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Epigenetic representation of cocaine-context association in the dorsal dentate gyrus of male mice

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The dorsal hippocampus plays a central role in drug-context associations. These contextual memories are long-lasting and in part, contribute to relapse. Drug-induced epigenetic changes are one molecular mechanism involved in these persistent memories. Using cocaine conditioned place preference (CPP), we analyzed the dorsal dentate gyrus methylomes of male mice and found thousands of differentially methylated regions (DMRs) between cocaine and saline groups. Many DMRs mapped to intermediately methylated (IM) areas of the genome. These regions represent cell-to-cell methylation heterogeneity and have been associated with enhancers, some of which are methylation sensitive. Since cocaine shifted the percentage of cells methylated at a given CpG, our data suggest that cocaine alters the proportion of cells that have methylated, and thus inactive, enhancers. Exercise, enriched environment, and stress targeted similar, but substantially fewer, regions, indicating that cocaine has more profound epigenome-altering potential than natural environments. Given the large number of cocaine-modified IM regions, the drug reorganizes the methylation and functioning of the enhancer network at cellular and population levels. These findings were replicated in cocaine self-administering mice, strengthening the link between context-paired drug, IM regions, and reward seeking. Additionally, we found cocaine CPP shifted fully methylated and unmethylated regions to IM, creating epigenetic and functional heterogeneity in previously uniform areas across cells. Overall, cocaine-context association is represented by a massively reorganized methylome, both at IM enhancers and normally stable epigenetic regions that, via gene expression and altered cellular states, is proposed to contribute to drug dependence and relapse.