

Name: Drew Kiraly
PI Name: Drew Kiraly
Presentation preference:

Email: drew.kiraly@mssm.edu
PI email: drew.kiraly@mssm.edu

The gut microbiome as a critical regulator of fentanyl seeking and proteomic regulation in the nucleus accumbens

Rebecca S. Hofford^{1,2}, Katherine R. Meckel^{2,3}, Weiwei Wang⁴, Michelle Kim^{2,3}, Arthur Godino^{2,3}, Tukiet T. Lam⁴, & Drew D. Kiraly^{1,2,3}

¹Department of Psychiatry, ²Friedman Brain Institute, ³Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, ⁴Yale/Keck MS & Proteomics Resource, Yale University

There is growing evidence that the presence of a diverse gut microbiome is important for normal neuronal and behavioral plasticity. Maladaptive alterations of the microbiome have been demonstrated in neuropsychiatric conditions including substance use disorders. Recently, we demonstrated that microbiome knockdown alters conditioned place preference for morphine as well as regulation of gene expression in the nucleus accumbens (NAc). Here, we utilized a translationally-relevant fentanyl self-administration paradigm to test the hypothesis that depletion of the microbiome would lead to increased opioid intake and seeking. Adult Sprague-Dawley rats were randomly assigned to be treated with control water or antibiotics to knockdown the microbiome. Rats were trained to administer fentanyl to equal levels on an FR1 paradigm before testing on multiple drug seeking paradigms. Depletion of the gut microbiome with antibiotics leads to increased fentanyl intake on an increasing fixed ratio schedule and to higher break points on a progressive ratio task. Dose-response analysis demonstrates a marked left-shift in the fentanyl dose-response curve. We coupled these behavioral analyses with a multi-omics analyses approach to integrate genomic content of the microbiome, levels of bacterially produced signaling molecules using quantitative discovery metabolomics analysis, and proteomics analysis of the NAc. Microbial sequencing and metabolomics analyses identify patterns of microbial composition and resultant metabolites associated with increased drug intake. Proteomic analysis of the NAc show altered opioid receptor signaling and synaptogenesis pathways. These findings demonstrate clear effects of the microbiome on drug seeking and provide important foundational data to identify molecular mechanisms underlying these behavioral effects.