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# Investigating multi-omic Mechanisms Underlying Opioid Addiction Vulnerability: A Multi-Omics Study

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Early life adversity (ELA) is associated with opioid addiction in humans, and we find in rats that ELA similarly augments heroin vulnerability and relapse in a sex-divergent manner. Although understanding is incomplete, the enduring nature of changes induced by ELA suggest that epigenetic mechanisms may underlie them. In this new U01 project, we ask how ELA is epigenetically encoded, thereby increasing risk for opioid abuse. Further, we ask whether heroin differentially affects the epigenome and transcriptome in those with ELA history, thus promoting vulnerability to opioids. We will test the hypothesis that both ELA and heroin use regulate epigenomic processes, coordinating gene expression to impact cellular signaling and OUD-like behaviors. Epigenomic and transcriptomic changes induced by ELA and heroin will be determined in both sexes by employing bulk- and single-cell multi-omics in brain regions across the OUD trajectory. This is complemented by sampling CSF and blood extracellular vesicle miRNA profiles, enabling identification of predictive markers of OUD risk and/or progression. Coupled with modern bioinformatic analyses of behavior-relevant gene regulatory networks, we will identify novel targets for OUD prevention and intervention. As a pilot project, we processed samples from two brain regions (nucleus accumbens and prefrontal cortex) of male and female rats for total RNA sequencing, comparing heroin-exposed and yoked saline controls. We found changes in gene expression patterns associated with several relevant pathways relevant to addiction. Our findings set the stage for the upcoming U01 project, which will improve understanding of the molecular mechanisms underlying adversity-related disorders including heroin addiction.