The Elevated Brain Manganese Concentration Induced Neurotoxicity: Review

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Summary
Manganese (Mn) is an essential trace element and it is required for many ubiquitous enzymatic reactions. While Mn deficiency rarely occurs in humans, Mn toxicity is known to occur in certain occupational settings through inhalation of Mn-containing dust. The brain is particularly susceptible to this excess Mn and accumulation there can cause a neurodegenerative disorder known as manganism. Characteristics of this disease are described as Parkinson-like symptoms. The similarities between the two disorders can be partially explained by the fact that the basal ganglia accumulate most of the excess Mn compared with other brain regions in manganism, and dysfunction in the basal ganglia is also the etiology of Parkinson's disease. The mechanisms by which increased Mn levels can cause neuronal dysfunction are yet to be elucidated. However, emerging studies are beginning to provide significant evidence of Mn effects on cortical structures and cognitive function at lower levels than previously recognized.

Abbreviation: *Mn- Manganese.*
Key words: *manganese, neurotoxicity, manganism, oxidative stress, reactive oxygen species.*

INTRODUCTION

Manganese (Mn) is an essential trace metal that is required for a number of enzymes important for normal cellular functions. While this metal is inhaled from the atmosphere, diet is normally a far greater source of human exposure to Mn. Because there are homeostatic systems of regulation for absorption and excretion of Mn in the body, the levels found in tissues are usually very stable, regardless of intake levels. However, Mn can accumulate in certain brain regions following elevated exposures, and Mn -induced neurotoxicity can ensue. The symptomatic cases of this neurotoxicity are known as manganism and clinically this presents with a Parkinson-like motor dysfunction.

ESSENTIALITY

Mn is found in all body tissues as it is essential for many ubiquitous enzymatic reactions, including synthesis of amino acids, lipids, proteins, and carbohydrates.[1] Also particularly noteworthy for neurotoxicity studies is the requirement for Mn in the reactions catalyzed by arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase and Mn-dependent superoxide dismutase.[2]An adequate intake (AI) level for Mn was set by the U.S. National Academies' Institute of Medicine and this level is 2.3 mg per day for men and 1.8 mg per day for women. The tolerable upper intake level (UL) is set at 11 mg for adults. Mn requirement were made in consideration of pregnancy (2.0 mg/day), lactation (2.6 mg/day), and the developmental stages of childhood (0.003-2.2 mg/day, depending on age and sex).[3]Studies have demonstrated that the female gastrointestinal tract is more efficient at absorbing Mn than in men.[4] Mn deficiency can cause a wide range of problems, including impaired growth, skeletal defects, reduced fertility, birth defects, abnormal glucose tolerance and altered lipid and carbohydrate metabolism. [5, 6]

SOURCES OF MANGANESE

Most adults have a daily intake of Mn below 5 mg Mn/kg, with a reported range of 0.9 to 10 mg Mn per day.[1,7]Grains, tea, and green leafy vegetables contain the highest amounts of Mn in the normal adult male diet as reported in the Total Diet Study.[8]The Mn content of human milk has been found to vary with stages of lactation.[9-11]There are also reports human studies of much higher Mn absorption in the neonatal period.[12-15] This evidence is consistent with the higher Mn levels believed to be required for brain development at early stages. Infant formulas tend to have more Mn than human milk, and this has been a cause for some concern. [16, 17]

Sometimes the Mn is found as an unintended contaminant.[18,19] There have been reported intoxications from parenteral nutrition (TPN) solutions containing 0.1 mg Mn/ day. The symptoms and Mn measurements were consistent with other forms of Mn toxicity; withdrawal from the TPN alleviates symptoms. [20, 21]

Airborne Mn can exist as fumes, aerosols, or suspended particulate matter. This Mn "dust" can be inhaled and deposited in parts of the upper or lower respiratory tract, where the Mn can then be absorbed into the bloodstream. The levels of Mn in the air vary, depending on the industries nearby, wind erosion, and other factors.[22]

ABSORPTION AND TRANSPORT

Only about 1-5% of the Mn ingested by humans is absorbed into the body by the gastrointestinal tract under normal conditions.[4,23,24] This value is reportedly higher when measurements are taken less than 24 h postingestion, but similar studies in animals indicate that much of the Mn that is retained for shorter time periods is localized to the liver and intestinal tract and eliminated through biliary excretion.[25,26] As such, it would not reach the brain or other systemic tissues in significant amounts.

The molecular details of oral Mn absorption are not well understood. Furthermore, there are many factors that have been found to affect Mn absorption, including dietary Mn levels,[27-32] dietary levels of various minerals,[33] age and developmental state of the individual,[13-15,34] and especially iron status. Several studies have demonstrated that iron deficiency increases transport of orally administered Mn into the body as well as delivery to the brain. [35-39]

Absorption of Mn via the lungs has only recently been investigated and it seems to depend largely on particle solubility. Whereas MnCl2, which is a soluble salt, is quickly taken into the bloodstream, insoluble MnO2 given at similar doses was very slowly absorbed and at much lower overall levels.[40] This report also showed that the soluble salt was more readily delivered to the brain.[41] Also showed that inhaled MnSO4 was cleared from the lung faster than the less soluble phosphate or tetroxide Mn compounds, and transport into the brain and other tissues reflected this pattern based on particle solubility as well.

Blood Mn is largely bound to β-globulin and albumin (~80%), and a small percentage of trivalent (3+) Mn is found complexed to transferrin.[42-43] Nevertheless, because of the large number of unoccupied binding sites, transferrin has been implicated as a potential transport system for Mn to traverse the blood-brain barrier and other membranes.[44] Typical serum concentrations of Mn are in the range of 0.8-2.1 μg Mn/L. Neonates generally have the highest levels, a decreasing trend is observed through the first year, and adults have the lowest serum Mn content [45,46.] Increased concentration of Mn is found in tissues rich in mitochondria and pigmentation.

Bone, liver, pancreas, and kidney tend to have higher Mn levels than other tissues. [47, 48] Liver especially accumulates Mn after high exposures, and most absorbed Mn is excreted in bile. Liver disease, therefore, is a risk factor for increased accumulation of Mn in the brain. [49, 50]

Transport of Mn into the central nervous system (CNS) has been directly investigated in a limited number of studies. These reports implicate three sites of Mn entry into the brain. The cerebral capillaries, the cerebrospinal fluid (CSF) and the olfactory nerve.[51-53] Intravenous injections of large amounts of Mn leads to a saturable transferrin-independent transport across the blood-brain barrier via either active or passive processes.[49,54] The choroid plexus, the site of CSF production, is where]Mn first appears in rodent brain.[55,56] However, at relevant Mn exposure levels, the capillary endothelium seems to represent the route that is physiologically most germane to Mn entry into the CNS. Furthermore, the likeliest modes of transport are by transferrin/transferrin receptor and divalent metal transporter (DMT-1).

Mn, Iron, and other metals are able to be complexed and carried by some of the same transporters. Transferrin/ transferrin receptor and DMT- 1, especially, are thought to transport both of these metals, with iron being far more prevalent under normal circumstances. Evidence from Suarez and Eriksson and Aschner and Gannon [57] strongly suggests transport of trivalent Mn complexed to transferrin into the brain capillary endothelium. As such, the high concentration of transferrin receptors in the nucleus accumbens and caudate putamen, which provide efferent fibers to areas rich in Mn (ventral pallidum, globus pallidus, and substantia nigra), is consistent with transferrin-mediated Mn transport. The role of DMT- 1 in brain Mn transport is currently an area of intense investigation. It has been suggested that much of the Mn that gains access to the CNS does so via DMT- 1 in brain endothelium. Absorption of Mn in the gut is thought to be mediated by DMT-1. Studies of the Belgrade rat, which carries a mutation in the DMT- 1 gene, show that (in addition to frank deficiency in uptake of iron) the homozygote demonstrates lower uptake of radiolabeled Mn than the heterozygote.[58] Additional experiments to elucidate the role of DMT- 1 in Mn transport into rat brain endothelial cells are under way.

It has been well documented that xenobiotics can travel directly to the brain via the olfactory system. Axonal transport of Mn has also been conclusively demonstrated.[59-63] Delivery of inhaled Mn is likely through direct intra-axonal transport and it has been reported in rat, mouse and freshwater pike after intranasal instillation.[60,64,65] Additionally, Dorman et al.[66] have studied inhalation of various Mn containing particulates and also found delivery along the olfactory route. The striatum and other nonolfactory brain structures do not seem to accumulate much Mn through this route.[66, 67] Further, there are substantial physiological differences known between human and rodent nasal and brain anatomy that complicate interpretation of comparative studies.[68]

Mn toxicity studies have revealed that distribution of the metal to the various brain regions is not homogeneous and may even differ across species. Magnetic resonance imaging (MRI) techniques show that, in exposed humans Mn concentrations is highest in striatum, globus pallidus and substantia nigra.[69-71] Brenneman and coworkers [72] have reported that rat striatum and globus pallidus do not preferentially accumulate Mn after excess exposure. However, a very recent study showed that, after dietary iron deprivation, Mn accumulated in globus pallidus, hippocampus, and substantia nigra of rat brain. This suggests that iron

deficiency in humans might also lead to a higher tendency toward Mn accumulation in brain regions normally rich in iron.

TOXICITY

Inhalation of particulate Mn is the most recognized occupational risk for human toxicity. This Mn dust in various forms irritates lungs of humans causing an inflammatory response[73] as do many other particulates. A recent report shows that oxidative stress in lungs and heart is observed after 5-h inhalation exposure to concentrated ambient particles containing a mixture of metals including Mn.[74] this suggests that the lung inflammation may be a general response to inhaled metal particulates. Nevertheless, there are significant neurological effects specific to Mn particulate inhalation. Impotence and loss of libido have been reported in Mn-exposed workers, but the later-stage neurological effects are the most compelling cause for concern about Mn exposure.

Chronic exposure to high levels of inhalable Mn (>1-5 mg Mn/m3) is the most frequently observed cause of Mn-induced neurotoxicity.[75, 76] Ingestion of very large amounts of Mn in water from contaminated wells has also been reported to cause neurotoxicity. [77, 78]

The disorder known as manganism is strongly associated with elevated levels of Mn in the brain. Specifically, structures of the basal ganglia—caudate putamen, globus pallidus, substantia nigra and subthalamic nuclei, all of which contain substantial levels of nonheme iron—represent regions of highest Mn concentration.[79] The earliest symptoms associated with abnormal Mn accumulation are psychiatric. Compulsive or violent behavior, emotional instability, and hallucinations are characteristic and patients may also suffer from fatigue, headache, muscle cramps, loss of appetite, apathy, insomnia and diminished libido. The most severe forms of manganism present with prolonged muscle contractions- dystonia, decreased muscle movement - hypokinesia, rigidity and muscle tremors. The physical traits of this disorder thus resemble Parkinson's disease, but there are distinguishing features.[80]While generalized bradykinesia and rigidity are found in both syndromes, the dystonia of manganism is a neurological sign attributed to damage to the globus pallidus and is only minimally observed in Parkinson's patients. Other features of manganism that differ from parkinsonism were noted in a comprehensive survey of patients with these disorders, and they include less frequent resting tremor, a propensity to fall backward, little or no sustained response to levodopa therapy and normal fluorodopa uptake.

Glutamate from cortical neurons along with γ-aminobutyric acid (GABA) and dopamine from other basal ganglia structures all influence striatal control of motor activity.[81]In Parkinson's disease, the nigrostriatal pathway is affected due to demise of dopaminergic neurons in the substantia nigra. The etiological damage in manganism is likely to occur to the output pathways downstream of the nigrostriatal dopaminergic pathway. [82]

MANGANESE-INDUCED OXIDATIVE STRESS

Oxidative stress and its effects on mitochondrial energy metabolism have lately been implicated in a wide range of pathological processes, and especially in neurodegenerative conditions such as Parkinson's or Alzheimer's disease.[83] Furthermore, the intense investigation surrounding the free radical theory of aging is leading many scientists to believe that aging mitochondria are the primary culprits.[84] They are more susceptible to oxidative damage and less efficient at repairing this damage than young mitochondria. Witholt et al.[85] recently investigated increased risk to Mn-induced damage using a preparkinsonian rat model treated with low cumulative doses of Mn. They report exacerbation of both neurochemical and motor function changes in the senescent group. A previous report showed that exposure of neurons to MMT resulted in rapid increases in reactive oxygen species followed by mitochondrially induced apoptosis. [86, 87]

Oxygen radicals can damage components of the electron transport and oxidative phosphorylation machinery and this leads to generation of more reactive oxygen species. The new radicals exacerbate the damage and a "down-ward spiral" ensues. [88] In this scenario cells are ultimately subjected to energy failure as ATP production declines. The membrane potential is lost as the mitochondria undergo permeability transition, which then leads to cell death. [89] This mitochondrial dysfunction coincides with decreased cerebral metabolic rates in Alzheimer's disease, Parkinson's disease, Huntington's disease, and other neurodegenerative disorders. Albin et al.[90] reviewed a variety of basal ganglia toxicants and concluded that the probable mechanism of action for almost all known basal ganglia neurotoxins is inhibition of mitochondrial function. Studies of this interrelationship are clouded by the fact that mitochondrial function declines as a normal part of the aging process, and age itself is a risk factor for these neurodegenerative diseases.

On the subcellular level Mn is most concentrated in mitochondria.[91] However, the overall percentage of Mn found in the mitochondria of specific brain regions did not increase after Mn exposure in neonatal rats, which indicates that there is not additional selective uptake into this organelle at higher Mn levels. Nevertheless, decreased complex I activity, increased oxidative damage and altered activities of antioxidant defense enzymes have been demonstrated in Parkinson's disease. This supports a growing body of literature on oxidative stress in neurodegeneration.

Gavin et al.[92] showed evidence suggesting that the ATPase complex is inhibited at very low levels of mitochondrial Mn and that complex I is inhibited only at higher Mn concentrations. In another study, treatment of striatal neurons with Mn showed dose-dependent losses of mitochondrial membrane potential and complex II activity.[93] collectively, these results indicate that Mn may trigger apoptoticlike

neuronal death secondary to mitochondrial dysfunction. However, it is possible that necrosis may be involved to some extent as Roth et al. [94] found that caspases were not involved in Mn-induced neuronal death.

Zwingmann and colleagues recently reported that neurons treated for 5 days with MnCl2 are extremely susceptible to oxidative stress and energy failure through the resulting mitochondrial dysfunction,[95] whereas astrocytes fare slightly better after the same treatment. When the cells were co-cultured, comparative NMR data showed "disturbed astrocytic function and a failure of astrocytes to provide neurons with substrates for energy and neurotransmitter metabolism, leading to deterioration of neuronal antioxidant capacity (decreased glutathione levels) and energy metabolism". These results are consistent with previous reports from our lab and others demonstrating the important role of astrocytes in effectively buffering the extracellular environment to protect the more sensitive neurons. It has also been reported in many cases that astrocytes have higher levels of glutathione and some other antioxidant defenses than neurons. [96, 97]

A final factor in Mn toxicity is the oxidation state of the metal. It has been shown that trivalent Mn is more effective at inhibiting complex I, [98-100] but the divalent form is by far the predominant species within cells and is largely bound to ATP. Nevertheless, Mn in any state will spontaneously give rise to infinitesimal amounts of trivalent Mn and HaMai et al.[101] demonstrated that trivalent Mn, even at trace amounts, can cause formation of reactive oxygen species. Interestingly, the mitochondria also paradoxically rely heavily on Mn for antioxidant protection as it is the critical cofactor for the important superoxide dismutase enzyme specific to this organelle. In fact, mice lacking the mitochondrial isoform of SOD have a mean life span of 8 days, whereas mice deficient in cytosolic or extracellular SODs have a very benign phenotype.

Conclusion:

Atmospheric levels of Mn have significantly increased in urban cities since its introduction as a fuel additive. This is particularly relevant based on recent studies indicating that people with compromised liver function may be at considerably greater risk than the normal population to the toxic actions of Mn. Mn is a potent neurotoxin which is capable of producing a variety of neurological symptoms characterized by severe extrapyramidal dysfunction resembling the dystonic movements associated with Parkinson's disease. With the realization of increased environmental exposure to Mn, it becomes necessary to delineate the fundamental biochemical and molecular mechanisms responsible for its selective neurotoxic actions in order to prevent and identify individuals with Mn toxicity.

REFERENCE

1. FINLEY, J.W. & C.D. DAVIS. 1999. Manganese deficiency and toxicity: are high or low dietary amounts of manganese cause for concern? Biofactors 10: 15-24.
2. TAKEDA, A. 2003. Manganese action in brain function. Brain Res. Brain Res. Rev. 41: 79-87.
3. NAS. 2002. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Available at www.nap.edu/books/0309072794/html/.
4. FINLEY, J.W., P.E. JOHNSON & L.K. JOHNSON. 1994. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. Am. J. Clin. Nutr. 60: 949-955.
5. FREELAND-GRAVES, J. & C. LLANES. 1994. Models to study manganese deficiency. In Manganese in Health and Disease, pp. 115-120. CRC Press. Boca Raton, FL.
6. KEEN, C.L. et al. 1999. Nutritional aspects of manganese from experimental studies. Neurotoxicology 20: 213-223.
7. AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY. 2000. Toxicological profile for manganese. U.S. Department of Health and Human Services Public Health Service. Available at www.atsdr.cdc.gov/toxprofiles/tp151.html/.
8. PENNINGTON, J.A. & S.A. SHOEN. 1996. Total Diet Study: estimated dietary intakes of nutritional elements, 1982-1991. Int. J. Vitam. Nutr. Res. 66: 350-362.
9. CASEY, C.E., K.M. HAMBIDGE & M.C. NEVILLE. 1985. Studies in human lactation: zinc, copper, manganese, and chromium in human milk in the first month of lactation. Am. J. Clin. Nutr. 41: 1193-1200.
10. STASTNY, D., R.S. VOGEL & M.F. PICCIANO. 1984. Manganese intake and serum manganese concentration of human milk-fed and formula-fed infants. Am. J. Clin. Nutr. 39:872-878.
11. VAUGHAN, L.A., C.W. WEBER & S.R. KEMBERLING. 1979. Longitudinal changes in the mineral content of human milk. Am. J. Clin. Nutr. 32: 2301-2306.
12. GRUDEN, N. 1977. Suppression of transduodenal manganese transport by milk diet supplemented with iron. Nutr. Metab. 21: 305-309.
13. KEEN, C.L., J.G. BELL & B. LONNERDAL. 1986. The effect of age on manganese uptake and retention from milk and infant formulas in rats. J. Nutr. 116: 395-402.
14. ZLOTKIN, S.H., S. ATKINSON & G. LOCKITCH. 1995. Trace elements in nutrition for premature infants. Clin. Perinatol. 22: 223-240.
15. DORNER, K. et al. 1989. Longitudinal manganese and copper balances in young infants and preterm infants fed on breast-milk and adapted cow's milk formulas. Br. J. Nutr. 61:559-572.
16. KRACHLER, M. & E. ROSSIPAL. 2000. Concentrations of trace elements in extensively hydrolysed infant formulae and their estimated daily intakes. Ann. Nutr. Metab. 44: 68-74.
17. LONNERDAL, B. 1994. Nutritional aspects of soy formula. Acta Paediatr. Suppl. 402: 105-108.
18. HAMBIDGE, K.M. et al. 1989. Plasma manganese concentrations in infants and children receiving parenteral nutrition. J. Parenter. Enteral Nutr. 13: 168-171.
19. KURKUS, J., N.W. ALCOCK & M.E. SHILS. 1984. Manganese content of large-volume parenteral solutions and of nutrient additives. J. Parenter. Enteral Nutr. 8: 254-257.

BERTINET, D.B. et al. 2000. Brain manganese deposition and blood levels in patients undergoing home parenteral nutrition. J. Parenter. Enter. Nutr. 24: 223-227.

21. KAFRISTA, Y. et al. 1998. Long-term outcome of brain manganese deposition in patients on home parenteral nutrition. Arch. Dis. Child. 79: 263-265.
22. LIOY, P.J. 1983. Air pollution emission profiles of toxic and trace elements from energy related sources: status and needs. Neurotoxicology 4: 103-112.

23. DAVIS, C.D., L. ZECH & J.L. GREGER. 1993. Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. Proc. Soc. Exp. Biol. Med. 202: 103-108.
24. DAVIDSSON, L. et al. 1988. Intrinsic and extrinsic labeling for studies of manganese absorption in humans. J. Nutr. 118: 1517-1521.
25. BALLATORI, N., E. MILES & T.W. CLARKSON. 1987. Homeostatic control of manganese excretion in the neonatal rat. Am. J. Physiol. 252: R842-R847.
26. GARCIA-ARANDA, J.A., R.A. WAPNIR & F. LIFSHITZ. 1983. In vivo intestinal absorption of manganese in the rat. J. Nutr. 113: 2601-2607.
27. BELL, J.G., C.L. KEEN & B. LONNERDAL. 1989. Higher retention of manganese in suckling than in adult rats is not due to maturational differences in manganese uptake by rat small intestine. J. Toxicol. Environ. Health 26: 387-398.
28. BRITTON, A.A. & G.C. COTZIAS. 1966. Dependence of manganese turnover on intake. Am. J. Physiol. 211: 203-206.
29. DORMAN, D.C. et al. 2001. Influence of dietary manganese on the pharmacokinetics of inhaled manganese sulfate in male CD rats. Toxicol. Sci. 60: 242-251.
30. MALECKI, E.A. et al. 1996. Biliary manganese excretion in conscious rats is affected by acute and chronic manganese intake, but not by dietary fat. J. Nutr. 126: 489-498.
31. DAVIDSSON, L. et al. 199 1. The effect of individual dietary components on manganese absorption in humans. Am. J. Clin. Nutr. 54: 1065-1070.
32. LAI, J.C. et al. 1999. Manganese mineral interactions in brain. Neurotoxicology 20: 433-444.
33. PLANELLS, E. et al. 2000. Effect of magnesium deficiency on enterocyte Ca, Fe, Cu, Zn, Mn, and Se content. J. Physiol. Biochem. 56: 217-222.
34. GRUDEN, N. 1977. Suppression of transduodenal manganese transport by milk diet supplemented with iron. Nutr. Metab. 21: 305 -309.
35. DAVIS, C.D., E.A. MALECKI & J.L. GREGER. 1992. Interactions among dietary manganese, heme iron, and nonheme iron in women. Am. J. Clin. Nutr. 56: 926-932.
36. GUNSHIN, H. et al. 1997. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. Nature 388: 482-488.
37. CHANDRA, S.V. & G.S. SHUKLA. 1976. Role of iron deficiency in inducing susceptibility to manganese toxicity. Arch. Toxicol. 35: 319-323.
38. SHUKLA, A., K.N. AGARWAL & G.S. SHUKLA. 1989. Effect of latent iron deficiency on metal levels of rat brain regions. Biol. Trace Elem. Res. 22: 141-152.
39. ERIKSON, K.M. et al. 2002. Manganese accumulates in iron-deficient rat brain regions in a heterogeneous fashion and is associated with neurochemical alterations. Biol. Trace Elem. Res. 87:143-156.
40. ROELS, H. et al. 1997. Influence of the route of administration and the chemical form (MnCl2, MnO2) on the absorption and cerebral distribution of manganese in rats. Arch. Toxicol. 71: 223-230.
41. DORMAN, D.C. et al. 2001. Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. Toxicol. Appl. Pharmacol. 170: 79-87.
42. CRITCHFIELD, J.W. & C.L. KEEN. 1992. Manganese +2 exhibits dynamic binding to multiple ligands in human plasma. Metabolism 41: 1087-1092.
43. UEDA, F. et al. 1993. Rate of 9Fe uptake into brain and cerebrospinal fluid and the influence thereon of antibodies against the transferrin receptor. J. Neurochem. 60: 106-113.
44. ASCHNER, M. & J.L. ASCHNER. 1990. Manganese transport across the blood-brain barrier: relationship to iron homeostasis. Brain Res. Bull. 24: 857-860.
45. ASCHNER, M., K.M. ERIKSON & D.C. DORMAN. 2003. Manganese dosimetry: species differences and implications for neurotoxicity. Crit. Rev. Toxicol. In press.
46. MIZOGUCHI, N. et al. 2001. Manganese elevations in blood of children with congenital portosystemic shunts. Eur. J. Pediatr. 160: 247-250.
47. KEEN, C.L. & S. ZIDENBERG-CHERR. 1994. Manganese toxicity in humans and experimental animals. In Manganese in Health and Disease, pp. 193-205. CRC Press. Boca Raton, FL.
48. REHNBERG, G.L. et al. 1980. Chronic manganese oxide administration to preweanling rats: manganese accumulation and distribution. J. Toxicol. Environ. Health 6: 217-226.
49. MALECKI, E.A. et al. 1999. Iron and manganese homeostasis in chronic liver disease: relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. Neurotoxicology 20: 647-652.
50. HERYNEK, V. et al. 2001. Chronic liver disease: relaxometry in the brain after liver transplantation. MAGMA 12: 10-15.
51. MURPHY, V.A. et al. 1991. Saturable transport of manganese(II) across the rat blood-brain barrier. J. Neurochem. 57: 948-954.
52. RABIN, O. et al. 1993. Rapid brain uptake of manganese(II) across the blood-brain barrier. J. Neurochem. 61: 509-517.
53. BRENNEMAN, K.A. et al. 2000. Direct olfactory transport of inhaled manganese ((54)MnCl(2)) to the rat brain: toxicokinetic investigations in a unilateral nasal occlusion model. Toxicol. Appl. Pharmacol. 169: 238- 248.
54. WADHWANI, K.C. et al. 1992. Saturable transport of manganese (II) across blood-nerve barrier of rat peripheral nerve. Am. J. Physiol. 262: R284-R288.
55. TAKEDA, A., J. SAWASHITA & S. OKADA. 1998. Manganese concentration in rat brain: manganese transport from the peripheral tissues. Neurosci. Lett. 242: 45-48.
56. MALECKI, E.A. et al. 1999. Existing and emerging mechanisms for transport of iron and manganese to the brain. J. Neurosci. Res. 56: 113-122.
57. ASCHNER, M. & M. GANNON. 1994. Manganese (Mn) transport across the rat blood-brain barrier: saturable and transferrin-dependent transport mechanisms. Brain Res. Bull. 33: 345-349.
58. CHUA, A.C. & E.H. MORGAN. 1997. Manganese metabolism is impaired in the Belgrade laboratory rat. J. Comp. Physiol. B167: 361-369.
59. MATHISON, S., R. NAGILLA & U.B. KOMPELLA. 1998. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J. Drug Target 5: 415-441.
60. GIANUTSOS, G., G.R. MORROW & J.B. MORRIS. 1997. Accumulation of manganese in rat brain following intranasal administration. Fundam. Appl. Toxicol. 37: 102-105.
61. HENRIKSSON, J., J. TALLKVIST & H. TJALVE. 1999. Transport of manganese via the olfactory pathway in rats: dosage dependency of the uptake and subcellular distribution of the metal in the olfactory epithelium and the brain. Toxicol. Appl. Pharmacol. 156:119-128.
62. LIN, C.P. et al. 2001. Validation of diffusion tensor magnetic resonance axonal fiber imaging with registered manganese-enhanced optic tracts. Neuroimage 14: 1035-1047.
63. SALEEM, K.S. et al. 2002. Magnetic resonance imaging of neuronal connections in the macaque monkey. Neuron 34: 685-700.
64. TJALVE, H. & J. HENRIKSSON. 1999. Uptake of metals in the brain via olfactory pathways. Neurotoxicology 20: 181-195.
65. TJALVE, H., C. MEJARE & K. BORG-NECZAK. 1995. Uptake and transport of manganese in primary and secondary olfactory neurones in pike. Pharmacol. Toxicol. 77: 23-3 1.
66. DORMAN, D.C. et al. 2002. Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. J. Toxicol. Environ. Health A65: 1493-15 11.
67. TJALVE, H. et al. 1996. Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. Pharmacol. Toxicol. 79: 347-356.
68. DORMAN, D.C., J.G. OWENS & K.T. MORGAN. 1997. Olfactory Neurotoxicology. In Comprehensive Toxicology. Volume 11: Nervous System and Behavioral Toxicology, pp. 281-294. Elsevier. Cambridge, UK.

69. CALNE, D.B. et al. 1994. Manganism and idiopathic parkinsonism: similarities and differences. Neurology 44: 1583-1586.
70. ERIKSSON, H. et al. 1992. Manganese induced brain lesions in Macacafascicularis as revealed by positron emission tomography and magnetic resonance imaging. Arch. Toxicol. 66: 403-407.
71. NAGATOMO, S. et al. 1999. Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. J. Neurol. Sci. 162: 102-105.
72. BRENNEMAN, K.A. et al. 1999. Manganese-induced developmental neurotoxicity in the CD rat: is oxidative damage a mechanism of action? Neurotoxicology 20: 477-487.
73. ROELS, H. et al. 1987. Relationship between external and internal parameters of exposure to manganese in workers from a manganese oxide and salt producing plant. Am. J. Ind. Med. 11: 297-305.
74. GURGUEIRA, S.A. et al. 2002. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environ. Health Perspect. 110: 749-755.
75. MERGLER, D. et al. 1994. Nervous system dysfunction among workers with long-term exposure to manganese. Environ. Res. 64: 151-180.
76. PAL, P.K., A. SAMI & D.B. CALNE. 1999. Manganese neurotoxicity: a review of clinical features, imaging, and pathology. Neurotoxicology 20: 227-238.
77. KAWAMURA, R. et al. 1941. Intoxication by manganese in well water. Arch. Exp. Med. 18: 145-169.
78. KONDAKIS, X.G. et al. 1989. Possible health effects of high manganese concentrations in drinking water. Arch. Environ. Health 44: 175-178.
79. VIEREGGE, P. et al. 1995. Long term exposure to manganese in rural well water has no neurological effects. Can. J. Neurol. Sci. 22: 286-289.
80. BEUTER, A. et al. 1994. Diadochokinesimetry: a study of patients with Parkinson's disease and manganese exposed workers. Neurotoxicology 15: 655-664.
81. CARLSSON, M. & A. CARLSSON. 1990. Interactions between glutamatergic and monoaminergic systems within the basal ganglia-implications for schizophrenia and Parkinson's disease. Trends Neurosci. 13: 272-276.
82. VERITY, M.A. 1999. Manganese neurotoxicity: a mechanistic hypothesis. Neurotoxicology 20: 489-497.
83. ALBERS, D.S. & M.F. BEAL. 2000. Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease. J. Neura Transm. Suppl. 59: 133-154.
84. BECKMAN, K.B. & B.N. AMES. 1998. Mitochondrial aging: open questions. Ann. N.Y. Acad. Sci. 854: 118-127.
85. WITHOLT, R., R.H. GWIAZDA & D.R. SMITH. 2000. The neurobehavioral effects of subchronic manganese exposure in the presence and absence of pre-parkinsonism. Neurotoxicol. Teratol. 22: 851-861.
86. ANANTHARAM, V. et al. 2002. Caspase-3-dependent proteolytic cleavage of protein kinase Cδ is essential for oxidative stress-mediated dopaminergic cell death after exposure to methylcyclopentadienyl manganese tricarbonyl. J. Neurosci. 22: 1738-175 1.
87. KITAZAWA, M. et al. 2002. Oxidative stress and mitochondrial-mediated apoptosis in dopaminergic cells exposed to methylcyclopentadienyl manganese tricarbonyl. J. Pharmacol. Exp. Ther. 302: 26-35.
88. MELOV, S. 2000. Mitochondrial oxidative stress: physiologic consequences and potential for a role in aging. Ann. N.Y. Acad. Sci. 908: 219-225.
89. BLASS, J.P. 2001. Brain metabolism and brain disease: is metabolic deficiency the proximate cause of Alzheimer dementia? J. Neurosci. Res. 66: 851-856. 104. ALBIN, R.L. 2000. Basal ganglia neurotoxins. Neurol. Clin. 18: 665-680.
90. ASCHNER, M., U. SONNEWALD & K.H. TAN. 2002. Astrocyte modulation of neurotoxic injury. Brain Pathol. 12: 475-481.
91. MAYNARD, L.S. & G.C. COTZIAS. 1954. The partition of manganese among organs and intracellular organelles of the rat. J. Biol. Chem. 214: 489-495.
92. GAVIN, C.E., K.K. GUNTER & T.E. GUNTER. 1999. Manganese and calcium transport in mitochondria: implications for manganese toxicity. Neurotoxicology 20: 445-453.
93. MALECKI, E.A. 2001. Manganese toxicity is associated with mitochondrial dysfunction and DNA fragmentation in rat primary striatal neurons. Brain Res. Bull. 55: 225-228.
94. ROTH, J.A. et al. 2000. Manganese-induced rat pheochromocytoma (PC 12) cell death is independent of caspase activation. J. Neurosci. Res. 61: 162-171.
95. ZWINGMANN, C., D. LEIBFRITZ & A.S. HAZELL. 2003. Energy metabolism in astrocytes and neurons treated with manganese: relation among cell-specific energy failure, glucose metabolism, and intercellular trafficking using multinuclear NMR-spectroscopic analysis. J. Cereb. Blood Flow Metab. 23: 756- 771.
96. HAZELL, A.S. 2002. Astrocytes and manganese neurotoxicity. Neurochem. Int. 41: 271-277.
97. TIFFANY-CASTIGLION, E. & Y. QIAN. 2001. Astroglia as metal depots: molecular mechanisms for metal accumulation, storage, and release. Neurotoxicology 22: 577-592.
98. ARCHIBALD, F.S. & C. TYREE. 1987. Manganese poisoning and the attack of trivalent manganese upon catecholamines. Arch. Biochem. Biophys. 256: 638-650.
99. ALI, S.F., et al. 1995. Manganese-induced reactive oxygen species: comparison between Mn2 and Mn13. Neurodegeneration 4: 329-334.
100. CHEN, J.Y. et al. 2001. Differential cytotoxicity of Mn(II) and Mn (III): special reference to mitochondrial [Fe-S] containing enzymes. Toxicol. Appl. Pharmacol. 175: 160-168.
101. HAMAI, D., A. CAMPBELL & S.C. BONDY. 2001. Modulation of oxidative events by multivalent manganese complexes in brain tissue. Free Radical Biol. Med. 31: 763-768.