Dopaminergic Cell Toxicity of N-Substituted Derivatives of Parkinsonian Toxin 1-Methyl-4-phenylpyridinium (MPP+)

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Parkinson's disease (PD) is a neurodegenerative disease whose etiology is unknown but genetics, environmental factors, and mitochondrial mutations may play a role. 1-Methyl-4-phenylpyridinium (MPP+) is a model for PD since it causes PD-like-symptoms in mammals. MPP+ inhibits mitochondrial complex I and increases oxidative stress in dopaminergic neurons. Synaptic accumulation of cytosolic MPP+ through vesicular monoamine transporter-2(VMAT2) has been proposed as an *in vivo* detoxification mechanism. Our previous studies have shown that N-substituted MPP+ derivatives, [N-(2-phenypropene)-4-phenylpyridinium (MPP-APP)] were potent inhibitors of VMAT, suggesting these should increase MPP+ toxicity. The present studies show that MPP-APP derivatives themselves are more toxic to dopaminergic cells than MPP+. MPP-APP accumulates in cells through diffusion and increases ROS production in dopaminergic cells. The cell death is due to the ROS induced apoptosis similar to MPP+. The implications of these findings to the mechanism of MPP+ toxicity could lead to future treatments for PD.