

## 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  $2.9 \times 10^{-5}$  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  $27 \times 10^{-5}$  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.