Dopaminergic Cell Toxicity of a Derivative of Parkinsonian Toxin, 4-methyl-phenylpyridinium (MPP+)

Lickteig, Bryan, & Dr. Kandatege Wimalasena, Department of Chemistry, Wichita State University

Parkinson's disease (PD) is a neurodegenerative disease that has been studied for several decades with no definitive answer to its origin. It has been hypothesized that genetics, environmental factors, and mitochondrial mutations are linked to PD, but the etiology of PD has not been fully understood. 1-Methyl-4-phenylpyridinium (MPP+) has been used as a model for PD due to the finding that it causes PD symptoms in humans and other primates. MPP + inhibits the mitochondrial complex I and increase oxidative stress of dopaminergic neurons. Our lab previously characterized 3-Amino-2-phenylpropene (APP), as an irreversible inhibitor of vesicular monoamine transporter-2 (VMAT2) and also reported that it is toxic to the dopaminergic cells. Since the synaptic accumulation of MPP+ is proposed to be a detoxification mechanism, it was hypothesized that the conjugate of MPP+ and APP, N-(2-phenypropene)-4-phenylpyridinium (MPP-APP), would be more toxic to dopaminergic cells. To test this hypothesis, the dopaminergic toxicity of MPP-APP was determined using MN9D cells. The results showed that MPP-APP is more toxic to MN9D cells than either the MPP+ or APP themselves. MPP-APP accumulates in cells through simple diffusion and similar to MPP+ it increase the ROS production specifically in dopaminergic cells. Experiments with fluorescence dye DAPI shows that the cell death is due to the ROS induced apoptotic pathway and antioxidants protects cells from the toxicity. These studies will not only help to understand the mechanism of the specific dopaminergic toxicity of MPP+ and similar toxins, but also lead to the development of preventive strategies for PD.