Name: Vidhya Kumaresan Email: vidhya@bu.edu

Abstinence from Escalated Cocaine Intake Alters the microRNA Landscape in the Medial Prefrontal Cortex

Vidhya Kumaresan[1], Yolpanhchana Lim[2,3], Allison Tipton[1], Poorva Juneja[2,3], Ying Liu[2], Giordano de Guglilelmo[4], Lieselot L.G. Carrette[4], Marsida Kallupi[4], Lisa Maturin[4], Olivier George[4], Huiping Zhang[2,3]

[1]Department of Pharmacology, Physiology & Biophysics, Boston University Chobanian & Avedisian School of Medicine, Boston MA 02118;
[2]Department of Psychiatry, Boston University Chobanian & Avedisian School of Medicine, Boston MA 02118;
[3]Department of Medicine (Biomedical Genetics), Boston University Chobanian & Avedisian School of Medicine, Boston MA 02118;
[4]Department of Psychiatry, University of California San Diego, La Jolla, CA 92093

Cocaine use disorder (CUD) is a complex, polygenic disorder. Epigenetics plays a predominant role in CUD. Investigations of postmortem brain tissue of CUD subjects reveals dysregulated gene expression and gene regulatory networks. Our hypothesis is that miRNAs, an epigenetic mechanism, due to their key role in regulating gene expression, play a pivotal role in determining vulnerability or resilience to CUD. A translational model of escalated cocaine self-administration and abstinence (4-5 weeks) was used to investigate dysregulation of miRNA landscape in the medial prefrontal cortex and accumbens of Heterogenous (HS) stock rats. Transcriptomic changes in the miRNA landscape were profiled using Small RNA sequencing. We identified differentially expressed miRNAs (DEmiRNA) in the prelimbic (PL) and infralimbic (IL) cortex during key phases of the addiction cycle (fold -change>1.5 and $p<0.05$). The mRNAs potentially targeted by these DEmiRNA expressed during withdrawal (18 hours) were enriched in pathways such as Wnt signaling, protein processing in endoplasmic reticulum, MAPK signaling, and cocaine addiction. The potential mRNA targets of DEmiRNA that were differentially expressed during abstinence include oxytocin signaling, ECM-receptor interaction, estrogen signaling, cocaine addiction, amphetamine addiction, cGMP-PKG signaling, etc. In addition, a three-way, pairwise comparison of miRNAs that were differentially expressed during either withdrawal or abstinence with miRNA from naïve rats revealed DEmiRNAs that were expressed uniquely during acute withdrawal or protracted abstinence and those that were persistently expressed during both withdrawal and abstinence. These findings highlight the importance of understanding the temporal dynamic of miRNA expression during the addiction cycle for understanding CUD.