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Mitochondrial gene ontology pathways and transcriptional regulators impacted by cocaine in C57Bl/6 mice

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Exposure to illicit drugs and subsequent chronic use profoundly impacts behavior, neuronal structure and firing, and gene expression through multiple brain regions. Some of these sweeping changes are mediated by and supported by changes in cellular energy homeostasis and mitochondrial function. Cocaine self-administration significantly alters mitochondrial size in nucleus accumbens medium spiny neurons, and disruption of proper mitochondrial fission is sufficient to blunt responding for cocaine. Beyond mitochondrial fission, many genes altered by cocaine self-administration are related to cellular metabolism and mitochondrial function. We conducted gene ontology analysis on an RNA-seq data set generated from mice that had undergone either cocaine self-administration or an acute dose of 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 transcriptionally regulated genes in metabolism and mitochondrial related gene ontology terms in multiple brain regions, with differing regions showing the highest representation at each time point. Further, predictive analysis of transcription factor regulation of identified mitochondrial-related genes identified multiple transcription factors across brain regions that may control cocaine-related changes in mitochondrial function. Ongoing work is examining expression of identified mitochondrial- and metabolism-related genes and predicted transcription factors in neurons from prefrontal cortex, basolateral amygdala, and ventral hippocampus that project into the nucleus accumbens. Understanding circuit specific transcriptional changes will inform how cellular metabolism impacts the cellular and behavioral responses to cocaine self-administration throughout brain reward circuits.