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Mitochondrial Dynamics in Ventral Hippocampal Neurons After Prolonged Abstinence From Cocaine Self-Administration

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We previously showed that transcription factor early growth response 3 (Egr3) regulates mitochondrial mechanisms and morphology implicated in maladaptive behavioral responses associated with cocaine use disorders. Specifically, reducing Egr3 expression in dopamine receptor-1 containing medium spiny neurons (D1-MSNs) in the nucleus accumbens (NAc) blocks cocaine-induced increases in small-sized mitochondria in dendrites, mitochondrial fission, and the rewarding effects of cocaine. Furthermore, blocking mitochondrial fission 24 hours after cocaine self-administration (SA) blunts cocaine-evoked AMPA-NMDA ratios in D1-MSNs, suggesting altered plasticity in the NAc D1-MSN synapses. Interestingly, previous studies reported an enhancement of AMPA-NMDA ratios at ventral hippocampus (vHippo)-NAc D1-MSN synapses after 30 days of abstinence from cocaine SA, indicating plasticity changes in vHippo NAc-projecting neurons. However, the mitochondrial mechanisms during prolonged abstinence from cocaine SA in the vHippo-NAc circuit are poorly understood. In this study, mice received a retrograde Cre AAV injection in the NAc and a Cre-inducible eYFP + mito-dsRed AAV injection into the vHippo to fluorescently label mitochondria. Mice then underwent 10 days of cocaine SA on a fixed ratio 1 schedule of reinforcement, followed by abstinence for 24 hours or 30 days. After abstinence, mice were tested for cocaine-seeking behavior and were immediately sacrificed. We examined mitochondrial size, length, and frequency in relation to dendritic spines in vHippo neurons projecting to the NAc to assess whether mitochondrial fission, indicated by smaller-sized mitochondria, is enhanced in these neurons. Additionally, we will examine mitochondrial-related transcriptomes in vHippo-NAc neuron subtypes in these conditions.