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Compulsive methamphetamine intake and abstinence in the presence of punishment are associated with differential hydroxymethylation of miRNAs in the rat nucleus accumbens

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Methamphetamine use disorder (MUD) is a neuropsychiatric disorder characterized by compulsive drug use in the presence of adverse consequences. The syndrome is thought to be due to epigenetics and transcriptional changes in the reward circuitry during chronic exposure to the drug.

The present study was conducted to identify potential differences between rats that compulsively self-administered methamphetamine (shock-resistant, SR) and those that suppress their intake (shock-sensitive, SS) in the presence of contingent footshocks used to mimic the 'adverse consequences' criterion of the DSMV. The rats were euthanized two hours after the last session of methamphetamine self-administration plus footshocks. The nucleus accumbens was removed and used for genome-wide hydroxymethylated DNA immunoprecipitation (hMeDIP) sequencing.

The genowide-wide sequencing identified differentially hydroxymethylated peaks in the SRvCT, SSvCT, and SrvSS comparisons. Several miRNAs were impacted. These included Mir17-1, Mir551b, and Mir708 that showed increases in the SRvCT comparison. In addition, Mir124-2, Mir153, Mir181b1, and Mir206 showed increases whereas Mir6322 showed decreased hydroxymethylation in the SSvCT comparison. In the SRvSS comparison, Mir124-1, Mir145, Mir146a, Mir3099, and Mir3596 showed increases whereas Mir29 and Mir185 showed decreased DNA hydroxymethylation peaks.

The present observations implicate DNA hydroxymethylation in the behavioral manifestations of compulsive methamphetamine taking and abstinence in the presence of punishment. Our results suggest that small non-coding RNAs known to participate in post-transcriptional regulation and modulation of synaptic plasticity might play a role in the development and maintenance of methamphetamine use disorder.