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Prenatal Co-Exposure to Cannabinoids and Alcohol Disrupts Transcriptomic and Microbial Profiles of Alcohol-Seeking Offspring

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Background & Research Objectives: Cannabinoids and alcohol are two of the most consumed psychoactive substances by pregnant individuals today, and prenatal exposure to either substance is associated with an increased risk of developing an alcohol use disorder. The goal of this investigation was to determine whether prenatal polysubstance exposure imposes distinct outcomes from single-drug exposures on gut microbiota and dorsostriatal gene expression, a regulatory region of alcohol-seeking behaviors.

Methods: Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed-only, cannabinoid-exposed-only or polysubstance-exposed. Adult offspring were assessed for operant self-administration of ethanol prior to biological sample collection. Dorsal striatal tissue was collected for bulk RNA-sequencing and transcript quantification of preselected genes, while fecal samples were collected for shotgun sequencing and high-throughput metabolomics.

Results: In the absence of single-drug-exposure changes, prenatal polysubstance exposure significantly dysregulated the expression of genes associated with cannabinoid signaling and synaptic remodeling. This same exposure produced distinct microbial shifts, particularly in the Firmicutes phylum, and altered key amino acid and polyphenolic metabolites in fecal samples. Comparisons of gene expression and behavior revealed that polysubstance exposure shifted the correlation between striatal cannabinoid signaling networks and alcohol-seeking from negative to positive in male offspring, while the opposite shift was observed in female offspring.

Conclusions: Prenatal polysubstance exposure to cannabinoids and alcohol imposes distinct changes in striatal gene expression and microbial composition from offspring with single- or no-drug exposure. Subsequent analyses of cortical tissue in these subjects will facilitate network-level analysis of corticostriatal gene expression and alcohol-seeking behaviors.