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Neuroepigenomics of THC and CBD Exposure during Pregnancy in the Developing Brain

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The landscape around cannabis use is dramatically changing, swifting the clinical interest towards substance abuse during pregnancy and the effects on the offspring. Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) can cross the placental barrier and influence the molecular and behavioral outcome of the offspring. Only a limited number of studies utilizing animal models have evaluated prenatal Δ9-THC exposure and offspring adverse outcomes, with most of them focusing on males. Despite recent research efforts, significant gaps in our understanding remain. We aim to elucidate the neuroepigenetic mechanisms by which prenatal THC and CBD exposure influence long-term neurodevelopmental outcomes in offspring. To achieve this, we will employ a translational approach using both animal models and human brain organoids, with controlled, matched dosing and exposure duration. Behavioral assessments will focus on evaluating cognitive and social behaviors in adolescent mice. Tissue samples will be collected at key developmental stages—gestational day 18 (G18), postnatal day 9 (PND9), and postnatal day 50 (PND50)—to capture developmental trajectories and identify molecular changes over time. We will perform whole-genome analysis from fluorescence-activated cell sorting (FACS) isolated neurons of the prefrontal cortex (PFC). This will target neural progenitors, as well as excitatory and inhibitory neurons. Long-read Nanopore sequencing will be used to map epigenetic modifications, specifically 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) at all contexts, in samples from both mice and brain organoids. The results of this study will shed light on the epigenetic pathways implicated in cannabis consumption during pregnancy and the protracted offspring neurodevelopmental outcomes, revealing new targets for personalized therapies.