

Chromatin Remodeling Complex in Accumbal Neurons Regulates Reward and Pleasure

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Nucleus accumbens (NAc) neurons play a central role in mediating reward, pleasure, and drug seeking behaviors. Among the neuronal types of the NAc, the cholinergic interneurons (ChIs) are thought to play a major role in encoding reward by controlling both the inputs to and the outputs from the NAc, but the molecular mechanisms that regulates their function in encoding reward, pleasure and drug abuse remain largely unknown.

Using chemogenetics in mice, we found that the activity of NAc ChIs correlates with mesolimbic dopaminergic transmission and regulates reward, pleasure, and physiological responsivity to cocaine. At the molecular level, ChI function is dynamically modulated by regulating the gene expression of a Hyperpolarization-Activated and Cyclic Nucleotide-Gated (HCN) channel, under the control of a dynamic chromatin remodeling complex. Transgenic models and behavioral paradigms that impair reward and pleasure induce a change in the composition of the chromatin remodeling complex resulting in a transcriptional down regulation of the channel, diminished tonic activity of NAc ChIs and impaired dopaminergic mesolimbic transmission.