Role of dorsal striatal histone deacetylase 5 in incubation of methamphetamine craving

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Background: Methamphetamine (Meth) seeking progressively increases after withdrawal (incubation of Meth craving). We previously demonstrated an association between histone deacetylase 5 (HDAC5) gene expression in rat dorsal striatum and incubation of Meth craving. Here we used viral constructs to study the causal role of dorsal striatal HDAC5 in this incubation.

Methods: In Exp. 1 (over-expression), we injected adeno-associated virus (AAV) bilaterally into dorsal striatum to express either GFP (control) or a mutant form of HDAC5 (mHDAC5), which strongly localized to the nucleus. After training rats to self-administer Meth (10 days, 9 h/d), we tested the rats for relapse to Meth seeking on withdrawal days 2 and 30. In Exp. 2 (knockdown), we injected AAV bilaterally into dorsal striatum to express either a short hairpin RNA against luciferase (shLUC, control) or against HDAC5 (shHDAC5). After training rats to self-administer Meth, we tested the rats for relapse on withdrawal days 2 and 30. We also measured gene expression of other HDACs and potential HDAC5 downstream targets.

Results: We found that HDAC5 overexpression in dorsal striatum increased Meth seeking on withdrawal day 30 but not day 2. In contrast, HDAC5 knockdown in dorsal striatum decreased Meth seeking on withdrawal day 30 but not day 2; this manipulation also altered other HDACs (*Hdac1* and *Hdac4*) and potential HDAC5 targets (*Gnb4* and *Suv39h1*).

Conclusions: Results suggest that HDAC5 plays both a sufficient and necessary role in incubation of Meth craving. These findings set up future work to identify HDAC5 targets which mediate this incubation.