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

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Ten-eleven translocation methylcytosine dioxygenases (TET1, TET2, TET3) convert methylated DNA to 5-hydroxymethylcytosine which can be further catalyzed into additional forms of DNA epigenetic modifications and lead to DNA demethylation. We previously found that TET1 in mouse nucleus accumbens (NAc) regulates cocaine addictive behavior. As the vast majority of neurons in NAc are dopamine D1 receptor-expressing and dopamine D2 receptor-expressing medium spiny neurons (MSNs), which play distinct roles in addiction, we hypothesize that TET1's function is also neuron subtype specific. By selectively knocking-out *Tet1* in D1- or D2-MSNs, we observe an increased cocaine conditioned place preference (CPP) in D1-*Tet1* KO male mice and a decreased CPP in D2-*Tet1* KO females. In addition, female KOs demonstrate an opposite behavioral phenotype as compared to the male counterparts of the same genotype. This suggests TET1's function is not only neuron subtype-specific, but also sex-specific. By using cocaine intravenous self-administration, we reveal that *Tet1* KO in D1 neurons enhances cocaine acquisition in males and promotes cocaine extinction in females. Furthermore, viral mediated *Tet1* overexpression in *Tet1* KO neurons in NAc reverses addiction behaviors. To obtain an underlying epigenetic insight, we carry out whole-genome bisulfite sequencing to profile DNA methylation in D1- or D2-*Tet1* KO neurons of both sexes. The methylome analysis is underway with the potential to be integrated with our ongoing higher order genome organization characterization. In summary, our study demonstrates a sex dependent neuron-specific role of DNA epigenetics in cocaine addiction.