Published in final edited form as:

Cell Biol Toxicol. 2009 ; 25: 185–215. doi:10.1007/s10565-008-9080-z.

Changes in Dietary Iron Levels Affect Brain Manganese Accumulation and Distribution

Vanessa A. Fitsanakis¹, Yoram Finkelstein², Michael Aschner³

¹King College, Department of Biology, Bristol, TN 37620

²Unit and Service of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel

³Departments of Pediatrics and Pharmacology, and the Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Department of Pediatrics, Nashville, TN 37232

Keywords

Brain; Citrate Transporter; Divalent Metal transporter (DMT-1); Manganese; Transferrin; ZIP8

A. Manganese exposure and Manganism:

Manganese (Mn) is an essential trace metal necessary for normal growth and development throughout an organism's life cycle. It is a crucial component of various enzymes involved in functions ranging from metabolism of macromolecules, bone development, wound healing and antioxidant capacities (Keen et al., 1996; Lai et al., 1999; Nielsen, 1999; Rothand Garrick, 2003). Both dietary excess and deficiency of Mn can lead to various neurological disorders, although Mn intoxication is more common than Mn deficiency. The strongest correlation between any type of environmental exposure and increased susceptibility to PD is observed in Mn-exposed populations (Gorell et al., 1999a; 1999b). Occupational exposure to Mn for >20 years or combined long-term exposures to Mn and Al (>30 years) are associated with the increased prevalence of PD (Gorell et al., 1999a; Normandin et al., 2002). Mn toxicity results in symptoms similar to those seen in patients with PD, including rigidity, tremors, dystonia and bradykinesia (Calne et al., 1994). Recent studies suggest that the prevalence of Parkinsonism is higher among welders vs. age-standardized individuals in the general population (Racette et al., 2001; 2005a). Finally, positron emission tomography (PET) in a welder with Parkinsonism confirms that the clinical features of Mn-induced Parkinsonism overlap with those of PD, characterized by prolonged L-dopa responsiveness and reduced [¹⁸F]fluorodopa uptake (Racette et al., 2005b). In general, Mn toxicity is related to specific occupations, such as Mn mining (Mergler et al., 1999; Dietz et al., 2001; National Institute of Occupational Safety and Health, 2002), and those exposed to high Mn levels often suffer from neurological symptoms attributed to excessive Mn exposures (Newland, 1999; Pal et al., 1999; Myers et

Corresponding author: Michael Aschner, Department of Pediatrics, B-3307 Medical Center North, 1162 21st Avenue South, Vanderbilt University School of Medicine, Nashville, TN 37232-2495 USA. Tel: +1 615 322 8024, Fax: +1 615 322 6541, Michael.Aschner@vanderbilt.edu.

al., 2003). There are also numerous reports of Mn intoxication related to long-term total parenteral nutrition (TPN) (Reimund et al., 2000), and from long-term liver failure (Sugihara et al., 2001; Park et al., 2003). Intermediate and late signs and symptoms of Mn toxicity include difficulty walking backward, severe dystonia of the trunk, psychosis and tremor of the upper extremities (Pal et al., 1999). Once the symptoms of Mn intoxication develop, the disease, termed 'manganism,' is often progressive, even if the patient is removed from the source of Mn exposure (Pal et al., 1999).

B. Iron and Iron Deficiency:

Iron (Fe) is the most abundant transition metal in the brain. Like Mn, it is an essential nutrient and important cofactor for many enzymes (Yip and Dallman, 1996; Beard and Dawson, 1997). However, because Fe is highly redox-active and toxic, organisms are equipped with overlapping mechanisms to ensure exquisite regulation of Fe concentration and compartmentalization. Although Fe overload is the focus of much research, problems have also been noted to occur from Fe deficiency (World Health Organization, 1996; 2003; Chua and Moran, 1996). Currently, the World Health Organization (WHO) estimates that between 4 and 5 billion people worldwide suffer from Fe deficiency. Of these, 2 billion, or approximately 30% of the world's population, are actually classified as anemic. Although Fe deficiency can occur in any population, it is most often observed in the developing world or in lower socio-economic strata due to a lack of proper nutrients and Fe-rich foods. This becomes particularly problematic when considering that several large Mn mines are located in developing countries (International Manganese Institute, 2007).

C. Interdependence of Mn and Fe:

A number of studies have elucidated the transport and storage mechanisms of Fe (Connors, 2003). Fe is bound to transferrin (Tf) in plasma and is subsequently taken up by cells via the Tf receptor (TfR). Once bound to the TfR, the Fe-TfR complex undergoes endocytosis, forming an endosome. As the pH of the endosome decreases, Fe is released from both the Tf and the TfR, and transported out of the endosome to the cytoplasm via the divalent metal transporter (DMT-1; also known as Nramp or DCT-1) (Malecki et al., 1999). Mn can also be transported into cells via the same mechanism (Chua and Morgan, 1996; 1997; Roth and Garrick, 2003) (Figure 1). The ability of Mn and Fe to share the same transporters is likely based on their chemical similarities, as both are first-row transition metals with similar atomic masses (54.94 amu *versus* 55.85 amu). Although the atomic radius of Mn is slightly larger than Fe (127 pm *versus* 125 pm), they share many other chemical similarities: electronic structure or configuration ($[Ar] 3d^5 4s^2$ *versus* $[Ar] 3d^6 4s^2$), chemical bonding involving the d-shell electrons, number of oxidation states, and electronegativity (1.55 *versus* 1.83). Since Fe and Mn use similar transport systems, it is likely that anemic populations are more susceptible to Mn intoxication, even when exposed to low or normal levels of Mn. Conversely, it is likely that populations already identified as vulnerable to Mn intoxication could benefit from Fe supplementation, given the propensity of increased blood Fe levels to down-regulate transport systems common to both metals, thus resulting in reduced uptake of Mn into the brain.

D. Previous Research Models of Mn and Fe Interactions:

Several studies have examined the interplay between Fe and Mn, and various transporters. The Belgrade rat, which lacks a functional DMT-1 transporter due to a glycine to arginine (G185R) mutation, has been shown to have not only decreased Fe levels, but also abnormal Mn levels and Mn metabolism (Chua and Morgan, 1997). Other studies have demonstrated that, in the presence of low Fe, both DMT-1 and TfR are up-regulated to maximize the body's ability to sequester metal; however, this also results in an increase in Mn transport. The converse is also true: in the presence of high levels of Fe, DMT-1 and TfR levels are decreased, resulting in decreased Mn transport (Table 1) (Rouault, 2001; Conrad and Umbreit, 2002; Kaplan, 2002; Oshiro et al., 2002). These data also suggest that a Fe-deficient person may be at a greater risk of Mn intoxication, and that groups already exposed to high levels of Mn might benefit from Fe supplementation. Researchers have further attempted to characterize the relationship between Fe and Mn transport *in vitro* using cells from the liver and CNS. In these experiments, Mn transport was determined in cells pre-loaded with Fe. The converse was also examined, with cells being pre-loaded with Mn, followed by the examination of Fe transport (Malecki et al., 1999; Roth and Garrick, 2003; Oshiro et al., 2002). In both cases, when either metal was pre-loaded, transport of the other metal was significantly decreased. Other experiments further demonstrated that cell cultures maintained in the presence of low Fe, and that rodents receiving an Fe-deficient diet display increased Mn transport or higher brain Mn levels, respectively (Chua and Morgan, 1987; Erikson et al., 2002; Roth and Garrick, 2003). For example, rat studies from our laboratory (Erikson et al., 2002) corroborate a significant effect of Fe deficiency on decreasing Fe concentrations in the cerebellum and caudate putamen; and increasing Mn concentrations in caudate putamen, globus pallidus and substantia nigra. Transporter protein in brain regions also increase upon Fe deficiency, establishing the globus pallidus as a primary target for Mn accumulation that is associated with dietary iron deficiency. These results have also been replicated recently in Fe deficient Mn treated rats by means of magnetic resonance imaging (MRI; Fitsanakis et al., manuscript in preparation, 2008). Taken together, these findings give further credence to the hypothesis that Fe deficient populations may be at greater risk for Mn brain accumulation and subsequent toxicity, and that Fe supplementation may serve to ameliorate Mn deposition in high-risk groups.

E. Other Mn Transporters:

A small fraction of Mn is found in plasma as Mn-citrate (Crossgrove et al., 2003; Yokel and Crossgrove, 2004). In additional studies, these authors have assessed the regulation of Mn movement across the blood-brain barrier (BBB) with the *in situ* brain perfusion technique. The influx rates of Mn were compared to their predicted diffusion rates, which were determined from their octanol/aqueous partitioning coefficients and molecular weights. Results from these studies have suggested that a Mn citrate tridentate complex with a non-coordinated central carboxylate recognition moiety is likely a substrate for the organic anion transporter or a monocarboxylate transporter (MCT). Candidates for transport of Mn citrate may include MCT and/or members of the organic anion transporter polypeptide (OATP) or ATP-binding cassette (ABC) superfamilies. However, as pointed out by these authors, the most likely candidate for mediating transport of the Mn across the BBB is DMT-1.

Recent evidence also implies a role for the ZIP transporter proteins in Mn transport, though whether functional at the BBB has yet to be determined. The ZIP transporter proteins, members of the solute-carrier-39 (SLC39) metal-transporter family, having 14 members—highly conserved orthologs—between mouse and human (Eide, 2004). In plants, several ZIP proteins have been implicated in divalent metal transport, including zinc (Zn), Fe, and Mn. A recent in vitro study (He et al., 2006) in mouse fetal fibroblast cultures established that ZIP8 is a high affinity for Mn. The K_m of 2.2 μM for Mn^{2+} is close to physiological concentrations and within the same range determined in many cell lines or tissues. However, like many of the previously mentioned studies one has to be cautious in extrapolating into the intact animal, because the ability of this protein to transport a particular cation does not necessarily imply that this protein is physiologically relevant. Thus, whether Slc39 and organic transporters function in Mn transport remains to be tested under physiologically relevant conditions. It seems that to date the strongest evidence based studies on Mn imply a physiological role for the transport of Mn both by Tf receptors and DMT-1. Definitive studies to assess other protein functions (Slc39, MCT) in physiological roles have yet to be carried out.

Acknowledgements:

This review was partially supported by grants from NIEHS 10563, DoD W81XWH-05-1-0239, and the Gray E.B. Stahlman Chair of Neuroscience.

Abbreviations

ABC	ATP-binding cassette
BBB	blood-brain barrier
CNS	central nervous system
DMT-1	divalent metal transporter
Fe	iron
Mn	manganese – Mn
MCT	monocarboxylate transporter
OATP	organic anion transporter polypeptide
SLC39	solute-carrier-39
Tf	transferrin
Tf R	transferrin receptor
TPN	total parenteral nutrition

References

Beard JL, Dawson HD. Iron in Handbook of nutritionally essential minerals, O'Dell BL and Sunde RA, Editors. New York: Marcel Dekker, Inc; 1997: 275–34.

- Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic parkinsonism: similarities and differences. *Neurology*. 1994; 44: 1583–86. [PubMed: 7936278]
- Chua ACG, Morgan EH. Effects of iron deficiency and iron overload on manganese uptake and deposition in the brain and other organs of the rat. *Biol Trace Elem Res*. 1996; 55: 39–54. [PubMed: 8971353]
- Chua ACG, Morgan EH. Manganese metabolism is impaired in the Belgrade laboratory rat. *J Comp Physiol*. 1997; 167: 361–9. [PubMed: 9265748]
- Connor JR. Iron transport proteins in the diseased brain. *J Neurol Sci*. 2003; 207: 112–113. [PubMed: 12614944]
- Conrad ME, Umbreit JN. Pathways of iron absorption. *Blood Cells Molec Dis*. 2002; 29: 336–55. [PubMed: 12547224]
- Crossgrove J, Allen D, Bukaveckas B, Rhineheimer S, Yokel R. Manganese distribution across the blood-brain barrier. I. Evidence for carrier-mediated influx of manganese citrate as well as manganese and manganese transferrin. *Neurotoxicology*. 2003; 24: 3–13. [PubMed: 12564377]
- Crossgrove J, Yokel R. Manganese distribution across the blood-brain barrier III. The divalent metal transporter-1 is not the major mechanism mediating brain manganese uptake. *Neurotoxicology*. 2004; 25: 451–60. [PubMed: 15019308]
- Dietz MC, Ihrig A, Wrazidlo W, Bader M, Jansen O, Triebig G. Results of Magnetic Resonance Imaging in Long-Term Manganese Dioxide-Exposed Workers. *Environ Res*. 2001; 85: 37–40. [PubMed: 11161650]
- Eide DJ. The SLC39 family of metal ion transporters. *Pflueg Arch Eur J Physiol*. 2004; 447: 796–800.
- Erikson K, Shihabi ZK, Aschner JL, Aschner M. Manganese accumulates in iron-deficient rat brain regions in a heterogeneous fashion and is associated with neurochemical alterations. *Biol Trace Elem Res*. 2002; 87: 143–56. [PubMed: 12117224]
- Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicology*. 1999a; 20: 239–47. [PubMed: 10385887]
- Gorell JM, Rybicki BA, Cole Johnson C, Peterson EL. Occupational metal exposures and the risk of Parkinson's disease. *Neuroepidemiology*. 1999b; 18: 303–8. [PubMed: 10545782]
- He L, Girijashanker K, Dalton TP, Reed J, Li H, Soleimani M, Nebert DW. ZIP8, Member of the solute-carrier-39 (SLC39) metal-transporter family: characterization of transporter properties. *Mol Pharmacol*. 2006; 70: 171–80. [PubMed: 16638970]
- International Manganese Institute, International Manganese Institute Membership. Accessed 15 December 2007, <http://www.manganese.org/imni2/PHPAddress/membership1.php3>.
- Kaplan J. Mechanisms of cellular iron acquisition: Another iron in the fire. *Cell*. 2002; 111: 603–6. [PubMed: 12464171]
- Keen CL, Zidenberg-Cherr S. Manganese, in *Present Knowledge in Nutrition*, Ziegler EE and Filer LJ, Editors. Washington D.C: ILSI Press, 1996: 334–43.
- Lai JCK, Minski MJ, Chan AWK, Leung TKC, Lim L. Manganese mineral interactions in brain. *Neurotoxicology*. 1999; 20: 433–44. [PubMed: 10385902]
- Malecki EA, Devenyi AG, Beard JL, Connor JR. Existing and emerging mechanisms for transport of iron and manganese to the brain. *J Neurosci Res*. 1999; 56: 113–22. [PubMed: 10777372]
- Mergler D, Baldwin M, Belanger S, Larribe F, Beuter A, Bowler R, Panisset M, Edwards R, DeGeoffroy A, Sassine MP, Hundnell K. Manganese neurotoxicity, a continuum of dysfunction: Results from a community based study. *Neurotoxicology*. 1999; 20: 327–42. [PubMed: 10385894]
- Myers JE, teWaterNaude j, Fourie M, Zogoe HBA, Naik I, Theodorou P, Tassel H, Daya A, Thompson ML. Nervous system effects of occupational manganese exposure on South African manganese mineworkers. *Neurotoxicology*. 2003; 24: 649–56. [PubMed: 12900078]
- National Institute of Occupational Safety and Health (NIOSH), Nomination of welding fumes for toxicity studies. 2002, National Institute of Occupational Safety and Health: Washington, DC.
- Newland MC. Animal models of manganese's neurotoxicity. *Neurotoxicology*. 1999; 29: 415–32.
- Nielsen FH. Ultratrace minerals, in *Nutrition in Health and Disease*, Shils M, Olson JA, Shike M, and Ross AC, Editors. Baltimore; Williams & Wilkins: 1999; 283–303.

- Normandin L, Panisset M, Zayed J., Manganese neurotoxicity: behavioral, pathological, and biochemical effects following various routes of exposure. *Rev Environ Health*. 2002; 17: 189–217. [PubMed: 12462483]
- Oshiro S, Nozawa K, Hori M, Zhang C, Hashimoto Y, Kitajima S, Kawamura K-I. Modulation of iron regulatory protein-1 by various metals. *Biochem Biophys Res Comm*. 2002; 290: 213–8. [PubMed: 11779155]
- Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. *Neurotoxicology*. 1999; 20: 227–38. [PubMed: 10385886]
- Park NH, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, Kim HK, Kim SR, Jeong TH, Park J. Whole blood manganese correlates with high signal intensities on T₁-weighted MRI in patients with liver cirrhosis. *Neurotoxicology*. 2003; 24: 909–15. [PubMed: 14637385]
- Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmuter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. *Neurology*. 2001; 56: 8–13. [PubMed: 11148228]
- Racette BA, Tabbal SD, Jennings D, Good L, Perlmuter JS, Evanoff B. Prevalence of Parkinsonism and relationship to exposure in a large sample of Alabama welders. *Neurology*. 2005a; 64: 230–5. [PubMed: 15668418]
- Racette BA, Antenor JA, McGee-Minnich L, Moerlein SM, Videen TO, Kotagal V, Perlmuter JS. [¹⁸F]FDOPA PET and clinical features in Parkinsonism due to manganism. *Mov Disord*. 2005b; 20: 492–6. [PubMed: 15648057]
- Reimund JM, Dietemann JL, Warter JM, Baumann R, Duclos B. Factors associated to hypermanganesemia in patients receiving home parenteral nutrition. *Clin Nutr*. 2000; 19: 343–48. [PubMed: 11031073]
- Roth JA, Garrick MD. Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese. *Biochem Pharm*. 2003; 66: 1–13. [PubMed: 12818360]
- Rouault TA. Systemic iron metabolism: a review and implications for brain iron metabolism. *Ped Neurol*. 2001; 25: 130–7.
- Sugihara S, Suto Y, Kamba M, Ogawa T. Comparison of various techniques of iron oxide-enhanced breath-hold MR imaging of hepatocellular carcinoma. *Clin Imag*. 2001; 25: 104–9.
- World Health Organization, Trace elements in human nutrition and health. Geneva: World Health Organization, 1996.
- World Health Organization, Micronutrient deficiencies: Battling iron deficiency anaemia. World Health Organization, 2003.
- Yip R and Dallman PR, Iron, in *Present Knowledge in Nutrition*, Ziegler EE and Filer LJ, Editors. Washington D.C.; ILSI Press: 1996; 277–92.

Figure 1:

Under normal conditions, Fe and Mn compete for TfR and DMT-1. When Fe levels are low, both TfR and DMT-1 are upregulated, resulting in greater transport of Mn, even with normal Mn concentrations. (Figure modified from [6].)

Table 1:

Relative effect of Fe concentration on transporter and Mn levels. During conditions of normal [Fe], both DMT-1 and TfR are at normal levels, with normal [Mn]. However, changes in [Fe] not only modulate the relative amounts of each transporter, but it also has an effect on how much Mn is transported to tissues.

Fe Concentration	DMT-1 & TfR Levels	Mn Transport
Normal	Normal	Normal
High	Low	Decreased
Low	High	Increased