Disordered Iron Metabolism Following Manganese Exposure: From Systemic Iron Homeostasis to Cellular Iron Regulation

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ABSTRACT

Intracellular iron (Fe) homeostasis is post-translationally regulated by one of the iron regulatory proteins (IRPs), namely cytoplasmic aconitase (ACO1) or IRP-I. Our previous studies demonstrate that manganese (Mn)-induced neurodegenerative toxicity may be partly due to its action on ACO1. We further investigated whether Mn exposure influenced the homeostasis of Fe in vivo, the cellular Fe regulation in vitro, and the transport of Fe at blood-CSF barrier (BCB) in vitro. Following chronic exposure to MnCl2 at the dose of 6 mg Mn/kg/day, ip, for 30 days, Mn-treated rats showed a 32% decrease in plasma Fe ($p<0.01$) and no changes in plasma total iron binding capacity (TIBC) compared to the control rats. However, Mn treatment increased CSF Fe by 3 fold ($p<0.01$). Exposure of cultured neuronal PC12 cells to Mn caused a significant increase in cellular uptake of 59Fe by 110% that of controls. The promotive effect of Mn on Fe uptake was Mn-concentration dependent within the range of 50-200 μM Mn in culture medium. When the cultured PC12 cells or choroidal epithelial cells, which were derived from rat choroid plexus, were incubated with MnCl2, the expression of TfR mRNA was enhanced by 30% and 50% that of controls for PC12 cells and plexus cells, respectively. In a two-chamber BCB transport model study, Mn exposure facilitated the influx of 59Fe from the blood to the CSF side. In addition, we found that Mn toxic effect was selectively associated with its valent status. Mn(III) species was evidently more effective than Mn(II) in inhibition of ACO1. Consequently, Mn(III) appeared to be more cytotoxic than Mn(II) on the growth kinetics of cultured PC12 cells. The results suggest that Mn can interact with Fe at multiple levels, from the systemic circulation to brain barrier transport and to cellular Fe regulation. A disordered Fe metabolism may contribute to Mn-induced neurotoxicity. (Supported by NIEHS RO1 ES08146)