Aberrant histone dopaminylation in the ventral tegmental area promotes relapse to cocaine

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Drug abuse is characterized by loss of control over drug intake, as well as persistent drug-seeking behaviors, despite negative consequences to both the drug abuser and those directly affected by their behavior. Given that drug addicts continue to crave and pursue drugs of abuse following extended periods of abstinence and/or treatment indicates that life-long changes in brain may occur to promote these behavioral phenotypes. Persistent changes in neuronal gene expression are known to promote physiological alterations implicated in drug addiction. More recently, cell-type and brain region specific epigenetic mechanisms have also been demonstrated to regulate transcriptional programs contributing to addictive-like behaviors; however, our understanding of how these mechanisms mediate life-long addiction remains limited. Dopaminergic neurotransmission in the central nervous system plays a critical role in psychostimulant-induced neural plasticity, with alterations in dopamine production/function being implicated in both the development and treatment of substance use disorders. Although packaging of dopamine by the vesicular monoamine transporter is essential for numerous aspects of reward, recent data have demonstrated the additional presence of 'reserve' pools of extravesicular monoamines in the nucleus of monoamine producing neurons. Dopamine, as well as other monoamines, has previously been shown to form covalent bonds with certain cytoplasmic proteins catalyzed by the tissue Transglutaminase 2 enzyme. Our laboratory has recently identified histone proteins as robust substrates for dopaminylation *in vivo*, specifically on histone 3 glutamine 5 (H3Q5dop). In addition, our data demonstrate that chronic withdrawal from volitional administration of extended access cocaine in rodents results in high levels of dopamine accumulation in the nucleus of dopamine producing neurons in the ventral tegmental area (VTA), and a robust increase in histone dopaminylation. Furthermore, we have demonstrated that inhibiting dopaminylation in VTA is sufficient to block cocaine-seeking behaviors following periods of extended withdrawal without impairing reinforcement by nature rewards (e.g., food). Taken together, these potentially paradigm-shifting studies will aid in our understanding as to how monoamines, specifically dopamine, function in brain to regulate neurotransmission-independent neuronal plasticity and cocaine-mediated behaviors.