

Mitochondrial impairment as an early event in the process of apoptosis induced by glutathione depletion in neuronal cells: relevance to Parkinson's disease.

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In Parkinson's disease (PD), dopaminergic cell death in the substantia nigra was associated with a profound glutathione (GSH) decrease and a mitochondrial dysfunction. The fall in GSH concentration seemed to appear before the mitochondrial impairment and the cellular death, suggesting that a link may exist between these events. The relationships between GSH depletion, reactive oxygen species (ROS) production, mitochondrial dysfunction and the mode of cell death in neuronal cells remain to be resolved and will provide important insights into the etiology of Parkinson's disease. An approach to determine the role of GSH in the mitochondrial function and in neurodegeneration was to create a selective depletion of GSH in a neuronal cell line in culture (NS20Y) by inhibiting its biosynthesis with L-buthionine-(S,R)-sulfoximine (BSO), a specific inhibitor of gamma-glutamylcysteine synthetase. This treatment led to a nearly complete GSH depletion after 24 hr and induced cellular death via an apoptotic pathway after 5 days of BSO treatment. By using the reactive oxygen species-sensitive probe 2',7'-dichlorofluorescein, we observed that the rapid GSH depletion was accompanied, early in the process, by a strong and transient intracellular increase in reactive oxygen species evidenced after 1 hr with BSO, culminating after 3 hr when the GSH level decreased to 30% of normal. GSH depletion induced a loss of mitochondrial function after 48 hr of BSO treatment. In particular, the activities of complexes I, II and IV of the respiratory chain were decreased by 32, 70 and 65%, respectively as compared to controls. These results showed the crucial role of GSH for maintaining the integrity of mitochondrial function in neuronal cells. Oxidative stress and mitochondrial impairment, preceding DNA fragmentation, could be early events in the apoptotic process induced by GSH depletion. Our data are consistent with the hypothesis that GSH depletion could contribute to neuronal apoptosis in Parkinson's disease through oxidative stress and mitochondrial dysfunction.

