BET bromodomains regulate neurobehavioral responses to psychostimulants

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Because drugs of abuse are known to alter numerous genes in reward-related brain regions, epigenetic-based therapies are intriguing targets for therapeutic innovation in substance use disorder. In particular, the BET family of histone acetyl-lysine reader proteins (BRD2, BRD3 and BRD4) represents a novel, druggable class of epigenetic targets. BET proteins bind to acetylated histones and interact with protein complexes that regulate transcriptional activation, elongation and super-enhancer activity. BET proteins have also been implicated in the pathophysiology of several diseases, and multiple companies have recently developed selective, small molecule BET inhibitors that are currently being tested in clinical trials for cancer. Given that histone acetylation mechanisms are importantly involved in drug-induced neuroadaptations, we hypothesized that BET proteins may also play a vital role in substance use disorder. Here, we report that the BET inhibitor JQ1 reduced conditioned responses to cocaine, amphetamine and nicotine but not morphine. LiCl-induced conditioned place aversion and contextual fear conditioning, however, were not altered by JQ1, indicating that BET inhibition does not affect all types of learning. Repeated exposure to psychostimulants increased BRD4, but not BRD2 or BRD3, proteins levels in the nucleus accumbens (NAc). Differences in phopho-BRD4 levels were also found following acute psychostimulant but not opioid administration. Repeated cocaine administration increased BRD4 binding to the *Bdnf* promoter in the NAc, and JQ1 attenuated cocaine-induced expression of *Bdnf* and other genes. Together, these studies indicate that the displacement of BET proteins from chromatin may have therapeutic efficacy in substance use disorder. Ongoing transcriptomic and viral-mediated knockdown studies will identify additional mechanisms by which BRD4 regulates molecular, physiological and behavioral responses to psychostimulants.