Synergism between maternal and offspring high fat diet feeding in the non-human primate neuroactive metabolome

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OBJECTIVE: The microbiome produces small molecules, including neuroactive metabolites crucial for normal lifelong behavior. In a non-human primate (NHP) model, offspring exposed to maternal high fat diet (mHFD) display physiological changes compared to offspring exposed to maternal control diet (mCTR). To investigate the relationship between maternal diet and offspring post-weaning diet, we hypothesized that mHFD exposure plus a post-weaning high fat diet (HFD) will produce a persistently altered gut metabolome profile in vivo compared to mCTR exposure.

STUDY DESIGN: Japanese macaque dams were fed mHFD, mCTR, or a mHFD-to-mCTR reversal diet during pre-pregnancy, gestation, and lactation (Fig 1). Offspring were weaned onto a HFD at 6 months. Serum and fresh stool were collected longitudinally, while collection of intestinal tissue was performed at necropsy (G130/early third trimester or 15 months of age). Serum and polar metabolite extractions of stool and intestine were analyzed by quantitative liquid chromatography-mass spectrometry targeting 34 metabolites spanning neuroactive pathways (serotonin, GABA, dopamine) and short chain fatty acids.

RESULTS: We have data on 34 neuroactive metabolite levels in n=191 serum, n=129 stool, and n=250 intestinal samples from n=79 fetal and n=61 juvenile (15 months old) NHP offspring. In mHFD exposed juveniles compared to mCTR exposure, we observe depression of the GABA and serotonin neuroactive metabolite levels in stool (Fig 2). Specifically, we observed decreased serotonin (p=0.009), tryptophan (p=0.051), 5-hydroxyindoleacetic acid (p=0.052), GABA (p=0.001), and glutamate (p=0.009) in association with mHFD exposure.

CONCLUSION: Our findings indicate that the gut neurometabolites of NHP offspring are sensitive to maternal diet/post-weaning diet synergism. Exposure to mHFD in juveniles weaned onto HFD is associated with changes in multiple neuroactive metabolite levels compared to mCTR animals also weaned onto HFD. These data suggest a programmable feedback mechanism within the gut present in early life that may be critical to development of the gut-brain axis in primates.
Enhanced Placental Angiopoietin-like Protein 2 Levels in Fetal Growth Restriction

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OBJECTIVE: Angiopoietin-like protein 2 (ANGPTL2) maintains cell stemness by preventing differentiation and promotes endothelial dysfunction by impairing endothelium-dependent vasorelaxation. Angptl2 also acts as pro-inflammatory mediator in metabolic syndromes, atherosclerosis, and tissue injury. Mesenchymal to hemangiogenic cell differentiation is crucial for adequate placental vasculogenesis. Inadequate vascularization and/or endothelial dysfunction causes placental insufficiency, a primary feature of fetal growth restriction (FGR). Thus, we hypothesize that FGR-associated placentas display elevated levels of ANGPTL2, that contribute to inadequate vascularization and/or endothelial dysfunction.

STUDY DESIGN: After obtaining written consents, placental villi were obtained from gestational age and maternal BMI-matched control and FGR-complicated pregnancies (n=10/each) and analyzed by qPCR and immunohistochemistry. ANGPTL2 mRNA levels after β-actin normalization were calculated using the 2^(-ΔΔCt) values. Paraffin sections were immunostained with ANGPTL2 antibody and evaluated by a histologic scoring (HSCORE). Results were analyzed using a t-test with P<0.05 considered statistically significant.

RESULTS: Significantly higher ANGPTL2 mRNA levels were found in FGR complicated vs. control placentas (Mean ±SEM: 2.90 ±0.48 vs. 1.24 ±0.27, P=0.008). In placental villi, ANGPTL2 immunoreactivity were primarily detected in endothelial, mesenchymal and Hofbauer cells of the mature and immature intermediate villi, with no staining in villous cytotrophoblasts and syncytiotrophoblasts. ANGPTL2 HSCORE was significantly higher in FGR-complicated vs. control placentas (143.62 ±18.61 vs. 49.48 ±6.72, P<0.001).

CONCLUSION: These results show that FGR is associated with elevated placental ANGPTL2 mRNA and protein levels. We postulate that such elevations impair placental vasculogenesis and/or endothelial dysfunction to cause placental insufficiency. Further studies are required to determine whether enhanced ANGPTL2 levels is a cause or effect of FGR and whether it can serve as a biomarker of impending FGR.