Submitter Name: Anna Moszczynska
Submitted Email: ei2744@wayne.edu

The Role of PARKIN in Methamphetamine Use Disorder

Anna Moszczynska

Department of Pharmaceutical Sciences, Wayne State University

There is no FDA-approved medication for methamphetamine (METH) use disorder. New therapeutic approaches are needed, especially for people who use METH heavily and are at high risk for overdose. PARKIN is a ubiquitin-protein ligase which has a role in some processes that mediate addictive behaviors. The role of PARKIN in drug addiction; however, was not previously investigated. We hypothesized that PARKIN would affect reinforcing/rewarding effects of METH and used genetically engineered rats to evaluate PARKIN as a potential target for METH use disorder. PARKIN knockout, PARKIN-overexpressing and wild-type young adult male Long Evans rats were trained to self-administer high doses of METH using an extended-access METH self-administration paradigm. Reinforcing/rewarding properties of METH were assessed by quantifying drug-taking behavior and time spent in a METH-paired environment. PARKIN knockout rats self-administered more METH and spent more time in the METH-paired environment than wild-type rats. Wild-type rats overexpressing PARKIN in the ventral striatum self-administered less METH and spent less time in the METH-paired environment than the wild-type rats. These results identified PARKIN as a novel drug target to treat heavy use of METH and indicated that rats with PARKIN excess or deficit were useful models for studying neural substrates underlying “resilience” or vulnerability to METH use disorder. Proteomic analysis of striatal tissue revealed that among proteins differentially affected by PARKIN overexpression *vs.* PARKIN knockout were those involved in glutamatergic neurotransmission, responses to stress, and cytoskeletal organization. Our results suggest that the role of PARKIN in METH use disorder includes modulation of these processes.