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Redox metabolismand dopaminergic cell death in response to mitochondrial and environmental pesticides

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Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantianigra pars compacta (SNpc). Besides the risk factors of aging and geneticpre-disposition, epidemiological data also suggest an association between PD and pesticide exposure. Oxidative stress is involved in dopaminergic cell death in PD. However, the molecular mechanisms remain unclear. Recent studies have demonstrated the strong interrelationship that exists between redox homeostasis and cellular metabolism. The metabolome is a valuable source of information to understand disease pathogenesis since metabolites are more proximal to disease than genetic or proteomic information. In this study, we investigated the alterations in the redox metabolome in dopaminergiccells exposed to environmental/mitochondrial toxins (paraquat, rotenone, MPP^+ and 6-OHDA) in order to identify potential biomarkers and novel mechanisms of disease progression.A combined metabolomic approach using 1D ^1H NMR and MS was used to identify specific patterns inthe metabolome of cells exposedto PD mimetics. We observed unique metabolic profile changes in response to all toxins,but paraquat exposure induced themost profound alterations.^{13}C-glucose flux analysis demonstrated that metabolites within the pentose phosphate pathway (PPP) such as fructose 6-phosphate, glucono-1,5-lactone and erythrose 4-phosphate were increased by paraquat treatment. Proteomic analysis also found an increase in the expression of enzymes in the PPP such as glucose 6-phosphate dehydrogenase (G6PD), which supplies reducing equivalents by regenerating nicotinamide adenine dinucleotide phosphate (NADPH) levels. Overexpression of G6PD was shown to selectively increase paraquat toxicity. These results suggest that paraquat "hijacks" the PPP to increase NADPH reducing equivalents. An increase inNADPH levels would stimulate paraquat redox cycling, oxidative stress and cell death. Our results demonstrate the importance of alterations in redox metabolic pathways in PD, and the importance of metabolomic studiesto identify novel molecular mechanisms regulating neuronal cell death in PD.

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