Trim3 mediates cocaine craving via INO80-dependent transcriptional regulation

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Although it is challenging for individuals with cocaine abuse disorder to achieve abstinence, the greatest challenge is avoiding relapse, which is triggered by drug-associated cues. Cue-evoked cocaine craving intensifies (or “incubates”) during abstinence in human cocaine abusers and pre-clinical substance abuse models, which is believed to contribute to persistent relapse vulnerability. Incubated cocaine craving is mediated in part by epigenetic plasticity in brain regions associated with reward and motivation, including the nucleus accumbens (NAc). The ubiquitin-proteasome system (UPS) governs epigenetic plasticity by regulating the expression and degradation of specific substrates which in part govern transcriptional adaptations following cocaine exposure. However, the role of the UPS in regulating cocaine-dependent epigenetic plasticity and relapse behaviors has not been explored. Here we examined E3 tripartite motif-containing protein 3 (trim3) and substrate INO80, a member of the SNF2 helicase family that is recruited by YY1 and remodels chromatin. Following extended-access cocaine self-administration, we found that trim3 was decreased, while INO80 was increased, in the NAc of cocaine-treated rats compared to saline controls on WD30. We then used viral-mediated gene transfer to determine the role of trim3 in incubated cocaine craving. We found that overexpression of nuclear-localized trim3 attenuated incubated cocaine craving, while dominant negative trim3 enhanced incubated cocaine craving. To examine how INO80 mediates long-term gene expression in the NAc, we performed chromatin immunoprecipitation followed by massively parallel DNA sequencing (ChIP-seq) on WD30. Genome-wide distribution patterns of INO80 differential sites were enriched at promoter sites, specifically. Furthermore, predicted pathways regulated by INO80 based on gene enrichment in cocaine-treated rats included cAMP response element binding (CREB) signaling, glutamate receptor signaling, axonal guidance signaling, synaptic long-term depression (LTD) signaling and synaptic long-term potentiation (LTP) signaling. Together, these results suggest trim3 mediates incubated cocaine craving via INO80-dependent transcriptional regulation.