

Submitter name: Marissa A. Ehringer  
Submitter email: [Marissa.Ehringer@colorado.edu](mailto:Marissa.Ehringer@colorado.edu)

## **Differential gene expression responses to oxycodone self-administration in the amygdala and prefrontal cortex of inbred rat strains**

Marissa A. Ehringer<sup>2,4</sup>, Lucy Hall<sup>2,4</sup>, Kyle T. Brown<sup>1,2</sup>, Daniel Foster<sup>3</sup>, Winona Booher<sup>2,4</sup>, Laura Saba<sup>3</sup>, Ryan K. Bachtell<sup>1,2</sup>

<sup>1</sup>Department of Psychology and Neuroscience University of Colorado Boulder; <sup>2</sup>Institute for Behavioral Genetics, University of Colorado Boulder; <sup>3</sup>Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus; <sup>4</sup>Department of Integrative Physiology, University of Colorado Boulder

To identify the genes and pathways involved in opioid use disorder, we utilized a longitudinal behavioral paradigm in male and female SHR/Ola and ACI inbred rat strains prior to performing RNA sequencing. Several phenotypes were measured including tests of analgesia, oxycodone intake, tolerance, and withdrawal. SHR/Ola rats were resistant to oxycodone-induced analgesia and showed minimal tolerance after chronic oxycodone self-administration. In contrast, ACI rats displayed an initial robust analgesic response that diminished after chronic oxycodone self-administration. Acquisition of oxycodone self-administration and escalation of oxycodone intake was similar across strains. The motivation to self-administer oxycodone was measured in a progressive ratio test conducted before and after escalated oxycodone intake. SHR/Ola rats showed minimal escalation in the motivation to self-administer oxycodone compared with ACI rats. Transcriptome expression differences were analyzed using RNA sequencing of amygdala and prefrontal cortex tissue collected from both strains following oxycodone self-administration. In the amygdala, 16 genes had a significant oxycodone effect and for 12 of these 16, the oxycodone effects differed significantly between strains. In the prefrontal cortex, 125 genes exhibited an oxycodone effect and in 9 of these genes, the effect of oxycodone differed between strains. Pathway-based analyses suggest genes involved in inflammatory response, cellular response to lipids, and neural function show oxycodone-related differences. These data demonstrate that genetics can influence both molecular responses to oxycodone exposure and behavioral responses in this oxycodone consumption paradigm. Supported by NIDA U01 DA051937 and NIDA P30 DA044223.