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Neuron subtype-specific role of methylated DNA cytosine dioxygenase TET1 in cocaine addiction

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The role of DNA methylation, a major epigenetic mechanism, has been increasingly appreciated in drug addiction. Recently, additional forms of DNA epigenetic modifications have been identified through the oxidation of methylated DNA cytosine to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5-fC), and 5-carboxylcytosine (5-caC). This was accompanied by the recognition of their catalyzing enzymes, ten-eleven translocation proteins (TET), which may lead to DNA demethylation. Though the three members of the TET family are expressed in the adult brain, their role in drug addiction is still largely unknown. Previously, we found that TET1 in the nucleus accumbens (NAc) is implicated in cocaine action, suggesting a functional role of DNA modifications in cocaine addiction. In the present study, we investigated the impact of *Tet1* deletion in either dopamine D1 receptor-expressing medium spiny neurons (D1-MSN) or dopamine D2 receptor-expressing MSNs (D2-MSN) in mice on behavioral responses to cocaine in reward- and addiction-related behavioral paradigms. The rewarding effect of cocaine in mice with *Tet1* deficiency in D1- or D2-MSNs was evaluated using the conditioned place preference (CPP) paradigm. Operant intra-venous self-administration (SFA) of cocaine was also evaluated. We found that D1-MSN specific knockout of *Tet1* in male mice enhances the rewarding value of cocaine, potentiates the vulnerability to cocaine binge, and amplifies the incentive motivation for taking cocaine. Currently we are performing similar studies in female mice and in intravenous cocaine self-administration. Our findings suggest a neuron subtype-specific role of DNA epigenetic modifications in cocaine addiction.