Public Abstract
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Title:THE MECHANISM FOR PARAQUAT TOXICITY INVOLVES OXIDATIVE STRESS AND INFLAMMATION: A MODEL FOR PARKINSON'S DISEASE

Parkinson’s disease (PD) is debilitating and has no cure. In a few patients mutations in specific proteins induce loss of neurons, but for most the cause of the disease is unknown. A higher incidence of PD has been noted in people living in areas where the herbicide paraquat has been used. In post-mortem studies, significantly higher numbers of activated microglia (immune cells in the brain) have been found in the brains of Parkinson’s patients compared to controls.

We investigated underlying signaling pathway generating reactive oxygen species or ROS (known to damage cells) after paraquat exposure in microglia. A highly expressed enzyme that generates ROS in microglia is NADPH oxidase. Paraquat induced ROS decreased after addition of NADPH oxidase inhibitors. These results imply that NADPH oxidase is the major ROS generator responsible for paraquat toxicity in microglia cells. The ROS generated from microglia appear to be the initial step spreading damage to neighboring neurons.

People who live in paraquat-contaminated areas are chronically exposed to multiple risk factors that may synergistically cause degeneration of neurons. In an immune response, inducible nitric oxide synthase (iNOS) is highly expressed which produces nitric oxide (NO). NO kills off invading bacteria but can damage good cells at concentrations too high. Paraquat greatly attenuated the NO generated yet still moderately enhanced ROS production in microglia. We believe paraquat might directly interact with iNOS to prevent generation of NO but increase production of ROS.

Most of our research has focused on the cells surrounding the neurons. We were also interested in toxicity of paraquat in neurons. NADPH oxidase is expressed in at low levels in neurons. In many diseases there is increased expression of NADPH oxidase. Paraquat also increased gene expression of NADPH oxidase in neurons. Increased gene expression of NADPH oxidase can lead to much higher amounts of ROS to damage the neurons.

In conclusion, our data suggest that NADPH oxidase plays a significant role in the paraquat toxicity, which lead to the development of PD. A better understanding of the underlying cause of this disease would help us to develop better strategies and pharmaceutical agents for prevention and treatment of PD.