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An Nr4a1-Cartpt pathway regulates cocaine reward behavior and presents a novel therapeutic target in cocaine use disorder.

Cocaine use disorder is a chronic psychiatric condition characterized by persistent craving during abstinence that ultimately promotes relapse. Persistent changes in gene expression and the epigenome occur during drug taking and increase during abstinence. We posit that a subset of abstinence-regulated genes function to reverse the pathology of chronic drug exposure. We applied biochemistry, bioinformatics, and mouse cocaine-self-administration to define gene regulation across abstinence. We discovered that cocaine increases expression of the transcription factor, Nr4a1, in brain reward areas and that injection of an Nr4a1 activator reduced mouse cocaine seeking. Our studies further revealed Cartpt (cocaine- and amphetamine-regulated transcript peptide), as a direct target of Nr4a1. Our central hypothesis is that Nr4a1 increases Cartpt expression in late abstinence, which signals through discrete cell types to suppress cocaine reinforcement. We have defined the temporal sequence by which chromatin remodeling, transcription-factor recruitment, and Cartpt gene expression unfold during cocaine abstinence using an integrated, cell-type-specific framework. We further define the cell-type specificity of Cartpt epigenetic regulation in cocaine reinforcement and test whether chromatin remodeling at this locus is necessary or sufficient for behavioral change. By integrating locus-specific epigenetic editing, temporally defined abstinence windows, and cell-type resolution, these experiments move beyond correlative transcriptional observations to establish direct mechanistic links between chromatin state and behavior. Finally, we have advanced Nr4a1 from mechanistic validation toward therapeutic relevance, by finding that systemic and intracranial pharmacological activation of Nr4a1 during cocaine abstinence promotes permissive chromatin and transcription of Cartpt and attenuates cocaine seeking.

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