Submitter Name: Philipp Mews
Submitted email: philipp.mews@mssm.edu
PI Name (if different): Eric Nestler
PI email (if different): eric.nestler@mssm.edu

Epigenetic Priming Drives Aberrant Gene Expression Linked to Cocaine Relapse

Philipp Mews[1], Hope Kronman[1], Yentl Van der Zee[1], Aarthi Ramakrishnan[1], Ashik Gurung[1], Molly Estill[1], Meagan Ryan[1], Abner A Reyes[1], Arthur Godino[1], Benjamin Garcia[2], Simone Sidoli[3], Li Shen[1], Eric J Nestler[1]

[1]Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Deptm. of Biochemistry and Biophysics, University of Pennsylvania, Philadelphia PA; [3]Deptm. of Biochemistry, Albert Einstein College of Medicine, New York, NY

Growing evidence implicates altered gene expression in mediating the lasting effects of cocaine, and more recent work supports a key role for epigenetic pathways in the molecular pathology of substance use disorder. Permanent changes in chromatin structure are hypothesized to underlie the transcriptional disruption caused by cocaine, particularly in the nucleus accumbens (NAc), a key brain region of reward learning. The NAc is composed of two functionally distinct types of medium spiny neurons (MSNs), the D1 and D2 dopamine receptor-expressing subtypes, thus making the identification of subtype-specific epigenetic changes critical. We surveyed circuit-specific chromatin accessibility in combination with unbiased histone modification profiling by mass spec and ChIP-seq. We discovered that chronic cocaine persistently alters NAc chromatin structure, especially in D1 MSNs, involving dramatic depletion of the histone variant H2A.Z, a recently identified memory suppressor, at key neuronal genes. Curiously, genome accessibility in D1 MSNs is prominently increased at these genes even after prolonged withdrawal, and is linked to dysregulation of gene expression upon relapse. Our mass spec also revealed that H3K79me2 is enriched after prolonged cocaine withdrawal. The methyltransferase DOT1L is the only known enzyme to catalyze H3K79me2, and we demonstrate that D1 MSN-selective DOT1L knockdown effectively blocks cocaine conditioned place preference (CPP). Together, our studies investigate an emerging view of epigenetic adaptation that may contribute to drug addiction, providing novel insight into circuit-specific epigenetic priming as an important mechanism whereby drugs of abuse alter gene expression and behavior in lasting ways.

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