Manganese Treatment Induces Dose-related Decreases in the Activities of Several Glycolytic and TCA Cycle Enzymes in Neuroblastoma and Astrocytoma Cells

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ABSTRACT

Manganese (Mn) is a trace metal required for normal growth and development. However, in Mn mining and steel making, over exposure of humans to Mn leads to development of symptoms of toxicity. Mn toxicity occurs in hospitals in some situations of long term parenteral nutrition. Human manganism exhibits an early psychotic phase, followed by chronic signs and symptoms resembling those of Parkinson's disease and dystonia. However, the underlying cellular and molecular mechanisms are still elusive. In previous studies, we have demonstrated, when added to the drinking water, Mn accumulates in brain (mainly in mitochondria, nuclei and nerve-endings) in a dose-related manner. Mn treatment of mitochondria in vitro interferes with oxidative phosphorylation and respiration. Based on these observations, we hypothesized Mn can induce apoptosis and alter energy metabolism in neural cells. We have investigated this hypothesis by studying the Mn effects on neuroblastoma (SK-N-SH) and astrocytoma (U87) cells. We found Mn treatment induced apoptosis in a concentration- and time-dependent manner in both SK-N-SH and U87 cells as indicated by apoptotic markers (e.g., morphological changes, MTT assay, and DNA laddering). To determine the relationship between Mn-induced apoptosis and cellular energetics, we have investigated further the Mn effects on several glycolytic and TCA cycle enzymes. At 0.1-4 mM, Mn treatment for 48 hours led to dose-related decreases in hexokinase, lactate dehydrogenase, malate dehydrogenase and citrate synthase. Thus, these results are consistent with our hypothesis and may have pathophysiological implications in Mn neurotoxicity in clinical as well as environmental settings.