Interactions between excessive manganese exposures and dietary iron-deficiency in neurodegeneration

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Abstract:
For nearly a century, manganese has been recognized as an essential nutrient for proper bone formation, lipid, amino acid and carbohydrate metabolism. While manganese deficiency is characterized by symptoms ranging from stunted growth and poor bone remodeling to ataxia, it is manganese toxicity that is far more devastating from a public health standpoint. Most cases of manganese toxicity are the result of occupational exposure to high levels of the metal, and are characterized by specific neurological symptoms referred to as manganism. While manganism shares many common features with Parkinson's disease, there are distinct differences between the two disorders suggesting that manganism might indirectly affect nigrostriatal dopaminergic function. Recent studies from our laboratory show that dietary iron deficiency is a risk factor for brain manganese accumulation and that the striatum is particularly vulnerable. This review briefly discusses manganese from nutritional and toxicological aspects.
Keywords: Manganese; Brain; Neurotoxicity; Iron deficiency

Article:
1. Manganese essentiality
Manganese is an essential trace metal that is found in all tissues and is required for normal amino acid, lipid, protein, and carbohydrate metabolism. Manganese is essential for immune system functioning, regulation of blood sugars and cellular energy, bone growth, defense against free radicals, and together with vitamin K, supports blood clotting. Manganese functions as a cofactor in several enzymes the most noteworthy are arginase (urea formation), glutamine synthetase (critical for brain ammonia metabolism), phosphoenolpyruvate decarboxylase (gluconeogenesis), and manganese superoxide dismutase (antioxidant) (Hurley and Keen, 1987).

Since there were insufficient data to set an estimated average requirement for manganese, no recommended dietary allowance (RDA) exists. However, the National Academy of Sciences (NAS) has established an adequate intake (AI) for manganese in adult men at 2.3 mg/day and adult women at 1.8 mg/day (NAS, 2001). The AI for manganese in adult men is higher than in women due to decreased gastrointestinal manganese absorption reported in men versus women (Finley et al., 1994), which is likely related to iron status and the higher serum ferritin concentrations found in men (Finley et al., 1994; NAS, 2001). Developmental life-stage can also influence dietary manganese requirements. Both pregnancy and lactation increase the manganese AI, 2.0 and 2.6 mg/day, respectively (NAS, 2001). Adequate intakes for newborn (<6 months of age) infants are approximately 0.003 mg/day while intakes increase to 0.6 mg/day at 7–12 months of age (NAS, 2001). Children between 1–3 years of age have an AI of 1.2 mg/day and children ages 4–8 years have an AI of 1.5 mg/day. By 9–13 years of age, the AI for males and females differs, 2.0 and 1.6mg/day, respectively. Finally, adolescent males have an increased AI of 2.2mg/day, whereas female adolescents remain at 1.6 mg/day (NAS, 2001).

2. Manganese deficiency
Manganese deficiency can lead to multiple effects, including impaired growth, poor bone formation and skeletal defects, irreversible ataxia, abnormal glucose tolerance, and altered lipid and carbohydrate metabolism (Freeland-Graves and Llanes, 1994; Keen et al., 1999). Manganese deficiency was first linked to bone growth in chickens with perosis (malformation of bones of chicks or poults), which developed due to a lack of sufficient

dietary manganese (Hurley and Keen, 1987). When pregnant rats are manganese deficient, their off-spring develop severe and irreversible ataxia. This condition is caused by underdeveloped otoliths due to a proteoglycan deficit that is likely caused by low activity of manganese-dependent glycosyltransferases (Keen et al., 1984). Although manganese deficiency has been observed in chickens, rodents and other species, to our knowledge, frank manganese deficiency has not been clinically recognized in humans. Some clinical signs and symptoms have been observed in human subjects placed on manganese deficient diets. Young men placed on manganese-depleted diet developed an acute dermatitis on their torsos, which disappeared upon dietary repletion (Friedman et al., 1987). Penland and Johnson (1993) reported that young women consuming a diet containing only 1 mg Mn/day developed altered mood and increased pain during the premenstrual phase of their estrous cycle.

Manganese intake by many individuals remains below the recommended dietary reference intake level of 1. 8–2.3 mg/day (Finley and Davis, 1999; Pennington and Schoen, 1996). Even when dietary levels of manganese are adequate, high dietary levels of fiber, phytate, ascorbic acid, iron, phosphorus, and calcium can limit the oral bioavailability and retention of manganese (Davidsson et al., 1991; Freeland-Graves and Lin, 199 1; Gibson, 1994; Greger, 1998; Lutz et al., 1993; NAS, 2001). Suboptimal manganese status may also occur in humans with epilepsy, osteoporosis, or exocrine pancreatic insufficiency, individuals undergoing chronic hemodialysis, and in children with Perthes' disease or phenylketonuria (Carl and Gallagher, 1994; Freeland-Graves and Llanes, 1994). However, given the known toxicity of high manganese intake (next section), supplementation appears unwarranted in humans that consume balanced diets.

3. Manganese toxicity

3. 1. Airborne exposure

Manganese toxicity is a well-recognized occupational hazard in humans exposed to high concentrations of respirable manganese dust. Respiratory symptoms such as cough, bronchitis, pneumonitis, and impaired pulmonary function (Roels et al., 1987) are associated with inhaled manganese particulate (e.g., manganese dioxide [MnO_2] or manganese tetroxide [Mn_3O_4]). These effects may reflect an indirect response to inhaled particulate matter or may be associated with direct pulmonary toxicity induced by manganese (ATSDR, 2000). Although the respiratory effects are important, the most sensitive organ is the brain and the greatest public health concern is manganese-induced neurotoxicity (manganism).

Manganese neurotoxicity most commonly occurs in workers that have been chronically exposed to aerosols or dusts that contain extremely high levels (> 1–5 mg Mn/m^3) of manganese (ATSDR, 2000; Mergler et al., 1994; Pal et al., 1999). Currently, the focus on airborne manganese has increased due to the replacement of lead with methylcyclopentadienyl manganese tricarbonyl (MMT), a fuel additive used in some unleaded gasolines. Although the levels of manganese in urban areas does not exceed tolerable levels set by the governments of Canada and the United States due to MMT, it still is unknown what neurotoxic effects may emerge due to chronic low level manganese exposure. This is especially a salient point in light of the risk of iron deficiency causing increased manganese transport into the brain (see factors influencing manganese transport into the brain).

3.2. Oral ingestion

Manganese-induced neurotoxicity may also occur following oral ingestion. In a recent report, a 10-year old boy with abnormal verbal and visual memory function had elevated serum manganese concentrations (0.90 μg/dL versus nor-mal value of < 0.265 μg/dL), following chronic ingestion of well water containing modestly elevated levels (~1.2 ppm) of manganese (Woolf et al., 2002). Kawamura et al. (1941) and Kondakis et al., (1989) described outbreaks of manganese toxicity in Japan and Greece due to the consumption of water from wells contaminated with extremely high levels of manganese Kawamura et al. (1941) reported an outbreak of manganism-like syndrome in a group of Japanese families that were exposed to high levels of Mn in drinking water. The syndrome was characterized by mask-like face, muscle rigidity and tremors, and mental disturbance. Several family members were severely affected (two died), whereas other exhibited mild, moderate or no effect.

The concentration of manganese in the well water was estimated at 14 mg/L. While many of the symptoms were characteristic of manganese exposure, the study is confounded by lack of information on the concentration of other metals in the water (having leached out of batteries). Uncharacteristic to the known consequences of manganese encephalopathy, two adults who came to assist the family rapidly developed symptoms (within 2–3 weeks), and those who were affected, recovered from the symptoms even before manganese levels in the water decreased significantly. Given the uncertainty regarding potential exposure to other metals, it is questionable as to whether these illnesses can be attributed to manganese exposure in the drinking water, and consideration should be given to the possibility that the well water was contaminated by additional xenobiotics.

In another report, Kondakis et al. (1989) studied the neurological effect of chronic manganese intake (1.8–2.3 mg/L) in the drinking water. Residents (average age of 67 years) were compared with matched controls where residents drank water with average Mn levels of 0.004–0.015 mg/L or 0.082–0.25 mg/L. The results from the study suggested that the neurological score of residents correlated with manganese levels in the drinking water and that higher-than-usual oral exposure to manganese might contribute to an increased prevalence of neurological effects. However, the neurological tests in the study were weighted towards ascertaining symptoms associated with Parkinson's disease and not manganism, and as mentioned above (and see below), the two syndromes exhibit significant clinical differences. Accordingly, this study is also of rather limited value in showing a causal relationship between neurological deficits and exposure to manganese from drinking water.

Similarly, studies performed by He et al. (1994) and Zhang et al. (1995) were poorly controlled for confounding variables, such as potential exposure to other metals, duration and amount of manganese uptake from flour fertilized with sewage, as well as health and nutritional status. Thus, they also fail to establish a heightened neurological risk for chronic consumption of manganese in drinking water. Other studies in human populations exposed to high levels of Mn in drinking water have failed to substantiate adverse health effects (Vieregge et al., 1995). For example, people (40 years or older) ingesting Mn from well water at a minimum concentration of 0.3 mg Mn/L for at least 10 years were indistinguishable from controls (drinking water with a concentration of manganese at 0.05 mg/L) in motor coordination tests (Vieregge et al., 1995).

4. Manganese neurotoxicity

Manganism is associated with elevated brain levels of manganese, primarily in iron-rich regions such as the caudate–putamen, globus pallidus, substantia nigra, and subthalamic nuclei. Manganism is initially characterized by a psychiatric disorder (*locura manganica*) that closely resembles schizophrenia. Symptoms include compulsive or violent behavior, emotional instability, as well as hallucinations. As the disease progresses, patients may develop prolonged muscle contractions (dystonia), decreased muscle movement (hypokinesia), rigidity, and muscle tremors (Pal et al., 1999). These signs are associated with damage to the nigrostriatal dopaminergic tract, which is associated with motor control.

Although individuals with manganism resemble Parkinsonian patients, these syndromes can be distinguished clinically (Beuter et al., 1994; Calne et al., 1994; Pal et al., 1999). For example, as manganism becomes more severe, dystonia (a neurological sign associated with damage to the globus pallidus) occurs which is absent in the etiology of Parkinson's disease (Calne et al.,1994). Similarities between Parkinson's disease and manganism include the presence of generalized bradykinesia and widespread rigidity. The following dissimilarities between Parkinson's disease and manganism were noted in manganism: (a) a less frequent resting tremor, (b) more frequent dystonia, (c) a particular propensity to fall backward, (d) failure to achieve a sustained therapeutic response to levodopa, and (e) failure to detect a reduction in fluorodopa uptake by positron emission tomography (PET; for further details see Calne et al., 1994; Pal et al., 1999). Given these differences, it has been proposed that manganese intoxication is associated with indirect alteration of the nigrostriatal dopaminergic pathway, perhaps through striatopallidal misfiring due to excessive manganese accumulation in the globus pallidus (Calne et al., 1994; Erikson et al., 2002; Pal et al., 1999; Verity, 1999).

The developing nervous system appears to be a target for adverse effects of manganese. A few report link children with excessive exposure to manganese with the development of neurotoxicity symptoms (Cawte, 1985;

Fell et al., 1996; Woolf et al., 2002). Rodent studies suggest that neonates, when compared to adult animals, are at an increased risk for manganese-induced neurotoxicity due to their ability to achieve higher brain manganese levels and altered brain dopamine concentrations following similar oral exposures (Chandra and Shukla,1978; Dorman et al., 2000; Kontur and Fechter, 1988; Pappas et al., 1997). Known pharmacokinetic processes that may contribute to the increased susceptibility of neonatal animals include increased manganese absorption from the gastrointestinal tract, an incompletely formed blood–brain barrier, and the virtual absence of biliary manganese excretory mechanisms until weaning (Ballatori et al., 1987; Miller et al., 1975; Rehnberg et al., 1982). Manganese concentration in the brain of developing rats is highest of all age groups, suggesting that manganese is required in a high amount during infancy, and that a sufficient manganese supply is critical for normal brain development (Takeda et al., 1994). Given this increased requirement of manganese for the proper development of the brain, accumulation of manganese in the brain of neonatal rats must be cautiously linked to neurotoxicity.

In a recent study, oral manganese chloride ($MnCl_2$) doses (0, 25, or 50 mg/kg body weight/day) were administered to neonatal rats throughout lactation (postnatal day [PND] 1 through 21) and to adult male rats for 21 consecutive days (Dorman et al., 2000). Increased manganese concentrations in the striatum and cerebellum were only observed in adult rats given 50 mg Mn/kg body weight. In contrast, increased striatal, hippocampal, hindbrain and cortical manganese concentrations were observed in rats aged PND 21 exposed to both 25 and 50 mg Mn/kg body weight. These results suggest that in the rat, manganese is more efficiently transported into the central nervous system of neonates compared to adults receiving equal oral doses of manganese.

An extensive body of literature exists regarding significant species differences in the neurotoxicity of manganese. Exposed monkeys retain manganese in their basal ganglia, they develop reduced dopamine and 3,4-dihydroxyphenylacetic acid concentrations in their striatum and pallidus, have decreased dopamine binding, and develop loss of dopaminergic neurons analogous to manganese-poisoned humans (Calne et al., 1994; Eriksson et al., 1992a,b; Nagatomo et al., 1999; Newland et al., 1989; Olanow et al., 1986). Similar regional brain manganese distribution, neurochemical, and neuropathological responses are inconsistently observed in manganese-exposed rodents (Brenneman et al., 1999; Chandra and Shukla, 1978; Dorman et al., 2000; Kristensson et al., 1986; Newland, 1999; Pappas et al., 1997). The available scientific literature also suggests that rodents do not develop an identical behavioral syndrome comparable to those seen in manganese-poisoned humans and monkeys (Boyes and Miller, 1998). When considered together, these findings suggest that species differences confound the extrapolation of neurotoxicity results obtained for manganese in rodents to humans, possibly as a result of differential distribution of manganese in the CNS of rodents versus primates.

5. Iron deficiency influences manganese transport into the brain

Recently, it has been reported that iron deficiency leads to increased manganese concentrations in the brain (Chua and Morgan, 1996; Erikson et al., 2002; Kwik-Uribe et al., 2000). Both manganese and iron transport to extrahepatic tissues, including the brain, is dependent upon transferrin-mediated endocytosis (Crowe and Morgan, 1992; Malecki et al., 1999). Iron deficiency causes increased brain regional transferrin and transferrin receptor concentrations especially in the striatum and substantia nigra regions (Chen et al., 1995a; Erikson et al., 1997; Pinero et al., 2000). It is noteworthy that these brain regions showed the greatest accumulation of manganese due to iron deficiency (Erikson et al., 2002).

The neurobiological consequences of iron-deficiency include alterations in behavior, cognition, and neurotransmitter metabolism (Beard, 2001; Erikson et al., 2000, 2001, 2002; Kwik-Uribe et al., 2000). Offspring of marginal iron dams demonstrate lower grip strength, attenuated startle responsiveness, as well as altered performance in the morris water maze. These differences in performance were found in association with lower brain iron concentrations. Notably, iron-deficiency is also associated with decreased dopamine D_2 receptors in striatum (Ashkenazi et al., 1982; Youdim et al., 1989), increased extracellular dopamine concentrations (Beard et al., 1994; Chen et al., 1995b; Nelson et al., 1997), decreased dopamine transporter and dopamine receptor functioning (Erikson et al., 2000, 2001), thus sharing a number of commonalities with manganese-induced neurotoxicity (Aschner et al., 2001). This raises the possibility that the neurological

sequelae of iron-deficiency are mediated, or possibly exacerbated, by increased central nervous system manganese concentrations. Fig. 1 depicts the proposed neurochemical disturbances associated with iron deficiency mediated manganese accumulation (see Erikson and Aschner, 2003 for review).

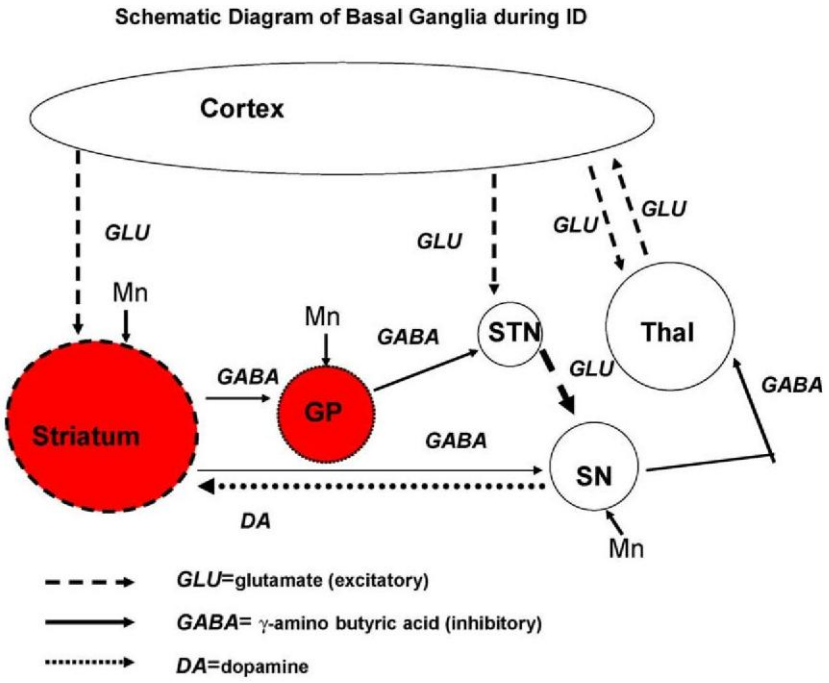

Fig. 1. During iron deficiency (ID), several brain regions (striatum, globus pallidus and substantia nigra) significantly accumulate manganese, but to a lesser extent than is reported in manganism. ID-associated manganese accumulation in the striatum is negatively correlated with GABA (Erikson et al., 2002). This relationship may reflect decreased GABAergic firing into the substantia nigra, which may contribute to the dopaminergic alterations characterized by ID (see Erikson et al., 2000, 2001). The thickness of the lines illustrate strength of neurotransmission. GP: globus pallidus, STN: subthalamic nuclei, Thal: thalamus, SN: substantia nigra. Adapted from Erikson and Aschner (2003).

Divalent metal transporter (DMT-1) mRNA levels are significantly increased in patients with iron deficiency, and hereditary hemochromatosis, whereas they are unchanged in patients with secondary iron overload (Zoller et al., 2001). Alterations in DMT-1 mRNA levels are paralleled by comparable changes in the duodenal expression of these proteins. In patients with normal iron status or iron deficiency, significant negative correlations between DMT-1 mRNA and serum iron level parameters have been noted. Manganese levels in these patients have not been determined, and no data are currently available on the potential that increased DMT-1 mRNA expression translates to increased plasma or brain manganese load. A recent study (Erikson et al., 2002) fed weanling rats one of three semi-purified diets: control, iron deficient (ID), or iron deficient/ manganese fortified (IDMn+). Plasma transferrin (significant increase) and iron concentrations (significant decrease) were characteristic of severe anemia in the ID and IDMn+ groups (Erikson et al., 2002).
Seven brain regions (caudate putamen, globus pallidus, thalamus, hippocampus, substantia nigra, cerebellum and cortex) were analyzed for manganese concentration. Both ID and IDMn+ diets caused significant increases in manganese concentration across brain regions compared to control diets. A follow-up study revealed that DMT- 1 levels are increased almost two-fold in the basal ganglia due to iron deficiency when compared to control levels and this change in DMT-1 is correlated with manganese accumulation (Erikson et al., 2004).

6. Conclusion

Manganese is an essential nutrient that is required in trace amounts. Excessive exposure to manganese, whether in occupational setting or via ingestion may result in neurological dysfunction. Because there is an increased requirement of manganese during brain development, optimal manganese homeostasis is critical during this developmental period. Recent studies suggest that an inverse relationship exists between brain iron and manganese concentrations. This relationship has been elucidated in studies showing that iron deficiency causes specific regional manganese accumulation compared to control animals. Increased transferrin receptor and/or DMT- 1 levels have been implicated in this iron deficiency-associated accumulation of manganese. This effect

is region-dependent with basal ganglia accumulating manganese to a greater extent than other brain regions (e.g., cortex and cerebellum) (Erikson et al.,2002).

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