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Prenatal Cannabis Exposure Alters Mirna Expression in the Developing Human Brain

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Tetrahydrocannabinol (THC), the major psychoactive component of cannabis, crosses the placenta and fetal blood-brain barrier, binding to the cannabinoid 1 receptor (CB1R), its primary neural target with undetermined neurodevelopment sequelae. CB1R is expressed early during gestation, primarily in the dopaminergic mesolimbic system, which is heavily implicated in executive function, and influences neuronal migration and synaptogenesis. We hypothesized that fetal central nervous system-derived extracellular vesicles (CNS-EVs) isolated from maternal blood samples contain miRNA biomarkers than can be used to non-invasively identify molecular effects of in-utero THC exposure. Our primary aim was to compare miRNA expression in CNS-EVs and matched fetal brain samples from THC users vs controls to determine a) the effect of THC on miRNA expression and b) the suitability of CNS-EVs as proxies for CNS tissue. Through miRNA microarray of CNS tissue samples, we identified miRNAs significantly altered by THC exposure. Confirmatory RT-PCR in CNS samples and CNS-EVs demonstrated significant downregulation across sexes of miR-381-5p, miR-6865-5p, and miR-3197 with greater effects in males. miR-216a-5p showed significant downregulation in females. miR-301a, miR-301b, and miR-374a showed significant upregulation among males. Effects size was comparable between fetal CNS samples and CNS-EVs. Alterations in CNS miRNAs may be one epigenetic mechanism for attention-deficit/hyperactivity disorder (ADHD) risk; miR-3197, miR-381a-5p, miR-6865-5p, miR-216a-5p, and miR-301a-3p target genes that comprise one ADHD polygenic risk score. Our data suggest that CNS-EVs collected from can be used to effectively investigate fetal responses to THC and be linked to neurodevelopmental outcomes in prospective or retrospective cohorts with maternal blood samples.