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Regulation of gene expression in striatal input regions by cocaine self-administration

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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. Cocaine self-administration significantly reduces mitochondrial size in nucleus accumbens neurons, and disruption of this process is sufficient to blunt cocaine seeking. Taking a brain-wide perspective, we examined bulk and circuit-specific transcriptional changes relating to cellular metabolism and mitochondria, concentrating on reward-related brain regions and inputs to the nucleus accumbens after IV cocaine self-administration. We conducted gene ontology analysis on bulk RNA-seq data generated from mice that had undergone either cocaine self-administration or received acute cocaine, with a focus on mitochondrial-related ontology terms. The sequencing data included tissue from the prefrontal cortex, nucleus accumbens, dorsal striatum, ventral pallidum, amygdala, hippocampus, and ventral tegmental area. We found significant representation of genes in metabolism and mitochondrial-related ontology terms, with regional and 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. In a circuit-specific analysis, we have conducted ribotag-based labeling, mRNA isolation, and sequencing of mRNA from neurons in the prefrontal cortex, basolateral amygdala, ventral hippocampus, and the ventral tegmental area that project into the nucleus accumbens after cocaine self-administration. Ongoing analysis is examining expression of metabolism-related genes, predicted transcription factors, and characterization of these projection-specific populations. Understanding circuit-specific transcriptional changes will inform how cellular metabolism supports responses to cocaine throughout reward circuits.