

Exploiting Orbitofrontal Cortex Enhancer Dynamics in Cocaine Use Disorder for Cell Type-Specific Epigenetic Targeting

Substance use disorder is a progressive neuropsychiatric disease defined as the compulsion to seek out and use drugs of abuse despite the negative emotional, physical, and social consequences. The orbitofrontal cortex (OFC), a key component of the reward circuitry, has been implicated in cocaine use disorder (CUD) due to its roles in positive memory formation, decision making, learning, emotional regulation, and incubation of drug anticipation and craving. Cocaine induces chromatin and transcriptional reorganization within mesocortical brain regions, but cocaine-induced transcriptional and chromatin reorganization in the OFC has not been examined. Drug-mediated changes in genomic regulatory elements known as enhancers are a fundamental molecular step that can regulate long-term effects of drug experience. Within the brain, enhancers play a widespread role in activity-dependent transcription and regulate key components of neuronal plasticity. Therefore, enhancers could be leveraged as genomic access points to alter defined cell subpopulations involved in CUD development. Here, single nucleus multiomic profiling was performed with OFC tissue taken from rats during a withdrawal period after cocaine intravenous self-administration to identify cocaine activated enhancers of interest. Using a sequence from one highly ranked enhancer that became accessible following cocaine exposure, we generated viral tools capable of expressing molecular cargo in selected cell populations in an experience-dependent manner. Chemogenetic silencing of this enhancer ensemble within the OFC reduced cocaine seeking following withdrawal, suggesting that this ensemble regulates motivation for cocaine. In ongoing experiments, we will use CRISPR regulatory constructs to activate this cocaine-induced enhancer site to identify unknown downstream gene targets that could explain how this enhancer region drives cocaine behavioral responses. These studies provide novel insight into the functional consequences of enhancer regulation and how this links epigenetic modifications, gene expression, and behavioral adaptations due to cocaine response and relapse to inform future intervention strategies for CUD.

Authors:

Submitter: Gabriella Silva, Postdoctoral Fellow, University of Alabama at Birmingham, Birmingham

Jeremy Day, Ph.D., University of Alabama at Birmingham

David Dietz, Ph.D., University at Buffalo, The State University of New York

Sasha Fulton, Ph.D., Icahn School of Medicine at Mount Sinai

Ana Garcia Lopez, B.S., University at Buffalo, The State University of New York

Ian Maze, Ph.D., Icahn School of Medicine at Mount Sinai

Cathy Newman, Ph.D., University of Alabama at Birmingham

Robert Phillips, Ph.D., University of Alabama at Birmingham

Jennifer Tuscher, Ph.D., University of Alabama at Birmingham