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Ubiquitin-Protein Ligase Parkin in Methamphetamine Use Disorder

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In the United States, there are close to 2,000,000 people with methamphetamine (METH) use disorder (MUD); however, there is no FDA-approved medication for this disorder, needed especially for people who abuse METH heavily. We previously demonstrated that overexpression of ubiquitin-protein ligase parkin in the nucleus accumbens (NAc) decreased METH intake and relapse to METH seeking in rat model of heavy METH use. The goal of the current study was to elucidate molecular pathways underlying the anti-addictive properties of parkin in this model. Towards this goal, we generated and compared proteomes from wild type vs. parkin overexpressing NAc collected from saline-yoked rats, rats that self-administered METH and were withdrawn from the drug for 10 days, and from rats that relapsed to METH seeking. We hypothesized that since parkin is neuroprotective, it will upregulate stress response pathways in the NAc. GSEA analysis of the proteomic data revealed that pathways most significantly upregulated by parkin in saline rats were stress response pathways Notch1 and NFkappB. Major biological processes altered by parkin overexpression in the NAc of METH-withdrawn rats were processes involved in tonic motor seizures, glutamate signaling, long term potentiation and inflammation. In rats that relapsed to METH seeking, the most altered pathways were those mediating Notch and chemical hypoxia responses. The leading-edge proteins within this cluster were proteins belonging the 19S proteasome and involved in Notch, NFT2L2, TNFR2, p53, and Hedgehog pathway. Our results suggest that parkin decreases METH taking and seeking through regulation of proteins belonging to the stress-response pathways.