Influx Kinetics of Manganese, Manganese Citrate and Manganese Transferrin into the Brain

Authors: J. S. Crossgrove, S. S. Rhineheimer, R. A. Yokel
Graduate Center for Toxicology and College of Pharmacy
University of Kentucky Medical Center
Lexington, KY 40536-0082.

ABSTRACT

Manganese (Mn) is an essential element and a neurotoxicant. Regulation of Mn entry into as well as its exit from the brain contributes to whether the Mn concentration is functional or detrimental. In serum, Mn exists in a protein-bound fraction and as Mn complexes with water and small molecular weight ligands. Mn speciation may influence the kinetics of Mn passage through the blood-brain barrier (BBB). This study compares the brain influx rates of Mn^{2+}, Mn-citrate and Mn-transferrin (Mn-Tf) in adult male Sprague-Dawley rats using the *in situ* brain perfusion technique (Takasoto *et al.*, Am. J. Physiol. 247:H484-493, 1984). The perfusion fluid contained a Mn species as ^{54}Mn and a vascular volume marker, ^{14}C-sucrose, which does not appreciably cross the BBB during these short experiments (15-180 seconds). Influx transfer coefficients (K_{in}), a measure of clearance from blood to brain, were determined with data from four perfusion durations for each Mn species in nine brain regions and the choroid plexus. Brain region values generally did not differ within Mn species and were found to be 15-30 x 10^{-5}, 20-55 x 10^{-5} and 1-15 x 10^{-5} ml/sec/g for Mn^{2+}, Mn-citrate, and Mn-Tf, respectively. The choroid plexus K_{in} values exceeded all brain regions by >10 fold for each species. Consistent with substrates of low extraction, Mn^{2+} influx did not differ with flow rates of 10 and 20 ml/min. When compared to calculated diffusion rates, these results suggest carrier-mediated brain influx of each Mn species. Furthermore, the greater K_{in} value for Mn-citrate than Mn^{2+} and Mn-Tf suggests separate influx mechanisms. Supported by Health Effects Institute Research Agreement #99-10.