Submitter Name: Caleb J Browne
Submitted email: Caleb.Browne@mssm.edu
PI Name: Eric J Nestler
PI email: Eric.Nestler@mssm.edu

Heroin self-administration and seeking induces transcriptional reprogramming throughout the brain's reward circuitry

Caleb J Browne[1], Rita Futamura[1], Aarthi Ramakrishnan[1], Xianxiao Zhou[2], Angélica Minier-Toribio[1], Freddyson Martínez-Rivera[1], Arthur Godino[1], Angélica Torres-Berrío[1], Molly Estill[1], Eric M Parise[1], Ashley M Cunningham[1], Peter J Hamilton[1], Deena M Walker[1], Bin Zhang[2], Yasmin L Hurd[1,3,4], Li Shen[1], Eric J Nestler[1,3,4]

[1]Nash Family Department of Neuroscience and Friedman Brain Institute, [2]Department of Genetics and Genomic Sciences and Icahn Institute for Data Science and Genomic Technology, [3]Department of Psychiatry, [4]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

Opioid abuse exacts a devastating toll on individuals, their families, and the healthcare system. Treatment of opioid addiction is made exceptionally difficult by prolonged susceptibility to relapse into compulsive drug-seeking and taking, often triggered by re-exposure to drug-associated cues or the drug itself. Long-term susceptibility to relapse is thought to be mediated in part by persistent changes to gene expression programs within interconnected reward-processing regions of the brain. However, few studies have performed transcriptome-wide analyses following volitional opioid intake. Here, we combine heroin self-administration in mice, RNA sequencing (RNA-seq), and advanced bioinformatic analyses to identify novel genes and gene networks throughout the reward circuitry that are regulated by opioids. Mice underwent a 15-day intravenous heroin self-administration paradigm and were then separated into two cohorts, euthanized either 24 hours after the last session or after a 30-day withdrawal period. In the 30-day condition, mice received either a saline or heroin injection and were placed back into self-administration chambers to measure context-induced and drug-primed reinstatement of heroin-seeking and euthanized 2 hours later. RNA-seq was conducted on six brain regions involved in reward-processing: medial prefrontal cortex, nucleus accumbens, dorsal striatum, basolateral amygdala, ventral hippocampus, and ventral tegmental area. Bioinformatic analysis of this rich dataset has uncovered numerous patterns of differential gene expression in a region- and condition-dependent manner, including gene networks in the ventral hippocampus that may drive susceptibility to relapse. Current work focuses on manipulating specific genes and networks in these brain regions and studying the impact on self-administration and relapse behavior.

Funded by P01DA047233