

Name: Akhil Sharma

Email: akhilsharma@wayne.edu

PI Name: Anna Moszczynska

PI email: amosz@wayne.edu

Comparing Responses of the Nucleus Accumbens and Ammon's Horn to Methamphetamine Neurotoxicity

Akhil Sharma¹, Viktoriia Bazylanska¹, Benpeng Miao²,
Xiaoyun Xing², Shaopeng Liu², Pamela Madden², Bo Zhang², Anna Moszczynska¹

¹Wayne State University, Detroit, MI; ²Washington University School of Medicine, St. Louis, MO

Methamphetamine (METH) is a highly addictive and neurotoxic psychostimulant. METH neurotoxicity is dopamine-dependent and region specific, with the striatum, prefrontal cortex, and hippocampus being the most affected brain areas. Despite dopaminergic innervation, the nucleus accumbens (NAc), the reward center of the brain, is relatively resistant to METH neurotoxicity. The molecular mechanisms that underlie this "resistance" are not known. To fill this gap in scientific knowledge we simultaneously assessed responses of the Ammon's horn (AH, CA1-CA3 regions of the hippocampus) versus NAc to neurotoxic METH regimen at the transcriptomic and epigenetic level. Sprague-Dawley male rats were treated with METH binge (4x10mg/kg, every 2h, i.p.) and sacrificed 24h later. RNA-seq analysis revealed that genes significantly upregulated in the NAc but not in the AH included those involved in inflammatory responses. Furthermore, genes involved in transcription and responses to stimulants were altered in opposite directions: downregulated in the NAc and upregulated in the AH. ATAC-seq analysis revealed that, in the NAc, the chromatin was opened around 30 genes mediating wound healing. Inflammation is a protective response preparing the tissue for repair and healing.

Downregulation of protein synthesis helps cells to cope with stress and promotes cell survival. Regarding the latter, protein synthesis inhibitors were reported to attenuate METH neurotoxicity. In view of these findings, our result suggests that the NAc has more effective stress recovery mechanisms than the AH.