Name: Leanne Holt
Email: leanne.holt@mssm.edu
PI Name: Eric Nestler
PI email: eric.nestler@mssm.edu

Elucidation of the astrocyte-specific transcriptome following cocaine self-administration

Leanne M. Holt[1], Angelica Minier-Toribio[1], Caleb J Browne[1], Rita Futamara[1], Freddyson Martinez-Rivera[1], Tamara Markovic[1], Trevonn Gyles[1], Szu-Ying Yeh[1], Eric Parise[1], Molly Estill[1], Yan Dong[2], Eric J. Nestler[1]

[1] Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine
[2] Department of Neuroscience, University of Pittsburgh

Drug addiction represents an enormous healthcare burden. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly indicates that astrocytes are also involved in disorders of the nervous system, including addiction. Indeed, candidate genes in astrocytes have been identified and, furthermore, manipulation of astrocyte function has been demonstrated to influence rodent behavioral responses to cocaine administration. However, the astrocyte-specific transcriptome following exposure to drugs of abuse has not yet been investigated. Therefore, we utilized whole cell sorting of astrocytes and RNA-sequencing to characterize the astrocyte transcriptome in several key brain regions involved in reward-processing, including the nucleus accumbens and prefrontal cortex, following cocaine self-administration, withdrawal, and "relapse". We determined that astrocytes exhibit a robust transcriptional response, including regionally- and contextually-specific transcriptional signatures. Interestingly, additional analysis revealed CREB as a predicted upstream regulator. We confirmed that cocaine exposure alters CREB phosphorylation in nucleus accumbens astrocytes and that viral-mediated manipulation of CREB activity selectively within astrocytes in this brain region modulates both addiction-related behaviors in a conditioned place preference paradigm and neuronal activation. Noteworthy, we find opposing effects on addiction related behaviors compared to neuronal-specific CREB modulation. Cut&Run and RNA-Sequencing identify the direct targets of astrocytic CREB and the downstream effects on gene expression, respectively. Current studies are extending our findings utilizing cocaine self-administration to establish astrocytic CREB's contribution to the pathophysiology of cocaine addiction.