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The role of E3 ligase parkin in neurotoxicity of psychostimulant methamphetamine

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In experimental animals and humans, exposure to methamphetamine (METH) can produce a loss of dopaminergic (DAergic) nerve terminal markers in the striatum. Furthermore, young adult chronic users of METH are at risk to develop Parkinson's disease (PD) later in life. Parkin is an ubiquitin-protein ligase with neuroprotective properties that plays an important role in neuroprotection and maintenance of DA neurons. Our laboratory has investigated the role of parkin in protection of DAergic terminals from METH neurotoxicity and in susceptibility of METH-exposed brain to develop PD in young adult rats. We have shown that high-dose METH oxidatively damages parkin and decreases its levels in rat striatum while overexpression of parkin in the nigrostriatal DA system protects DAergic terminals against METH neurotoxicity. We have subsequently investigated molecular mechanisms underlying the parkin-mediated neuroprotection. Loss-of-function mutations in Park2, a gene encoding the E3 ligase parkin, have been found in patients with familial PD and early onset sporadic PD. A deficit in parkin function also contributes to late onset sporadic PD. Despite intense investigation, the exact role of parkin in the development of PD is still unclear as parkin knockout (PKO) rats and mice do not display DAergic deficits and progressive nigrostriatal DA neuron degeneration. We have set to test the hypothesis that METH-mediated deficit in parkin combined with other factor(s) decreasing parkin function potentiates the susceptibility of DA to developing PD. We have found that parkin knockout (PKO) rats are hypersensitive to the neurotoxic effects of METH in the striatum and display Parkinsonian-like motor impairments. We have also determined that altered DA and phenylethylamine signaling mediate these effects. The relevance of our key findings to therapeutic strategies in METH abuse will be discussed.

KEY WORDS: Addiction Treatment, Attachment, Drug and Substances abuse.

Biography

Dr. Anna Moszczynska completed one of her two M.Sc. programs, her Ph.D. program, and one of three postdoctoral studies at University of Toronto in Canada. She subsequently completed additional two postdoctoral programs, at Guelph University in Canada and at Boston University in the USA. Dr. Moszczynska's experience combines chemical engineering, cellular and molecular neurobiology, neurochemistry, neurotoxicology, genetics and pharmacology. She is currently an Associate Professor at Wayne State University in Detroit, USA. Her research focus is on neurotoxicity of psychostimulant methamphetamine. Dr. Moszczynska is a recipient of several awards, including NIH/NIDA Pathway to Independence Award and Academy of Scholars WSU Junior Faculty Award, and NIH/NIDA R01 grant.

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