Hypertension and arterial stiffness may be secondary to vascular aging mediators. Advanced glycation end products (AGEs) and their receptors (RAGEs) mediate vascular aging through remodeling. We hypothesized that in a rat model of IUGR, IUGR offspring would have increased blood pressure (BP), AGEs and RAGEs when exposed to a maternal HFD, findings that would persist despite weaning to a regular rat chow.

Methods: Adult female rats were fed either a regular diet (RD) or a HFD prior to mating through gestation and lactation. IUGR was induced by uterine artery ligation. At weaning, offspring were weaned to either a RD or HFD through postnatal day (PND) 60. For both control (C) and IUGR (I) rats, this study design resulted in 3 diet groups: offspring from dams fed a RD and weaned to a RD (CRR and IRR), offspring rats from dams fed a HFD and weaned to a RD (CHR and IHR), and offspring from dams fed a HFD and weaned to a HFD (CHH and IHH). Tail-cuff blood pressures and aorta protein levels of AGEs and RAGEs were assessed at PND 60 and compared between groups within each sex.

Results:

Results: In females, IHH and IHR offspring had increased systolic BP (SBP) and IHH female rats had increased diastolic BP. Concordantly, IHH and IHR females had increased heart mass to body mass (HM:BM) ratios. IHH female rats had increased RAGEs and no change in AGEs. In males, IHH offspring had increased SBP compared to all other groups and increased HM:BM ratio compared to CRR. IHH males had increased AGEs and no change in RAGEs. In both sexes, weaning to a RD normalized AGEs and RAGEs in IHR rats compared to CRR rats. $p < 0.05$

Conclusion/Speculation: IUGR increased BP, cardiac mass, and induced vascular remodeling mediators when combined with a maternal and postnatal HFD. Weaning IUGR rats to a regular diet normalized levels of vascular remodeling mediators in both sexes without improving blood pressure or cardiac mass in females. We speculate that increased SBP in IUGR rats results from underlying IUGR-induced structural changes to the extracellular matrix that is not normalized by a RD after weaning.