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Epigenetic priming underlies transcriptional dysregulation in cocaine addiction

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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 addiction. Permanent changes in chromatin structure are hypothesized to underlie the transcriptional dysregulation caused by cocaine, particularly in the nucleus accumbens (NAc), a key brain region of reward learning. However, the molecular mechanisms responsible remain unclear. The NAc is composed of two functionally distinct types of medium spiny neurons (MSNs), the D1 and D2 dopamine receptor-expressing subtypes, therefore making the cell-type specific identification of epigenetic changes critical. Here, we investigated cocaine-induced changes in chromatin accessibility genome-wide by ATAC-seq in pure D1 and D2 MSN populations through which we distinguished immediate versus persistent alterations in chromatin in a cell-type specific manner. Combining these data with unbiased histone modification profiling by mass spectrometry and ChIP-sequencing, we found that chronic cocaine persistently alters the chromatin structure, especially in D1 MSNs, involving deposition of the histone variant H2A.Z at key neuronal genes. Remarkably, genome accessibility in D1 MSNs is prominently increased at these key H2A.Z-marked genes even after prolonged periods of withdrawal and, further, linked to long-lasting changes in subtype-specific gene expression. Together, these investigations provide novel insight into epigenetic priming as an important mechanism whereby drugs of abuse induce long-lasting transcriptional dysregulation in the striatum. Since epigenetic aberrations may be reversible, this mechanistic understanding of such chromatin ‘scarring’ by drugs of abuse could pave the way to novel epigenetic interventions to treat drug addiction.