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Integrated Analysis of Heroin-induced microRNA and mRNA Profiles in the Nucleus Accumbens Reveals Concerted Regulation of miRNA-mediated Pathways

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Opioid use disorder is a chronic relapsing disorder and a significant public health problem in the United States. Opioid use causes adaptive changes in cellular and synaptic function, affecting neuronal circuits and cellular components within the nervous system that promote opioid seeking. A critical barrier to reducing drug seeking is defining neuroadaptations and molecular mechanisms supporting opioid seeking. We sought to address this barrier by examining expression small, noncoding microRNAs (miRNAs) in the nucleus accumbens (NAc), a key region responsible for reward reinforcement, using a rat model of heroin self-administration. miRNAs regulate gene expression through the inhibition of protein translation. Our lab and others have demonstrated that individual miRNAs are critical participants in drug-seeking behaviors. While ~700 miRNAs are expressed in the mammalian brain, less than 1% have been functionally evaluated in opioid-seeking behaviors. We hypothesized that heroin regulates miRNA pathways in the NAc to support heroin seeking. We performed small RNA sequencing on the NAc following heroin (0.075mg/kg/infusion for 10 days, 6 hours/day) and reported 38 miRNAs significantly regulated, including downregulation of miR-369-3p. Using miRNA target prediction databases, we identified predicted targets of miR-369-3p and overlayed targets with mRNA sequencing data from a unique cohort of rats that self-administered heroin. Three miR-369-3p targets were significantly upregulated in the NAc after heroin: Hsph1 (Heat Shock Protein Family H Member 1), Nr3c1 (Nuclear Receptor Subfamily 3 Group C Member 1) and Homer1 (Homer Scaffold Protein 1). Thus, regulation of the NAc miR-369-3p pathway is a reproducible neuroadaptation following chronic heroin.