Name: Benpeng Miao Email: benpeng@wustl.edu
PI Name: Bo Zhang PI email: bzhang29@wustl.edu
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Methamphetamine induced regional-specific transcriptomic and epigenetic changes in rat brain

Benpeng Miao[1], Xiaoyun Xing[1], Anna Moszczynska[2], Bo Zhang[1]

[1]Department of Developmental Biology, Washington University in St. Louis; [2]Pharmaceutical Sciences Department, Wayne State University

Drug addiction is a relapsing disorder resulted from neural adaptations following repeated drug exposure. Methamphetamine (METH) is one strong central nervous system stimulant that can result in addiction. Abuse of METH is associated with neurologic and psychiatric disorder and overdose use of METH can cause brain damage and even death. Mounting evidence indicated impaired functions and epigenetic changes of brain structures due to addictive drugs. However, reaction of different brain structures to METH overdose remained unclear. In this study, we investigated transcriptomic and epigenetic responses to METH exposure in four brain structures, including Nuclear Accumbent, Dentate Gyrus, Ammon's horn and Subventricular zone. We found METH overdose induced hundreds of differential expressed genes (DEGs) and thousands of differential accessible regions (DARs) in those 4 rat brain structures, but few of those DEGs and DARs were simultaneously affected. The METH overdose also resulted in reversed patterns of gene regulation and chromatin accessibility between Dentate gyrus and Ammon's horn. Among those 4 rat brain structures, 149 transcription factors and 31 epigenetic factors were significantly affected by METH overdose. And TFs enriched in those DARs derived distinct gene regulatory network. Meanwhile, about 70% of METH-induced DARs were conserved in rat, mouse and human highly related with neurological processes, and many of conserved DAR could intersect with validated enhancers and GWAS SNPs. Our results suggested those 4 rat brain structures exhibited region-specific responses to METH overdose and emphasized transcriptomic and epigenetic roles in METH response. Our study also provided some candidate genes and chromatin accessible regions that may play roles in drug addiction.