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Spatial and Single-Cell Transcriptomics Reveal Region-Specific Metabolic and Developmental Reprogramming Following Prenatal E-Cigarette Exposure

Prenatal e-cigarette exposure (PeCE) has emerged as a public health concern because of its association with an increased risk of neurodevelopmental and psychiatric disorders. However, the spatially resolved molecular mechanisms through which maternal vaping perturbs brain development remain undefined. Here, we integrated spatial transcriptomics with single-nucleus RNA-sequencing and lipidomics in a rat PeCE model to map region- and cell type-specific transcriptional reprogramming in the early postnatal brain following PeCE. Spatial transcriptomic analysis revealed pronounced regional heterogeneity in vulnerability, with the caudate putamen (CPu) exhibiting the highest number of differentially expressed genes (DEGs) following PeCE. Across the brain, PeCE elevated Ca²⁺ influx capability and dopaminergic responsiveness and induced region-specific transcriptional perturbations and a marked metabolic shift. In the CPu, PeCE induced a shift toward increased reliance on lipid-based energy utilization, accompanying with the accumulation of silent synapses and delayed developmental progression of D1-medium spiny neurons. Concurrently, PeCE impaired cortical cholesterol biosynthesis during a critical window of circuit assembly, with GSEA revealing enriched downregulation of synaptic structure regulating pathway. Cross-mapping of PeCE-induced DEGs to curated databases of human neurodevelopmental disorders revealed significant enrichment of genes implicated in the autism spectrum disorder and psychiatric conditions. Collectively, these findings demonstrated a spatially resolved transcriptional reprogramming of the neonatal brain following PeCE, characterized by region-specific elevated susceptibility, metabolic shift, increased silent synapse formation, and delayed neuronal maturation in the CPu. Our study provides a systemic-level mechanistic framework linking PeCE to the increased risk of neurodevelopmental disorders.

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