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

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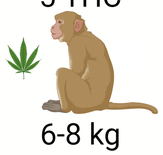
INTRODUCTION

- 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 (CB_1 and CB_2) on the fetal brain, arteries, and heart.[3]
- Endothelial cells express CB_1 and regulate cardiovascular development
- 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[6]

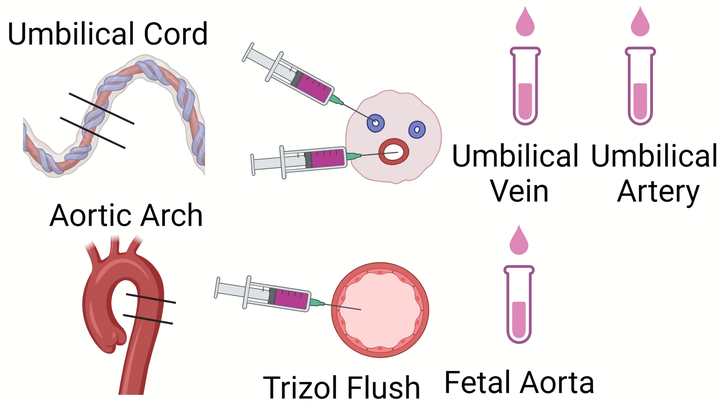


5 Control
5 THC

6-8 kg

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



FUNDING

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Umbilical Vein Differentially Expressed Genes

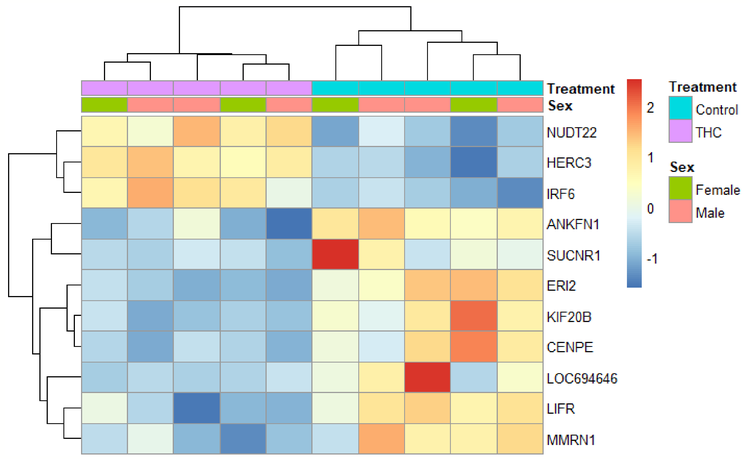

Figure 1. Heatmap of 11 differentially expressed genes (DEGs). DEGs show downregulation with THC treatment, specifically *LIFR*, *KIF20B*, and *ANKFN1*—genes involved in cellular proliferation. *MMRN1*, which regulates hemostasis and coagulation, and *SUCNR1*, a pro-atherosclerotic gene, were also downregulated.

Umbilical Artery Differentially Expressed Genes

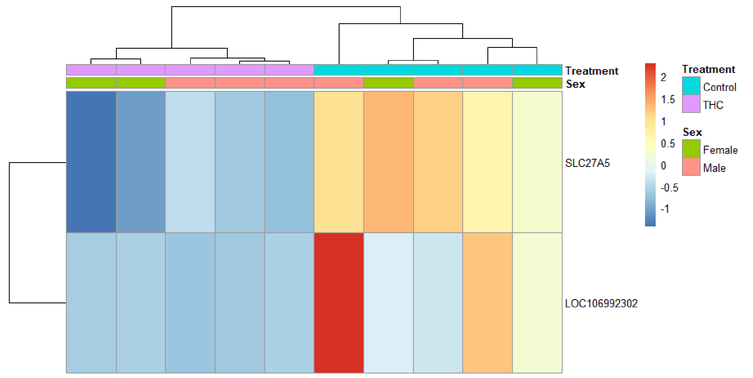

Figure 2. Heatmap of 2 differentially expressed genes (DEGs). DEGs showed downregulation with THC treatment, specifically *SLC27A5*, a gene involved with fatty acid metabolism.

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Fetal Aorta Differentially Expressed Genes

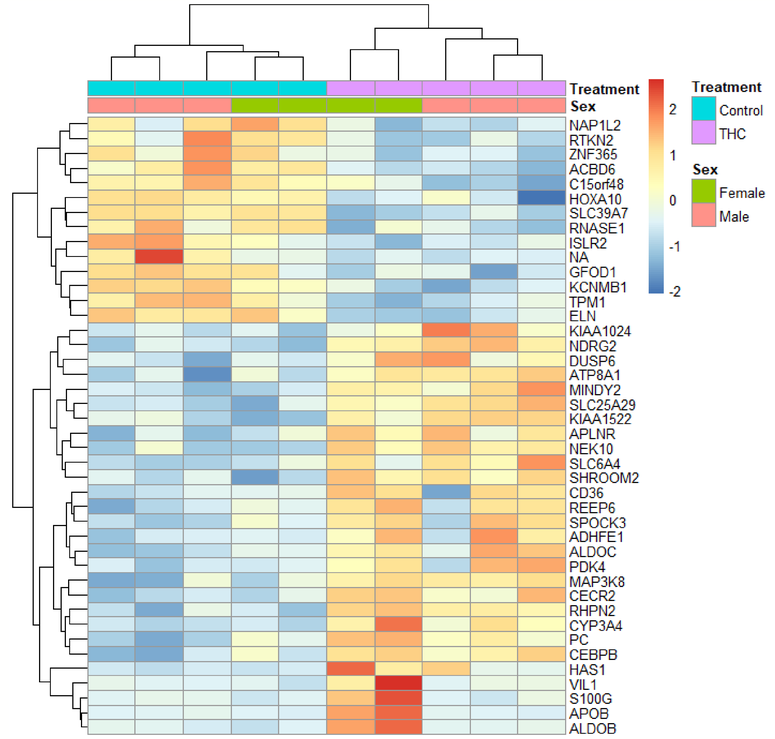

Figure 3. Heatmap of 42 differentially expressed genes (DEGs). DEGs showed upregulation with THC treatment of *CYP3A4*, a gene coding for enzyme involved in drug metabolism. *DUSP6*, *MAP3K8*, *CEBPB*, and *MINDY2*, which regulate inflammation, were also upregulated with THC treatment.

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.