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Revealing the dynamic epigenetic changes of nucleus accumbens induced by methamphetamine overdose

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In the height of the opioid crisis in our country, deaths from methamphetamine (MA) are on the rise. More than 72,000 Americans died from drug overdoses in 2017, and near 11,000 of those deaths were estimated to be caused by MA. There is no FDA-approved medication for MA Use Disorder or MA overdose; therefore, there is an urgent need to understand how brain responds to high doses of this drug. By performing the ATAC-seq on nucleus accumbens samples from young adult MA-overdosed rats, we systematically measured the dynamic epigenetic changes of chromatin accessibility in this drug reward-mediating brain area. We found that the chromatin accessibility of over than 6,000 genomic locations were significantly changed 24 h after the intake of MA. Over 95% of epigenetic changes happened on distal regulatory elements, which are far away from gene's promoter. Over 5,000 genomic locations significantly lost chromatin accessibility caused by MA overdose. Genes around these silenced regulatory elements, such as Glutamate Ionotropic Receptor Gria1 and 5-Hydroxytryptamine Receptor Htr2a, were highly enriched neuronal related function, including regulation of synaptic plasticity, memory formation, cognition, and etc. MA overdose also induced the activation of 1,100 regulatory elements in the nucleus accumbens. Interestingly, the genes around these drug-activated regulatory elements, such as Oligodendrocyte Transmembrane Protein Cldn11 and Homeobox protein Nkx6-2, were highly correlated to glial cells' function, including myelination, axon ensheathment, and oligodendrocyte differentiation. The results suggest that MA overdose might silence the neuronal cell but stimulate the glial cell in rat nucleus accumbens.