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Regulation of Metabolism-Related Gene Expression by Cocaine Self-Administration in Mouse Nucleus Accumbens Circuits

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Exposure to illicit drugs and subsequent chronic use profoundly impacts behavior, neuronal structure and firing, and gene expression in reward-related brain regions. Some of these changes are mediated by altered cellular energy homeostasis and mitochondrial function. Understanding the cocaine-induced transcriptional changes across reward-related brain region- in a region and circuit-specific manner will improve understanding of drug-induced plasticity. We examined bulk and circuit-specific transcriptional changes relating to cellular metabolism and mitochondria, concentrating on reward-related brain regions and inputs to NAc after IV cocaine self-administration in C57Bl/6 mice. Using differentially expressed genes (DEG) identified in previously published bulk RNA sequencing data sets we performed gene ontology analysis, with a focus on mitochondrial-related ontology terms. The sequencing data included tissue from the prefrontal cortex, NAc, dorsal striatum, ventral pallidum, amygdala, hippocampus, and ventral tegmental area. In a further circuit-specific analysis, we conducted ribotag-based labeling, isolation, and sequencing of mRNA from neurons in the prefrontal cortex, ventral hippocampus, and the ventral tegmental area that project into NAc as well as the input (bulk tissue) fraction of these samples after cocaine self-administration in male and female mice. DEG and gene ontology analyses we performed in addition to circuit-selective gene enrichment analysis. In bulk tissue samples we found significant representation of DEGs in metabolism and mitochondrial-related ontology terms, with regional and cocaine exposure-related variability. Further, predictive analysis of transcription factors regulating mitochondrial-related genes identified multiple transcription factors that may control cocaine-related changes in metabolic function. Ongoing analysis is examining expression of metabolism-related genes, predicted transcription factors, and projection-specific characterization in the circuit-specific transcripts. Together these data define the landscape of metabolism-related transcriptomic changes across reward regions in response to cocaine and provide the first circuit-selective transcriptomic characterization of NAc inputs after cocaine self-administration.