Name: Vivek Swarup Email:vswarup@uci.edu

Unraveling Transcriptomic Dynamics of Early-Life Adversity and its Sex-Dependent Impact on Opioid Addiction Vulnerability

Andres Alonso Castaneda[1,2,3], Kate A Lawson[1,2], Arshi Shahin[1,2], Christina M Ruiz[1,2], Hazael Ramirez[1,2], Yiyan Xie[1,2], Marcelo A Wood[1,2,3], Christie D Fowler[1,2], Tallie Z Baram[2,4,5,6], Stephen V Mahler[1,2], Vivek Swarup[1,2,3]

[1]Department of Neurobiology & Behavior, University of California-Irvine, Irvine, CA, USA
[2]Irvine Center for Addiction Neuroscience, University of California, Irvine, Irvine, CA, USA
[3] Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA
[4]Department of Anatomy/Neurobiology, University of California, Irvine, Irvine, CA, USA
[5]Department of Neurology, University of California, Irvine, Irvine, CA, USA
[6]Department of Pediatrics, University of California, Irvine, Irvine, CA, USA

Opioid use disorder (OUD) is a major public health crisis. Addressing this challenge requires both translationally-relevant animal models, and a deeper understanding of addiction's molecular mechanisms. We use a well-established model of early-life adversity (ELA) in outbred Sprague-Dawley rats to study developmental influences on addiction vulnerability, and discovered sex-dependent, addiction-relevant behavioral phenotypes, as well as altered heroin-induced protein expression in brain regions like the nucleus accumbens (NAc), amygdala (AMY), and prefrontal cortex (PFC).

Male and female rats underwent an ELA paradigm from postnatal days 2-9, a critical period for affective brain circuit development. In adulthood, rats were allowed to self-administer heroin, followed by RNA sequencing of brain regions and blood. Preliminary RNA-seq data reveal extensive transcriptomic and splicing alterations associated with ELA and heroin use, including sex-specific effects.

Weighted gene co-expression network analysis identified gene networks uniquely activated by ELA, heroin, or both, shedding light on biologically relevant pathways in each sex. We also found correlations between gene expression and heroin intake, highlighting individual differences in addiction vulnerability. Cross-referencing with human OUD datasets revealed parallels, suggesting partially-conserved molecular pathways across species.

This study forms the foundation of our ongoing investigation into the transcriptional mechanisms through which ELA impacts opioid addiction vulnerability, setting the stage for upcoming single-cell and blood microRNA analyses. Ultimately, these insights could inform novel strategies for OUD prevention and treatment, advancing translational understanding of addiction biology. Our work also generated additional brain samples available in collaboration.