

Brain Manganese Efflux through the Blood-Brain Barrier

R. A. Yokel, S. S. Rhineheimer, B. L. Bukaveckas
College of Pharmacy
University of Kentucky Medical Center
Lexington, KY, 40536-0082

ABSTRACT

Mn can enter the brain by carrier-mediated influx. There are no reports of the investigation of Mn efflux from the brain. We determined whether Mn^{2+} , Mn-citrate and Mn-transferrin (Mn-Tf) efflux from the brain through the blood-brain barrier (BBB) by carrier-mediated processes. We first estimated the diffusion rate of these three Mn species through the BBB based on their lipophilicity, molecular weight and the brain capillary surface area, as described by Levin (J. Med. Chem. 23:682-684, 1980) and Smith (In: Implications of the blood-brain barrier and its manipulation, 85-118, 1989). Predicted diffusion rates (a measure of clearance from blood to brain or brain to blood) were 4.8, 1.7, 3.4, and 2.9×10^{-5} ml/sec/g brain for Mn^{2+} , Mn-citrate, Mn-Tf, and sucrose, respectively. We then determined clearance from brain for these three Mn species as capillary efflux (K_{out}) using the method of Kakee *et al.* (J. Pharmacol. Exp. Ther. 227:1550-1559, 1996). These studies used ^{54}Mn species and ^{14}C -sucrose, which crosses the BBB by diffusion. K_{out} is calculated from the apparent elimination rate constant (K_{el}) \times the brain distribution volume (V_{brain}). K_{el} is determined from the reduction of brain Mn versus sucrose after discrete injection into the parietal cortex. V_{brain} is determined from Mn uptake into parietal cortex slices. After injection of each of the Mn species, brain Mn^{2+} decreased more rapidly over time than did sucrose. Initial estimates of K_{out} values for Mn^{2+} , Mn-citrate and Mn-Tf are 13, 10 and 27×10^{-5} ml/sec/g, respectively, suggesting slightly faster brain efflux than mediated by diffusion. These results suggest Mn^{2+} , Mn-citrate and Mn-Tf may be substrates for one or more brain efflux carriers. Supported by Health Effects Institute Research Agreement #99-10.