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Mimicking methamphetamine use disorder with footshock punishment: epigenetic and transcriptional consequences in the rat brain.

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Methamphetamine use disorder (MUD) is a major public health problem throughout the world. MUD is associated with severe neuropsychiatric complications. Investigations that have focused on the effects of methamphetamine on catecholaminergic systems have not helped to develop therapeutic agents against MUD. Therefore, we have hypothesized that the manifestations of MUD may be secondary to perturbations that involve long-lasting epigenetic, transcriptional, and/or biochemical changes in the brain. Rats were trained to self-administer methamphetamine over a period of a month. Thereafter, the animals received contingent shocks while self-administering the drug. Rats were then euthanized and used in various biochemical, transcriptional, or epigenetic experiments at various timepoints after withdrawal from methamphetamine self-administration. We measured genome-wide transcriptional changes using Illumina 22K Rat microarrays. We used a deep sequencing approach with Illumina HiSeq2500 to identify potential alterations in DNA hydroxymethylation. Rats exposed to methamphetamine during self-administration experiments escalated their methamphetamine intake. Contingent shocks separated methamphetamine-exposed rats into punishment-resistant (PR, addicted) rats that took methamphetamine compulsively and punishment-sensitive (non-addicted) rats that decreased their lever pressing. Genome-wide DNA sequencing revealed increased DNA hydroxymethylation of several potassium channels, with PCR showing increased expression of their mRNAs in the nucleus accumbens of PS rats. After one month of withdrawal, we found increased phosphorylation of several proteins that participate in the NGF-TrkA and p75NTR/MAPK signaling pathways in the dorsal striatum of punishment-sensitive rats at that time. Thus, prolonged exposure to compulsive methamphetamine self-administration does cause long-lasting epigenetic, transcriptional, and biochemical perturbations that could be targeted to treat MUD.