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Egr3 regulates mitochondrial nuclear gene expression in nucleus accumbens neuron subtypes after cocaine exposure

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Recently we demonstrated that mitochondrial dynamics are altered in specific neuron subtypes in the nucleus accumbens after cocaine self-administration or repeated cocaine exposure. To further investigate mitochondrial alterations occurring with repeated cocaine, we sought to examine mitochondrial nuclear genes, that perform mitochondrial function or transcriptional regulation. We focused on the subset of the mito-nuclear genes that have promoter binding sites for the transcription factor, Egr3, since we previously found Egr3 to play a dynamic role in cocaine action through NAc medium spiny neurons (MSNs), D1-MSNs and D2-MSNs. We performed chromatin immunoprecipitation (ChIP) using an Egr3 antibody on NAc tissue from mice that received repeated cocaine. Egr3 binding was significantly enriched on promoters for Drp1, Nrf2, Pgc1α, and Polγ in NAc of the cocaine group compared to the saline group. Using the RiboTag approach, we observe an upregulation of ribosome-associated mRNA of Drp1, Pgc1α and Tfam in D1-MSNs while mRNA of these genes is reduced in D2-MSNs after repeated cocaine. Additionally, we found that mRNA of many of these genes is increased in the NAc after cocaine self-administration and in postmortem NAc of cocaine dependent individuals. Next, to determine if the change in gene expression of these mito-nuclear genes has implications on mitochondria we are using a miRNA approach to knockdown Egr3 expression in D1-MSNs followed by examination of mitochondrial fission and activation of fission promoting Drp1. These findings demonstrate a novel role for the underlying molecular mechanisms that mediate mitochondrial dynamics in MSN subtypes in cocaine action.