Critical Role of Dopamine Signaling in Accumbal Cholinergic Interneurons for Compulsive Cocaine Seeking

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Striatal cholinergic interneurons (ChINs) play critical roles in processing value information for natural rewards and drugs of abuse, mainly by shaping the activity of medium spiny neurons of nucleus accumbens (NAc). However, their contribution to development of addiction and underlying mechanisms remain largely unknown. Using mouse models, we assessed seeking behaviors under a prolonged progressive ratio schedule of cocaine self-administration, which was followed by ChIN-specific RNA sequencing of striatal regions. ChINs, which were selectively isolated by fluorescence-activated cell sorting, were prepared for the transcriptome profiling with ChAT+ cells. Such cell-type specific transcriptome analysis revealed that dopamine D2 receptor (DrD2) are highly expressed in the NAc of mice that are more prone to cravings for cocaine. ChIN-specific DrD2 overexpression *per se* is sufficient to induce addiction-like behaviors, which could be normally evoked by repeated infusion of cocaine. We also found that *in vivo* activity of accumbal ChINs was diminished upon cocaine infusion. Collectively, our data establish a novel mechanism underlying core behavioral symptoms of drug addiction.

Keywords: Cholinergic interneurons, Nucleus accumbens, Cocaine craving, Dopamine D2 receptor