In utero exposure of Delta-9-tetrahydrocannabinol (THC) impacts the endothelial transcriptome in rhesus macaques

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INTRODUCTION

- Cannabis is the most frequently used federally illicit drug in pregnancy.1 Prevalence is due to increased availability and decreased perception of harm due to a lack of rigorous scientific studies.
- Cannabis is frequently used to treat pregnancy-associated nausea and pain in the first trimester when organogenesis occurs.2
- Delta-9-tetrahydrocannabinol (THC, primary active component of cannabis) can cross the placenta and bind to cannabinoid receptors (CB1 and CB2) on the fetal brain, arteries, and heart.3
- Endothelial cells express CB1 and CB2 receptors and regulate cardiovascular development.4
- Evidence showed that THC increases inflammation in endothelial cells,4 and in utero exposure resulted in cardiac remodeling.5
- Our hypothesis is that in utero THC exposure may adversely impact fetal cardiovascular development by impacting endothelial cell transcriptome.

MODEL

5 Control
5 THC

Week 1-3: 0.5mg
Week 4-6: 1mg
Week 7-9: 2mg
Week 10-12: 2.5mg
Mate with non-THC males
Pregnancy: Daily 2.5mg/7kg/day THC (Full term 168 days)
GD 155 C-section & Necropsy

METHOD

Umbilical Vein Differentially Expressed Genes

Umbilical Artery Differentially Expressed Genes

Fetal Aorta Differentially Expressed Genes

Figure 1. Heatmap of 11 differentially expressed genes (DEGs). DEGs show downregulation with THC treatment, specifically LIFR, KIF20B, and ANKFN1—genes involved in cellular proliferation. MMRN1, which regulates hemostasis and coagulation, and SUCNR1, a pro-atherosclerotic gene, were also downregulated.

Figure 2. Heatmap of 2 differentially expressed genes (DEGs). DEGs showed downregulation with THC treatment, specifically SLC27A5, a gene involved with fatty acid metabolism.

Figure 3. Heatmap of 42 differentially expressed genes (DEGs). DEGs showed upregulation with THC treatment of CYP3A4, a gene coding for enzyme involved in drug metabolism. DUSP6, MAPK38, CEBP8, and MINDY2, which regulate inflammation, were also upregulated with THC treatment.

CONCLUSION

- Our previous studies did not demonstrate significant changes in ECM, but current work showed prominent data from RNA-seq with most DEGs involved in cellular metabolism.
- DEGs in the umbilical vein regulate cellular metabolic processes, proliferation, and differentiation.
- Aortic DEGs regulate metabolism and inflammation.
- Alterations to these metabolic functions may result in cellular exhaustion, decreasing efficiency, and subsequently increasing risk for metabolic syndrome later in life.
- Our study in utero THC exposure alters cardiovascular development and requires future studies.
- Future directions include assessing the longevity of transcriptional changes and increasing power to analyze sex differences.

REFERENCES