Cocaine Exposure Alters D1 and D2 Medium Spiny Neuron Activity to Promote Relapse

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Learned associations between environmental cues and experience are the basis of decision-making and allow organisms to guide behavior towards advantageous outcomes (Steinberg et al., 2013). Dysfunction in the processes that regulate these associations, especially in the nucleus accumbens (NAc), is a critical factor in the pathology of addiction. The NAc is a heterogeneous region primarily composed of two opposing cell types: D1 and D2 medium spiny projection neurons (MSNs) (Self et al., 1996). Optogenetic stimulation of these cells results in divergent behavioral consequences (Kravitz et al., 2012); thus, it is important to study these populations in isolation to understand the cell-type specific signals that underlie learning processes.

Methods: Fiber photometry calcium imaging was combined with conditioned place preference or cocaine self-administration in transgenic mouse lines that express Cre-recombinase in D1 or D2 MSN populations to record cell-type specific neuronal activity in freely moving mice during behavior. Further, using designer receptors exclusively activated by designer drugs (DREADDs) we manipulated these signals to establish a causal role for each cell type in drug associations.

Results: First, we defined D1 MSNs as the specific population of cells in NAc that encodes information about positive drug associations, and elucidated the temporal profile with which D1 MSN activity is increased to drive cue-induced drug seeking. Chronic cocaine exposure dysregulated these D1 MSN signals to both prevent extinction and facilitate reinstatement of drug seeking to drive relapse. Conversely, D2 MSNs encoded information about negative stimuli. Chronic cocaine exposure reduced D2 MSN responses to cues associated with aversive stimuli leading animals to seek drug, even in the face of negative consequences. Finally, directly manipulating these D1 and D2 MSN signals using DREADDs was capable of altering the strength of these associations, thus, establishing a causal role of the signals in drug addiction.

Conclusions: Understanding the neural mechanisms for how cues are associated with the rewarding and reinforcing properties of drugs is integral to understanding initial drug taking, compulsive drug seeking, and relapse. These data outline distinct roles of temporally specific signaling originating from D1 and D2 MSNs in encoding information about positive and negative stimuli, respectively. Together, these data elucidate the underlying neural processes that control associative learning and how cocaine exposure dysregulates MSN signaling to drive relapse following abstinence. This not only expands our basic understanding of addiction, but also may lead to the development of novel therapeutic avenues as D1 and D2 MSNs contain receptors that can be easily selectively targeted using pharmacological approaches.

References: Steinberg, E.E., Keiflin, R., Boivin, J.R., Witten, I.B., Deisseroth, K., & Janak, P.H. (2013) A causal link between prediction errors, dopamine neurons and learning. Nat. Neurosci. 16: 966-73; Self, D.W., Barnhart, W.J., Lehman, D.A., & Nestler, E.J. (1996) Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science. 271:1586-9; Kravitz, A.V., Tye, L.D., & Kreitzer, A.C. (2012) Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat. Neurosci. 15: 816–818;

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