

Submitter Name: Erin S. Calipari
Submitted email: erin.calipari@vanderbilt.edu

Divergent molecular adaptations in the nucleus accumbens control cocaine reinforcement in males and females

Alberto J. López¹, Amy R. Johnson¹, Tanner Euston², Ansley Kunnath¹, Jennifer E. Zachry¹, Heather N. Haynes¹, Ashley Hendricks¹, Munir Gunes Kutlu¹, Lillian J. Brady¹, Kimberly C. Thibeault¹, Drew D. Kiraly,² and Erin S. Calipari¹

¹Department of Pharmacology, Vanderbilt University School of Medicine, ²Friedman Brain Institute, Mount Sinai School of Medicine

Cocaine use disorder is a chronic neuropsychiatric disorder characterized by cocaine-induced plasticity within reward-related brain regions that drives drug consumption, seeking, and relapse. Sex differences in cocaine effects in the NAc have been identified as key factors that enhance motivation for cocaine in females, making studies that identify the mechanisms underlying these processes critical to understanding and treating this disorder in women. To this end, we combined cocaine self-administration in male and female C57BL6/J mice with transcriptional and proteomic profiling to identify unique molecular signatures that underlie drug-induced plasticity in both sexes. We show that while there are not sex differences in drug consumption on low effort schedules of reinforcement, female mice are more motivated to self-administer cocaine when higher effort contingencies are introduced. By taking advantage of this dichotomy, we assessed cocaine-induced alterations in the proteomic and transcriptional landscape that occur in a sex-specific fashion independent of differences of drug intake. We find key sex differences in molecular effectors at baseline that could explain the increased sensitivity to cocaine and cocaine-induced plasticity in females. Additionally, of the 122 identified proteins dysregulated by cocaine self-administration, only 5 were dysregulated in both sexes showing that cocaine induces a sex-specific proteomic signature. Gene ontology analysis revealed that the cellular functions linked to these sex-specific proteomes showed a high degree of overlap, suggesting that different molecular mechanisms control similar plasticity processes. Together, understanding the unique sex-specific mechanisms that drive cocaine use disorder will be essential to developing widely efficacious treatments.