

## Gestational Cannabidiol (CBD) Consumption Impacts Offspring Hypothalamus Development and Metabolism in a Sex-Specific Manner

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Cannabidiol (CBD), a non-psychoactive component of cannabis, is marketed to pregnant people as a safe and natural alternative to traditional pharmaceuticals to alleviate morning sickness. Despite CBD consumption rates increasing, there has yet to be research to determine the safety of CBD consumption during pregnancy. CBD crosses the placenta and accumulates in fatty tissues including the fetal brain, liver, and gastrointestinal tract. CBD activates the metabolism and adiposity regulator, peroxisome proliferator-activated receptor (PPAR) $\alpha$ , in several tissues including the brain, pancreas, liver, skeletal muscle, and other organs which together regulate metabolism during fetal development. Fetal activation of PPAR $\alpha$  is associated with changes in energy sensing and oxidation, as well as insulin resistance. Therefore, **we hypothesized that gestational CBD exposure alters offspring feeding behavior, glucose tolerance, insulin resistance, and metabolism.** To test this, we administered vehicle or different doses of CBD by oral gavage to pregnant mice throughout gestation from embryonic day (E)5.5 to birth. We performed single cell RNA sequencing of the hypothalamus of male and female pups from both exposure groups. We found sex-dependent differences in the expression of genes important for regulating feeding behavior, insulin signaling, metabolism, and adiposity in CBD exposed pups. We found no differences in body composition or metabolism between vehicle and CBD exposed animals. We tested glucose tolerance in 14-week-old male and female mice from both exposure groups and found fetal CBD exposure significantly reduced glucose tolerance in male mice, but not females by this age. Glucose intolerance arose in female CBD exposed mice by 21 weeks of age. Female CBD-exposed mice were insulin resistant by 14 weeks of age. CBD-exposed males were insulin resistant in a dose dependent manner. These data suggest that fetal CBD exposure impacts hypothalamus development, glucose tolerance, and insulin resistance in a sex dependent manner.