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Role of dorsal striatal RASD1, a potential downstream target of HDAC5, in incubation of methamphetamine craving.

Addiction is a chronic relapsing disorder characterized by prolonged drug craving during abstinence and a high probability of relapse upon exposure to drug-associated cues. In rats, cue-induced methamphetamine (Meth) seeking progressively increases throughout abstinence, a phenomenon termed “incubation of Meth craving.” Our previous work demonstrates that dorsal striatal histone deacetylase 5 (HDAC5), an epigenetic enzyme that generally suppresses gene transcription, plays a critical role in the incubation of Meth craving. Specifically, we found HDAC5 overexpression and knockdown in the dorsal striatum (DS) increases and decreases Meth seeking after prolonged abstinence, respectively. Here, we aimed to identify the downstream targets of HDAC5 that underlie its role in Meth craving. We first injected adeno-associated viruses (AAVs) to either overexpress or knockdown HDAC5 in the DS of male rats. Next, we trained rats to self-administer Meth (0.1 mg/kg, 9 h/d) for 10 days. On abstinence day 35, we collected DS tissue for subsequent bulk RNA-sequencing (RNA-seq). RNA-seq data revealed that, during incubation of Meth craving, mRNA expression of dexamethasone-inducible Ras protein 1 (Rasd1) was decreased after HDAC5 overexpression but increased after HDAC5 knockdown in the DS on abstinence day 35, suggesting that Rasd1 may be a transcriptomic target of HDAC5. As a member of the Ras superfamily of small GTPases, RASD1 disrupts the cAMP-PKA-CREB signaling pathway by inhibiting adenylyl cyclase. Based on the RNA-seq data, we hypothesize that RASD1, a potential downstream target of HDAC5, plays a negative role in incubation of Meth craving. Ongoing studies are investigating the effect of RASD1 overexpression in the DS on the incubation of Meth craving.

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