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"Effects of High Fat Diet on Placental ACE2 Expression and Vascularization in Female Mice"

BACKGROUND: Obesity-induced metabolic dysfunction impairs cardiovascular and reproductive health in women, potentially through an imbalance within the Renin-Angiotensin System (RAS). Angiotensin II (Ang II), acting through angiotensin type I receptors (AT_1R), promotes vasoconstriction and oxidative stress whereas angiotensin-converting enzyme 2 (ACE2) metabolizes Ang II to anti-inflammatory/vasodilatory peptide Ang-(1-7). Previous studies from Dr. Yue's group have shown that female C57BL/6 mice fed a high fat diet (HFD) for 10-12 weeks developed cardiometabolic dysfunctions including reduced glucose and insulin tolerance, elevated blood pressure, and autonomic dysfunction compared to regular diet (RD) fed controls. Importantly, following mating with RD-fed males, offspring from HFD-fed females suffered low birth weight and increased postnatal mortality. Mechanistically, reduced expression of ACE2 was observed in placenta from HFD-fed females, and treatment with Ang-(1-7) improved the cardiometabolic and reproductive function in HFD-females.

OBJECTIVE: The objective of this study was to examine the expression and localization of ACE2 in placenta and its relationship with placental vascularization and tissue morphology in RD and HFD fed females and the potential therapeutic effects of Ang-(1-7) treatment.

METHODS: Formalin-fixed, paraffin-embedded mouse placenta sections (4 μm) were prepared for histological and immunohistochemical (IHC) staining. IHC with ACE2 and Wheat Germ Agglutinin (WGA) antibodies were performed on placenta sections to assess ACE2 expression and vascularization, respectively. Hematoxylin and Eosin (H&E) stained placenta sections were imaged to evaluate placental morphology, and average junctional zone-to-labyrinth ratios were measured using Cell Sense software. IHC images were acquired using a Keyence microscope, and ACE2 and WGA expression levels were quantified from 40X images in the labyrinth zone of the placenta. Lastly, RT-qPCR was performed using placental cDNA to quantify ACE2 mRNA expression.

RESULTS/CONCLUSIONS: In the labyrinth zone (LZ) of the placenta, ACE2 is expressed in syncytiotrophoblasts, the cell type that promotes nutrient exchange and fetal development. HFD leads to decreased ACE2 expression in the placental LZ and reduced labyrinth area compared to RD controls, which was alleviated by Ang-(1-7) treatment. Area measurements of the LZ and junctional zone (JZ) showed a higher average LZ area in the RD and ANG 1-7 treatment groups than in HFD. The average LZ area (pixels) was 5,399,313 ± 57,212 (mean ± standard error) in RD, 4,204,575.2 ± 345,931 in HFD, and 5,249,899.4 ± 154,304 in the Ang-(1-7) treatment group. One-way Anova statistical analysis showed that the LZ area was significantly lower in HFD compared to other treatment groups, but there was no significant difference between the LZ area in RD and Ang-(1-7) treatment group. WGA staining showed a simplification of the maze-like vascular network in the labyrinth in the HFD group compared to RD controls, and Ang-(1-7) treatment resulted in improved vascularization. RT-qPCR data showed a significant decrease in ACE2 mRNA levels in the HFD treatment group, consistent with the IHC results. Taken together, our study suggests that HFD downregulates ACE2 in the placenta, leading to reduced labyrinth growth and vascularization.

*** This was a joint project completed with L2 LSUHSC Medical Student Muntha Abbas ***