

Shared alterations in miRNA expression between Perinatal Cannabis Exposure and Risk of Attention Deficit Disorder

Prenatal cannabis exposure may increase risk for disorders of executive function. Several cord blood microRNAs have been associated with a childhood diagnosis and/or severity of Attention Deficit/Hyperactivity Disorder (ADHD). We hypothesized that prenatal cannabis exposure alters the expression of ADHD-associated miRNAs in the fetal brain. Fetal brain specimen miRNA expression was compared in 37 pregnancies (19 ♀; 18 ♂) with known cannabis exposure (assessed by maternal detailed questionnaires), and 36 (18 ♀; 18 ♂) without prenatal cannabis use (controls). Samples were obtained following elective pregnancy termination between 14 and 21.6 weeks' gestation. Expression was quantified by RT-qPCR normalized to miR-151a-5p (housekeeping). Ten target miRNAs were selected based on known association with ADHD. Group differences were evaluated using Bayesian regression on log-transformed fold-change values with tobacco use included as a covariate. Results are reported as percent differences in geometric means with 95% credible intervals and posterior probabilities (PP) to quantify evidence for group differences. A PP ≥90.9% was set as a threshold denoting strong evidence. Four of ten miRNAs showed evidence of altered expression with cannabis exposure. Down regulation was noted in both miR-34c-3p (-50.2% [-71.4%, -11.8%], PP=99.3%) and miR-125a-3p (-36.2% [-54.4%, -9.6%], PP=99.5%) without evidence of strong differences between fetal sexes. Down regulation was noted in females only for miR-32-5p (-46.2% [-68.1%, -7.9%], PP=96.8%). Opposite effects were noted in miR-15a-5p (PP=99.6%) with downregulation in females (-39.9% [-68.9%, 16.3%], PP=93.4%) and upregulation in males (111.1% [9.2%, 310.4%], PP=98.6%). Overall results were mixed with some miRNA changes associated with worsening of ADHD symptoms and some with neuroprotection. These findings provide important insights into the complex epigenetic alterations associated with prenatal cannabis exposure in the developing fetal brain and contribute to understanding potential molecular mechanisms underlying neurodevelopmental risk.

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