

**Title:****HDAC5 and NPAS4 regulate cocaine reward-environment associations****Author:**

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**Abstract:**

Cues associated with illicit drug use often develop into long-lasting triggers for drug seeking behaviors. We show here that enhanced nuclear accumulation of histone deacetylase 5 (HDAC5) in the nucleus accumbens (NAc) reduces contextual memories associated with cocaine reward, and it reduces cue- and drug prime-induced reinstatement of drug seeking behavior in cocaine self-administration. Using an unbiased, genome-wide analysis (ChIPseq) of HDAC5 gene targets, we found that the activity-sensitive gene, *Npas4*, is repressed by nuclear HDAC5. Following exposure to a novel environment, *Npas4* expression in the NAc is rapidly and transiently induced, and it is required in the adult NAc for the formation of cocaine reward-context associations without altering drug or natural reward sensitivity, fear-related contextual memory or anxiety-like behaviors. Together our data suggest that HDAC5 regulates the association between environmental cues associated with drug administration and cocaine reward, at least in part, through repression of *Npas4* expression.