Histone deacetylase 5 nuclear localization mediates epigenetic changes that limit drug reward and suppress relapse to drug-seeking

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Relapse to drug seeking remains a major obstacle in the treatment of cocaine addiction in individuals suffering from substance use disorders. Preclinical relapse models demonstrate that drug-induced neuroadaptations in regional components of reward circuits underlie relapse to drug-seeking. Cocaine and heroin increase D1 activation and cAMP levels in the medium spiny neurons within the nucleus accumbens (NAc), leading to lasting epigenetic alterations. Histone deacetylase 5 (HDAC5) is transiently dephosphorylated in a cAMP-dependent manner, which increases HDAC5 nuclear localization. We have shown that overexpression in the NAc of a dephosphorylated HDAC5 mutant suppresses cocaine conditioned place preference (CPP) and reinstatement to cocaine-seeking following self-administration. However, the molecular mechanisms and binding partners which mediate HDAC5's reduction in drug-seeking behavior are unknown. Following cAMP activation, there is a transient increase in endogenous HDAC5 association with MEF2 and AP-1 consensus binding motifs on the genome. While HDAC5-mediated suppression of cocaine CPP does not require direct binding to MEF2, the possible role of MEF2/AP1-regulated genes in drug-seeking remains unknown. We will present possible HDAC5 binding partners through which HDAC5 may mediate epigenetic changes to suppress drug-seeking. Furthermore, HDAC5's role in drug abuse in areas with critical efferents to the NAc has yet to be explored. Dysregulation of the pathway from the prefrontal cortex (PFC) to the NAc is heavily implicated in reinstatement and HDAC5-mediated regulation of targets such as NPAS4 and brain-derived neurotrophic factor implicate a regulatory role in functional cortical excitatory/ inhibitory synaptic balance. We will present preliminary data on the role of nuclear HDAC5 in cocaine-seeking in the prelimbic (PrL) and infralimbic (IL) PFC subregions that preferentially project to the core and shell of the NAc respectively. We hypothesize that overexpression of dephosphorylated HDAC5 in the PrL will suppress cocaine-seeking behaviors and expression in the IL may produce the reverse effect.