Manganese and its Role in Parkinson's disease: from Transport to Neuropathology.

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Abstract:

The purpose of this review is to highlight recent advances in the neuropathology associated with Mn exposures. We commence with a discussion on occupational manganism and clinical aspects of the disorder. This is followed by novel considerations on Mn transport (see also chapter by Yokel, this volume), advancing new hypotheses on the involvement of several transporters in Mn entry into the brain. This is followed by a brief description of the effects of Mn on neurotransmitter systems that are putative modulators of dopamine (DA) biology (the primary target of Mn neurotoxicity), as well as its effects on mitochondrial dysfunction and disruption of cellular energy metabolism. Next, we discuss inflammatory activation of glia in neuronal injury and how disruption of synaptic transmission and glial-neuronal communication may serve as underlying mechanisms of Mn-induced neurodegeneration commensurate with the cross-talk between glia and neurons. We conclude with a discussion on therapeutic aspects of Mn exposure. Emphasis is directed at treatment modalities and the utility of chelators in attenuating the neurodegenerative sequelae of exposure to Mn. For additional reading on several topics inherent to this review as well as others, the reader may wish to consult Aschner and Dorman (Toxicological Review 25:147–154, 2007) and Bowman et al. (Metals and neurodegeneration, 2009).

Keywords: manganese | Parkinson’s disease | neuroinflammation | GABA | glutamate | MRI | neuroscience | medicine

Article:

Introduction

Mn is an essential metal, yet excessive exposure to it, whether from air or food, is associated with neurological sequelae. Manganese (Mn) is an essential nutrient important to protein and energy metabolism, bone mineralization, metabolic regulation, and cellular protection from

reactive oxygen species. It is a cofactor for enzymes, such as mitochondrial superoxide dismutase (Hearn et al. 2003), arginase (Shishova et al. 2009), pyruvate carboxylase (Zwingmann et al. 2004), and glutamine synthetase (Takeda 2003).

Occupational exposure to Mn has been the principal cause of human Mn intoxication in individuals working in such industries as mining and the manufacturing of dry batteries, steel, aluminum, welding metals, and organochemical fungicides (Keen et al. 2000; Keen and Leach 1987). In addition, individuals receiving total parenteral nutrition (Bertinet et al. 2000) and patients with chronic liver failure are at higher risk of Mn intoxication (Hauser et al. 1994; Krieger et al. 1995). Mn exposure in the general population can occur from consumption of well water containing high levels of the metal (Kawamura et al. 1941; Wasserman et al. 2006), from soy-based infant formulas (Krachler and Rossipal 2000; Lonnerdal 1994), and possibly from Mn released into the atmosphere as a result of the addition of methylcyclopentadienyl manganese tricarbonyl (MMT) to gasoline as an anti-knock agent (Finkelstein and Jerrett 2007; Walsh 2007). Both in rats (Fitsanakis et al. 2008) and humans (Kim et al. 2005) with chronic iron (Fe) deficiency, Mn also accumulates at higher levels in the basal ganglia.

Manganism, characterized by excessive brain Mn deposition, shares multiple features with Parkinson's disease (PD). In the early stages of the disease patients with manganism display psychotic symptoms, which progress to chronic symptoms associated with disturbances in extrapyramidal circuits, such as akinetic rigidity, dystonia, and bradyskinesia (Olanow 2004; Pal et al. 1999). Neuronal loss and gliosis in the globus pallidus, the substantia nigra pars reticulata, and the striatum characterize manganism at the morphological level (Olanow 2004). Manganism is caused by neuronal injury in both cortical and subcortical brain regions, particularly the basal ganglia. The basis for the selective neurotoxicity of Mn remains incompletely understood but an increasing number of studies are elucidating underlying mechanisms through characterization of the transport of Mn into the brain, the effects on synaptic transmission and neuronal function, and the inflammatory response of populations of glial cells in affected brain regions. The pleiotropic effects of excess Mn on numerous metabolic and trophic pathways in the CNS suggest a complicated disease process that is dependent upon the dose and duration of Mn received, the age at which exposure occurs, and the nutritional status of the individual, particularly with respect to other metals, such as Fe. To date, chelation therapy in exposed individuals remains the primary treatment modality (Discalzi et al. 2000; Herrero Hernández et al. 2006), but neurological symptoms may worsen even years after the cessation of chronic exposure (Rosenstock et al. 1971). Therefore, elucidation of the cellular and molecular pathways underlying onset and progression of the disorder is likely the best hope for development of disease modifying therapeutic strategies.

Occupational Manganism

Occupational exposure generally occurs by inhalation of Mn dusts and fumes. The current threshold limit value time-weighted average (TLV-TWA) indicated by the American Conference of Governmental Industrial Hygienists for Mn is 0.2 mg/m3 (ACGIH 2009). Manganism, an extrapyramidal syndrome associated with exposures to excessive Mn levels, was first detected in 1837 in Mn dioxide-exposed workers (Couper 1837). The prevalence of occupational manganism is unknown, with a 0.5–2% rate reported among exposed workers in China (Gao et al. 2003; Wang et al. 2001; Wang 2003), where metal poisoning ranks among the 10 leading occupational diseases (Liang and Xiang 2004). In the US alone, about 750,000 welders (HSBC 2003) are or have been exposed to metal fumes and the legal litigation costs relating to occupational Mn-related disorders are estimated in billions of US$ (HSBC 2003).

Clinical Aspects

Manganism is not only an occupational disease, as, even in the absence of relevant exogenous exposures, it can affect patients with chronic liver failure (Hauser et al. 1994) (due to impaired biliary excretion of Mn), chronic iron deficiency (Boojar et al. 2002; Herrero Hernández et al. 2002) mostly due to Fe/Mn competition for transporters (review by Roth & Garrick 2003) (Roth and Garrick 2003), subjects on parenteral nutrition (Fell et al. 1996), drug addicts using high Mn injectable solutions (de Bie et al. 2007; Levin 2005; Meral et al. 2007; Sanotsky et al. 2007; Sikk et al. 2007), patients in chronic renal failure undergoing hemodialysis (da Silva et al. 2007; Ohtake et al. 2005) (for unclear reasons), and subjects with genetic defects affecting Mn homeostasis (Tuschl et al. 2008). It should be stressed that Fe deficiency affects about 2 billion subjects (Garcia et al. 2007) and is a risk factor for Mn neurotoxicity even in absence of relevant exogenous exposures. Mn toxicity from various sources has been repeatedly reported in children (Fell et al. 1996; Herrero Hernández et al. 2003; Komaki et al. 1999; Woolf et al. 2002), including cognitive effects (Wasserman et al. 2006).

In 1837, Couper of Glasgow described a neurologic disorder in five patients who worked in a Mn ore-crushing plant that bore similarity to the “shaking palsy” syndrome reported only 20 years earlier by James Parkinson (Couper 1837). This and later reports (Embden 1901; Rodier 1955; Scholten 1953; von Jaksch 1907; Voss 1939) described a chronic, progressive disorder of the basal ganglia, termed manganism that is characterized by extrapyramidal symptoms resembling PD. The clinical manifestations of workplace Mn neurotoxicity include behavioral changes, parkinsonism, and dystonia with gait disturbances (Cersosimo and Koller 2006). While it is generally recognized that manganism appears after several years of exposure, early reports described cases occurring after one or more months (Fairhall and Neal 1943; Rodier 1955), the latter occurring under extremely elevated exposures. Non-specific symptoms (headaches, muscular cramps, and fatigue) may precede overt manganism. A psychosis (locura manganica) marked by aggressivity was reported among workers exposed via dust to very high Mn levels. Long-term changes in neuromotor, cognitive, and mood domains have been described in exposed

occupational groups (Bouchard et al. 2007; Roels et al. 1985). Manganism can progress even after cessation of exposure and has long been considered irreversible (Huang et al. 1993). Neurological signs seem to reach a plateau after an initial 5–10 years of progression (Huang et al. 2007), but this observation is based on the follow up of four patients only. However, it has been documented, in a few cases and in uncontrolled studies (Discalzi et al. 2000; Herrero Hernández et al. 2003; Herrero Hernández et al. 2006; Ky et al. 1992; Ono et al. 2002; Penalver 1957; Tuschl et al. 2008) that manganism can be reversed if promptly diagnosed and treated with chelating drugs. Manganism frequently appears in young, active workers. The metal primarily targets the globus pallidus and the onset is generally symmetric. The syndrome includes hypertonia with cogwheel rigidity, limb action/postural tremor, bradykinesia, “cock walk”, and falling when walking backwards.

New Considerations Regarding Mn Transport

Mn can enter the CNS through the cerebral spinal fluid or by crossing cerebral capillary endothelial membranes. Physiological concentrations of Mn range from 2 to 8 μM in brain tissue (Pal et al. 1999), but can increase several-fold upon overexposure in rodents (Liu et al. 2006; Zheng et al. 1998) and humans (Crossgrove and Zheng 2004; Kessler et al. 2003). How Mn crosses the blood–brain barrier (BBB) has been the subject of much investigation and it appears that several pathways are operative, including facilitated diffusion and active transport by the divalent metal transporter 1 (DMT-1), ZIP8, and the transferrin receptor system [recently reviewed in (Aschner et al. 2007)]. Mn accumulates in multiple brain regions including the basal ganglia, frontal cortex, pre-optic area, and hypothalamus, indicated by analytical determination in autopsy samples (Yamada et al. 1986) and by T1-weighted magnetic resonance imaging (MRI) (Shinotoh et al. 1997; Kim et al. 1999; Herrero Hernández et al. 2002; Guilarte et al. 2006; reviewed by Aschner and Dorman 2007).

Consistent with a large number of observations, Mn and Fe share common cytoplasmic transporters, such as the divalent metal transporter-1 (DMT-1) and the transferrin (Tf)/transferrin receptor (TfR) system (Aschner et al. 2007). Mn may also be transported as a citrate complex, and candidates for this transporter include the organic anion transporter or a monocarboxylate transporter (MCT) and/or members of the organic anion transporter polypeptide (OATP) or ATP-binding cassette (ABC) super-families (Crossgrove et al. 2003). A role in Mn transport has also been ascribed to the ZIP transporter proteins in Mn transport, though not specifically in the brain. This family of transporter proteins is members of the solute-carrier-39 (SLC39) metal-transporter family; the family contains 14 members, which are all highly conserved between mouse and human (Eide 2004). It was recently suggested (He et al. 2006) ZIP8 possesses high affinity for Mn (K m close to physiological concentrations of Mn in various tissues). Notably, while to date the role of the transporter in Mn has been ascribed only in the testis (He et al. 2006), ZIP8 is expressed in brain capillaries (Girijashanker et al. 2008). Additional studies have

also established that bolus injections of Mn directly into the blood may lead to Mn diffusion across the BBB (Bock et al. 2008). As pointed by these authors, Mn can be transported via the cerebrospinal fluid and the ventricles and a significant difference in Mn transport, and regional brain accumulation exists between non-human primates and rodents.

Although Tf is the most likely carrier molecule for Mn3+ transport across the BBB, the existence of other transport mechanisms should also be considered. Clearly, binding of Mn2+ to alpha2-macroglobulin or albumin cannot be invoked in the transport of Mn across the BBB, because neither alpha2-macroglobulin nor albumin is transported across this barrier. Unlike many other metals, Mn2+ does not posses high affinity for any particular endogenous ligand [i.e., methylmercury (MeHg) and -sulfhydryl groups (–SH)]. There is almost no tendency for Mn2+ to complex to –SH groups and to amines. Metal ion hydrolysis interferes well before Mn2+ might complex to uni-dentate amines. Not surprisingly, Mn2+ does not have much variation in its stability constants for endogenous complexing ligands (log10 k = 3, 4, 3, and 3, for glycine, cysteine, riboflavin, and guanosine, respectively, where k is the affinity constant). The strongest stability constants occur with multi-dentate amino carboxylate ligands such as EDTA [log10 k = 13.5; (Martel et al. 1998)], the only effective chelator of extracellular Mn. EDTA supplies two nitrogen and four oxygen ligands to Mn, and a water molecule is also coordinated to Mn (Reardan et al. 1985). While noting the strong affinity of Mn to multi-dentate amino carboxylate ligands, it must be considered that in plasma, lipid soluble conjugates of Mn may exist. These may provide a mechanism, not only for the transport of Mn through the blood stream, but also for egression of the metal from the blood stream into cells. The greater acute, oral toxicity of the chloride–Mn salt compared to the oxide salt in the young rat (Holbrook 1976) may be primarily associated with the greater relative solubility of the chloride salt, and thereby enhanced uptake of Mn. It is likely that minute amounts of Mn2+ in plasma exist, according to the Mass Law Principle, as a chloride complex. While the amount of this complex in plasma at any one time must be minute, the Mass Law Principle states that a definite infinitesimal amount is always present. It also holds that if any Mn2+ should leave the system by dissolving in a lipid membrane that the protein–Mn2+ complex should dissociate to maintain equilibrium. The process of Mn dissolving in a membrane in not clear. Although the Mass Law Principle maintains some concentration of Mn in blood, it is not directly involved in the process of transport across membranes; it simply provides the Mn available for transport. The plausibility that this mechanism is involved in the transport of Mn across membranes remains open for experimentation.

Other transport mechanisms for Mn should be considered as well. Snyder et al. (1986) proposed a novel transport mechanism—the “sulfhydryl shuttle”—for the membrane transport of Auranofin 9, an antiarthritic agent, into macrophage cells. They suggest that the compound shuttles from albumin or cysteine to membrane –SH groups, and thence is internalized. Interestingly, Haest et al. (1977) found that approximately 80% of –SH groups in the erythrocyte membrane are close enough to each other to allow chemical interactions. Snyder et al. (1986)

used mainly indirect evidence to support this model. The key data was the observation that N-ethylmaleimide (NEM) blocked uptake of Auranofin 9, whereas metabolic inhibitors, such as 2,4-dinitrophenol (DNP) and sodium fluoride (NaF), did not exert an inhibitory effect. These results suggest that binding of membrane –SH by NEM blocked the "sulfhydryl shuttle", and that active transport processes of phagocytosis or endocytosis were not a part of the process. This feature led Snyder et al. (1986) to suggest that a "sulfhydryl shuttle" may comprise a generic phenomenon for transport, whereby, closely apposed fixed membrane –SH groups are "shuttling" solutes across the BBB. Gerson and Shaikh (1984) have published evidence in support of Cd2+ entry into hepatocytes by an –SH carrier.

The mechanisms considered so far are "shuttle" processes involving water soluble complexes of Mn that are transported on membrane carriers or a nonspecific exchange of Mn between closely apposed membrane –SH groups. Foulkes and McMullen (1987) proposed an intriguing mechanism for transport of metals across membranes. For example, the transport of Cd2+ across the intestinal membrane was postulated to consist of two distinct phases. The first is the binding of the metal to negatively charged groups on the surface of the membrane. This process is not specific to Cd2+ since several polyvalent cations can inhibit this step. The second transport phase involves the "internalization" of the membrane bound metal. Thus, less metal can be removed from the intestinal surface with non-penetrating complexing agents, such as EDTA, as a function of time and temperature. Once inside the cell, Cd2+ binds to metallothionein making it even less susceptible to mobilization by complexing agents. A similar scheme of events may be operative in the brain capillaries, as well as astrocytes and neurons (and other eukaryotic cells). Future studies could be profitably directed at testing the possibility for a two step entry process for Mn across biological membranes. It is noteworthy that when MPTP is given to mice, the expression of an isoform of DMT1 increases in the ventral mesencephalon of treated animals concomitant with iron accumulation, oxidative stress, and dopaminergic cell loss (Salazar et al. 2008). Thus, DMT1 mutation impairs iron transport and protects against MPTP and 6-hydroxydopamine. Whether specific SNP variants in other Mn transporters represent a risk factor for developing manganism (at reduced Mn exposures) or PD has yet to be studied.

Neuropathological Characteristics of Mn Exposure

Mn is generally described as a neurotoxicant selectively affecting the basal ganglia structures of the lower forebrain and midbrain, including the globus pallidus, striatum, subthalamic nucleus, and substantia nigra pars reticulata; nevertheless, involvement of other regions, such as the cortex and hypothalamus has also been reported (Yamada et al. 1986). The most prominent neuropathologic findings in human manganism are neuronal loss and reactive gliosis in the globus pallidus and substantia nigra pars reticulata (SNpr) (Yamada et al. 1986). Damage involving the striatum (caudate nucleus and putamen) and subthalamic nucleus has also been reported and, less frequently, the substantia nigra pars compacta (Calne et al. 1994; Perl and

Olanow 2007). This stands in contrast to idiopathic PD, where neuronal loss in the substantia nigra pars compacta with the appearance of Lewy bodies is a neuropathological hallmark of the disease (Pal et al. 1999). Notably, dopaminergic soma in the pars compacta are typically spared in manganism (Olanow 2004; Olanow et al. 1996). A key feature of the reactive gliosis observed in human and experimental manganism is the presence of Alzheimer type II astrocytosis (Bikashvili et al. 2001; Pentschew et al. 1963). Ultrastructural studies report that reactive astrocytes and microglia surround degenerating neurons and contain increased numbers of large secondary lysosomes, indicative of an active phagocytic process (Bikashvili et al. 2001). Additionally, it has been reported that Mn induces astrogliosis in the pre-frontal cortex of exposed Cynomolgus macaques and that activated astrocytes in this model were noted proximal to degenerating neurons that expressed amyloid-β precursor-like protein 1 (Guilarte et al. 2008b). Collectively, reports from human cases and animal models of manganism suggest a broad spectrum of neuropathological changes in both neurons and glia not only within the basal ganglia, but also within cortical regions as well, which may help to explain some of the non-motor symptoms of the disorder.

Effects of Mn on Norepinephrine

Due to the similarities of manganism and PD, most research in the area of Mn neurotoxicity has focused on dopamine (DA) biology; however, alterations in the biology of other neurotransmitters, such as norepinephrine (NE) (Autissier et al. 1982; Chandra et al. 1984; Seth and Chandra 1984) have been reported. It should be noted that depletion of NE in the substantia nigra by greater than 80% is a hallmark of idiopathic PD (Marien et al. 2004) and it is hypothesized that degeneration of the locus coeruleus may precede and potentially surpass dopaminergic degeneration in the substantia nigra (Rommelfanger and Weinshenker 2007), due to shared anatomical and biochemical similarities (Zecca et al. 2004). In this section, we aim to highlight some recent findings coupled with some older studies that suggest that disturbances in NE biology due to Mn exposure may be a part of the etiology of manganism.

Mn exposure has been found to affect brain tissue (Autissier et al. 1982) and extracellular concentrations (Anderson et al. 2009) of NE, as well as the uptake of NE (Anderson et al. 2009; Chandra et al. 1984; Lai et al. 1982) and expression of the NE transport and α2-adrenergic receptor protein and mRNA levels (Anderson et al. 2009). The effects of Mn on NE biology may potentially result from perturbations in the locus coeruleus, the main noradrenergic region of the brain (Troadec et al. 2001), and the neuromodulatory effect the region exerts on the nigrostriatal dopaminergic pathway (Meyer and Quenzer 2005). Studies using α2-adrenergic receptor antagonist treatment in rodents showed that attenuating NE neurotransmission significantly depleted DA release in the striatum, mimicking the neurochemistry observed due to PD (Lategan et al. 1990). Recently, it was reported that Mn exposure was associated with a two-fold reduction of both protein and mRNA levels of the α2-adrenergic receptor in the locus coeruleus and

substantia nigra (Anderson et al. 2009). Thus, it is plausible that the altered α2-adrenergic receptor levels and attenuated NE uptake caused by Mn accumulation in the locus coeruleus (Anderson et al. 2009), likely cause some of the behaviors associated with manganism (e.g., anxiety-like behaviors).

Effects of Mn on γ-aminobutyric Acid

Much more research has been performed on examining the role of γ-aminobutyric acid (GABA) in mediating the effects of Mn neurotoxicity compared to NE. Mn exposure has been shown to affect tissue concentrations in a differential manner depending upon species and type of exposure. A significant increase in striatal GABA due to Mn exposure was found in rats (Garcia et al. 2006, 2007; Gwiazda et al. 2002); while a marginally significant ($P < 0.1$) decrease in pallidal GABA concentrations in monkeys exposed to airborne $MnSO_4$ has been reported (Struve et al. 2007); and no statistical difference was found in brain regional GABA concentrations in primates injected with Mn intravenously (Burton et al. 2009). While tissue GABA concentrations can capture the overall status of GABA biology in an organism, it does not fully reflect the extracellular concentrations which are critical for neurotransmission. Recently, it was found that Mn exposure via the drinking water led to increased extracellular concentrations of GABA (Anderson et al. 2008), attenuation of striatal GABA uptake (Anderson et al. 2007), and alterations of GABA receptor and transporter expression (Anderson et al. 2008) (see Fig. 1 for summary). Currently, in vivo extracellular GABA data are lacking for Mn exposed primates.

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Alterations in extracellular GABA could potentially mediate the locomotor effects seen in Mn neurotoxicity, such as hyperkinesia, ataxia, and dystonia. Normandin et al. (2004) observed decreases in locomotor activity in Mn-exposed young adult rats, while motor deficits were also observed in a study utilizing a pre-Parkinsonian rat model and cumulative low-dose Mn exposure (Gwiazda et al. 2002). In both of these studies, DA was not altered, suggesting that changes in GABA may precede and facilitate changes in DA during manganism. GABAergic neurons in the striatum receive dopaminergic terminals from the substantia nigra (Smith and Bolam 1990), in turn modulating the dopaminergic functioning in the striatum (Galindo et al. 1999), with increased extracellular levels of GABA affecting GABA projection neurons to the substantia nigra (Koos and Tepper 1999), leading to dysregulation of the nigrostriatal pathway, a hallmark of Mn neurotoxicity (see Fig. 1).

Mitochondrial Dysfunction and Disruption of Cellular Energy Metabolism

Mitochondria are one of the most important sites of Mn-induced cellular dysfunction and early studies into the cellular actions of Mn reported that mitochondria are the principal intracellular repository for the metal (Cotzias and Greenough 1958). More recent data indicate that mitochondria actively sequester Mn, resulting in rapid inhibition of oxidative phosphorylation (Gavin et al. 1992), likely by the 2+ valence species (Gunter et al. 2006). Mn is rapidly transported into the mitochondrial matrix via the calcium (Ca^{2+}) uniporter, but is cleared slowly, which can result in accumulation and subsequent inhibition of Na^{+}-dependent and -independent Ca^{2+} efflux and a sustained increase in matrix Ca^{2+} levels (Gavin et al. 1990). Elevated matrix calcium increases formation of reactive oxygen species (ROS) by the electron transport chain (Kowaltowski et al. 1995) and results in inhibition of aerobic respiration (Kruman and Mattson 1999). Various studies report that Mn directly inhibits complex II (Singh et al. 1974) and complexes I–IV (Zhang et al. 2003) in brain mitochondria. Astrocyte mitochondria may also be a direct target of Mn, demonstrated by studies examining mitochondrial calcium responses in primary cortical astrocytes stimulated with ATP (Tjalkens et al. 2006). Pretreatment of astrocytes with concentrations of Mn as low as 1 μM resulted in large increases in mitochondrial calcium that were accompanied by osmotic swelling of mitochondria, loss of interconnected mitochondrial networks, and depletion of thapsigargin-releasable endoplasmic reticulum (ER) Ca^{2+} stores. Mn also decreases mitochondrial membrane potential and elevates intracellular reactive oxygen species (ROS) in cultured astroglial cells (Barhoumi et al. 2004).

The effects of Mn on mitochondria in both astrocytes and neurons suggest that disruption of cellular metabolism is a critical feature of Mn neurotoxicity. Studies using high-resolution multinuclear NMR-spectroscopy to examine cell-specific pathways of 1,13Cglucose metabolism by primary cultured astrocytes and neurons reported that Mn hindered the ability of neurons to compensate for mitochondrial dysfunction by oxidative glucose metabolism and predisposed neurons to energy failure (Zwingmann et al. 2003). These studies also reported that Mn inhibited glutamine synthesis and release in astrocytes that correlated with a failure of astrocytes to provide neurons with substrates for energy and neurotransmitter metabolism, leading to decreased neuronal glutathione levels and energy metabolism. Mn has been shown to decrease glutamate uptake and downregulate expression of the high-affinity glutamate transporter, GLAST, in cultured astrocytes (Erikson and Aschner 2002). Studies in rhesus monkeys exposed to Mn by inhalation also reported down regulation of GLAST in the globus pallidus in parallel to decreased levels of glutathione (Erikson et al. 2008), suggesting that oxidative stress and disruption of the glutamate–glutamine metabolic coupling cycle between astrocytes and neurons is an important etiological factor in the progression of Mn neurotoxicity. Because neurons rely on metabolic intermediates, such as pyruvate, lactate, and glutamine, provided by astrocytes to sustain energy metabolism (Deitmer et al. 2003; Sonnewald et al. 1991; Tekkok et al. 2005), disruption of astrocyte-neuron metabolic coupling by Mn may be an important mechanism underlying mitochondrial dysfunction and failure of neuronal metabolism in neurons following exposure to Mn.

Inflammatory Activation of Glia

Pathologic activation of both microglia and astrocytes is associated with the progression of neurotoxic injury following exposure to excessive Mn. Astrocytes were first implicated in Mn neurotoxicity following demonstration that glutamine synthetase, for which Mn is a required cofactor, is located solely in this cell type in the central nervous system (Martinez-Hernandez et al. 1977). It was subsequently shown that astrocytes selectively accumulate Mn at more than 50-fold greater concentration than neurons (Wedler et al. 1989) and possess a high affinity uptake system for the divalent metal (Aschner et al. 1992). Henriksson and Tjalve (2000) postulated that astrocytes were the initial target of Mn based upon their observation that Mn exposure in rats resulted in decreased immunoreactivity for glial fibrillary acidic protein (GFAP) and S100β in the absence of any apparent neuronal injury. This assertion is supported by more recent studies that noted an early upregulation of the 'peripheral-type' (mitochondrial) benzodiazepine receptor in adult rats exposed subacutely to Mn that was associated with Alzheimer type-II astrocytosis in the globus pallidus (Hazell et al. 2003). Spranger et al. (1998) speculated that activated astrocytes contribute to Mn neurotoxicity through excessive production of NO based upon their data demonstrating that Mn-induced neuronal injury required the presence of astrocytes and was associated with increased expression of the inducible isoform of nitric oxide synthase (NOS2). Collectively, these studies suggested that debilitation of astrocytic mitochondrial function and increased production of NO could be salient mechanisms in Mn neurotoxicity.

Mn enhances the release of inflammatory cytokines interleukin-6 and TNF-α from microglial cells (Chang and Liu 1999; Filipov et al. 2005) that can promote the activation of astrocytes and subsequent release of inflammatory mediators such as prostaglandin E2 and nitric oxide (NO) (Chen et al. 2006; Hirsch et al. 1998; Spranger et al. 1998). Mn also strongly potentiates NO production in cytokine-stimulated astrocytes, leading to apoptosis in co-cultured neurons (Liu et al. 2006; Spranger et al. 1998; Tjalkens et al. 2008). This observation is supported by studies demonstrating increased expression of NOS2 in activated astrocytes surrounding degenerating neurons in the striatum and globus pallidus of Mn-treated mice (Liu et al. 2006). Mn also enhances the capacity of bacterial lipopolysaccharide to promote NO production in both astroglial (Barhoumi et al. 2004) and microglial (Filipov et al. 2005) cells. Low concentrations of Mn can increase the capacity of TNF-α, interferon-γ, and IL-1β to induce expression of NOS2 and production of NO in astrocytes by promoting activation of the transcription factor NF-κB (Liu et al. 2005; Spranger et al. 1998). The mechanism underlying the pronounced effect of low-level Mn on expression of NOS2 in astrocytes appears to reside in the capacity of the divalent metal to potently stimulate soluble guanylate cyclase, leading to elevated intracellular levels of cGMP and MAP kinase-dependent activation of NF-κB (Moreno et al. 2008).

Disruption of Synaptic Transmission and Glial-Neuronal Communication

There is evidence that Mn affects both pre- and post-synaptic neurons within the nigro-striatal dopaminergic system. Neuropathological examination of the few cases of human manganism that have come to autopsy report the absence (Yamada et al. 1986) and presence (Ashizawa 1927; Scholten 1953) of lesions within the substantia nigra pars compacta. Loss of pigmented dopaminergic neurons within the substantia nigra pars compacta has also been reported in Mn-exposed monkeys (Gupta et al. 1980). Functional imaging studies using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) report similarly contrasting evidence. PET studies examining [18F]-6-fluoro-L-DOPA uptake in patients suffering from manganism (Shinotoh et al. 1997) and in Mn-intoxicated monkeys (Shinotoh et al. 1995) reported intact dopamine transporter function on pre-synaptic terminals in the striatum. In contrast, Kim et al. (2002) observed a decrease in binding of [123I]-1r-2β-carboxymethoxy-3β-(4-iodophenyl)tropane to pre-synaptic dopamine transporters using SPECT in two patients with chronic manganism, indicating either a direct effect on pre-synaptic nigrostriatal dopaminergic neurons or perhaps Mn intoxication with symptoms manifesting from underlying idiopathic Parkinson's disease. However, post-synaptic injury is most frequently observed in human Mn intoxication, noted studies by Kessler et al. (2003), who demonstrated markedly reduced striatal post-synaptic D2-receptor density by [18F]-methylspiperone PET imaging in an advanced case of chronic manganism. These data suggest a direct involvement of striatal-pallidal structures in the characteristic neurological dysfunction observed in manganism. In addition, studies in Cynomolgus macaques revealed that amphetamine-induced dopamine release was inhibited in Mn-exposed animals (Guilarte et al. 2008a), suggesting a direct involvement of pre-synaptic dopaminergic pathways.

There appears to be an excitotoxic component to manganism that may ensue from disruption of both astroglial and neuronal energy metabolism. Mn downregulates the glutamate transporter GLAST in astrocytes (Erikson and Aschner 2002) and decreases levels of glutamine synthetase in exposed primates (Erikson et al. 2008). Striatal lesions caused by direct injection of Mn in rats are prevented by the non-competitive glutamate receptor antagonist MK-801 (Brouillet et al. 1993). Interestingly, decreased ATP and lactate in this model seem to precede excitotoxic injury, suggesting a direct effect on astrocytes that subsequently impairs neuronal function. More recent studies report contrasting evidence in this regard. Neonatal rats exposed subcutaneously to lower levels of Mn for 4 weeks had increased levels of glutamate in the striatum and evident neurotoxicity that was prevented by MK-801 (Xu et al. 2009), whereas studies in which monkeys were exposed intravenously to Mn reported no change in glutamate levels or glutamate receptor density (PUBMED ID 19520674). Additional studies using the neonatal rat model indicated that both pinacidil, a potassium channel agonist, and nimodipine, a Ca channel antagonist, reversed Mn neurotoxicity and loss of glutamine synthetase activity, further implicating excitotoxicity in the mechanism of Mn-induced basal ganglia injury (Deng et al. 2009). A role for early dysfunction of astrocytes is also supported by data in Mn-exposed animals demonstrating

changes in markers of astrocyte activation, such as Sβ100 and the peripheral benzodiazepine receptor, prior to any evident neuronal lesion (Hazell et al. 2003; Henriksson and Tjalve 2000). Mn also inhibits ATP-dependent intercellular calcium waves in primary cultured astrocytes (Tjalkens et al. 2006), which are critical to heterosynaptic suppression of excitatory glutamatergic synapses (Haydon and Carmignoto 2006). Thus, excessive Mn may lead to excitotoxic neuronal injury both by decreased astrocytic uptake up glutamate and by loss of ATP-mediated inhibition of glutamatergic synapses.

Gene Expression Studies

The few studies available have addressed gene expression changes in Mn-treated cells of human (Sengupta et al. 2007) or rodent origin (Baek et al. 2004; HaMai et al. 2006). In a genome-wide study on cultured human astrocytes (Sengupta et al. 2007), Mn-induced expression changes were noted in genes involved in inflammation (upregulated), DNA replication, and repair (downregulated). Gene expression on Mn-treated mice brains (Baek et al. 2004) mainly showed an upregulation of the S100β gene, and the increase of the protein was confirmed by immunohistochemistry. Instead, neurofilament subunit genes were downregulated in the striatum and in the substantia nigra. Recent work on non-human primates (Guilarte et al. 2008b) detected Mn-induced brain gene expression changes mainly affecting apoptosis, protein folding and degradation, inflammation and axonal/vesicular transport. The most up-regulated gene was APLP1, and diffuse amyloid-β plaques were documented in the frontal cortex of the Mn-treated macaques (Guilarte et al. 2008b). These interesting results could support a link between advanced manganism and dementia, as occasionally reported (Bant and Markesbery 1977). However, few animals and a partial gene set were studied. Age, Mn exposure, dosage, and treatment duration showed some variability. Also, these animals were repeatedly anesthetized to undergo i.v. injections and neuroradiological studies (Guilarte et al. 2006), and general anesthesia could have affected gene expression. Further studies are needed and will probably clarify mechanisms of toxicity triggered by this metal and relate polymorphisms in Mn transporters and affected pathways with the human sensitivity to this metal.

Diagnosis

Clinical examination alone can fail in diagnosing manganism (Racette et al. 2001), and additional assessments (occupational history, detection of nonoccupational risk factors, brain magnetic resonance imaging, Mn analyses in biological fluids) are needed. Blood Mn concentration (Mn–B) seems to reflect current exposure (when exposure fluctuates as in occupational settings) and Mn body burden (in steady exposures) (Alessio et al. 2007). While less than an ideal biomarker, Mn–B can help diagnosis and follow up. Mn–B and urinary Mn concentration (Mn–U) have both been used to discriminate occupationally exposed from non-

exposed subjects. However, Mn–U is not a reliable biomarker because the metal is mainly eliminated through the biliary system, Mn–U is highly variable, subject to contamination and does not correlate with airborne Mn in exposed populations (Apostoli et al. 2000; Smith et al. 2007). Plasma Mn is only 6% of whole-blood Mn content and is considered to have very limited utility as a biomarker of Mn load (Smith et al. 2007).

Mn is paramagnetic and detectable by MRI because the metal's atom has unpaired electrons in level 3d. MRI is the most sensitive non-invasive method of detecting Mn in the brain. Figure 2 serves to illustrate typical accumulation of Mn in brain-specific regions upon excessive occupational exposure. A semiquantitative estimate of Mn content, known as the Pallidal Index (Krieger et al. 1995) (PI, a ratio between the intensity of the T1 signal in the pallidum and that of the frontal white matter) can be calculated on brain MRIs. The metal shortens the T1 relaxation time, causing hyperintensity of T1-weighted sequences, mainly in the basal ganglia. This abnormal signal, absent in Parkinson's disease (PD), assists differential diagnosis. The signal is observable in Mn-poisoned non-human primates, symptomatic and asymptomatic Mn-exposed subjects, patients with hepatic cirrhosis, and in subjects on parenteral nutrition (Fitsanakis et al. 2006; Kim 2006) for recent reviews), hemodialysis (Ohtake et al. 2005), or with chronic iron deficiency (Herr Hernández et al. 2002). T2 scans are normal. Brain Mn analysis in non-human primates (Park et al. 2007; Shinotoh et al. 1995) and in patients with chronic liver failure (Klos et al. 2006; Krieger et al. 1995) has proven that Mn is the cause of the abnormal signal, but the relationship between that signal and onset of symptoms is still unclear. The MRI signal tends to disappear 5 months-1 year after cessation of exposure (Newland et al. 1989; Ejima et al. 1992; Kim et al. 1999; Nelson et al. 1993), but symptoms can persist and progress (Huang et al. 1993; Nelson et al. 1993) in the absence of treatment to remove Mn.

Differences between manganism and PD can be detected by clinical, neuroradiological, toxicological, and histopathological means (Olanow 2004). Degeneration of the globus pallidus, and less severely of the putamen, caudate, and substantia nigra (but not the pars compacta, a hallmark of PD) is reported in human and animal manganism (Pentschew et al. 1963; Perl and Olanow 2007; Seth and Chandra 1988); the pons, cortex, thalamus, subthalamic nuclei, hippocampus, red nucleus, cerebellum, and anterior horn of the spinal cord may also be involved. Lewy bodies, another hallmark of PD, seem to be absent in manganism (Perl and Olanow 2007). Excess Mn causes gliosis and neuronal degeneration. PET with radiolabeled fluorodopa shows reduced striatal uptake of the tracer in PD patients, while normal uptake is generally seen in manganism (Kim 2006). Manganism is also distinguishable from PD by (a) a less frequent resting tremor, (b) more frequent dystonia, (c) a particular propensity to fall backwards, (d) a general failure to achieve a sustained therapeutic response to levodopa (though controversial), as well as (e) failure to detect a reduction in fluorodopa uptake by positron emission tomography PET (Pal et al. 1999). Given these differences, some have suggested that Mn intoxication is associated with preservation of the nigrostriatal dopaminergic pathway, and that chronic Mn intoxication causes parkinsonism-like effects by damaging output pathways downstream of the

nigrostriatal dopaminergic pathway, in areas such as the globus pallidus (Pal et al. 1999), an area with propensity to accumulate high amounts of Mn. Others (Guilarte et al. 2008a) indicate a decrease of dopamine release in absence of dopaminergic neuronal degeneration.

Treatment

PD cases respond to levodopa, while the drug is currently considered ineffective in manganism (Herrero Hernández et al. 2006; Koller et al. 2004; Lu et al. 1994), presumably because the nigrostriatal pathway remains relatively intact in the latter. Moreover, levodopa is contraindicated in manganism, as Mn catalyzes dopamine autooxidation to toxic quinones and semiquinones (Graham 1984; Lloyd 1995; Parenti et al. 1988). According to some studies (Discalzi et al. 2000; Herrero Hernández et al. 2003; Herrero Hernández et al. 2006; Ky et al. 1992; Ono et al. 2002; Penalver 1957) chelating treatment can reverse manganese poisoning with persistent clinical benefit for many years (Herrero Hernández et al. 2003; Herrero Hernández et al. 2006; Jiang et al. 2006). However, large controlled clinical trials are lacking.

Chelation therapy is the indicated treatment for metal poisoning. Chelators bind metal ions in a stable form and the compound chelator + metal is then excreted by the urinary and/or biliary routes. This therapy aims to lower the body's burden of the metal and consequently its toxicity (Sánchez et al. 1995). Ethylene diamine tetraacetic acid (EDTA) is a polyaminocarboxylic acid that chelates many divalent and trivalent metals, properties that find commercial application as a metal sequestrant in food additives. However, EDTA and its sodium salt can induce severe hypocalcemia, and these compounds have frequently been misused for non-scientific indications, sometimes with fatal consequences (CDC-MMWR 2006). Only the calcium disodium salt (CaNa2EDTA), which does not induce hypocalcemia, should be used for treatment. Recent data have shown CaNa2EDTA protects renal function and tissue integrity by increasing nitric oxide levels (Foglieni et al. 2006). However, it must be administered only by trained physicians to hospitalized patients, with temporal monitoring of renal function and essential trace elements. Polyaminocarboxylic acids mobilize Mn from internal organs, enhance its excretion, and prevent mortality induced by MnCl2 in poisoned animals (Rodier et al. 1954; Tandon and Khandelwal 1982). CaNa2EDTA decreases liver and brain Mn levels in Mn-intoxicated rats (Kosai and Boyle 1956); it also decreases Mn-induced dopamine autoxidation in vitro (Nachtman et al. 1987) and inhibits serum dopamine-β-hydroxylase in humans (De Paris and Caroldi 1994), potentially preserving dopamine levels. EDTA and CaNa2EDTA increase urinary Mn excretion in humans (Cook et al. 1974; Discalzi et al. 2000; Herrero Hernández et al. 2006; Sata et al. 1998) and have been used with dubious justification to "prevent" occupational manganism (Ritter and Marti-Feced 1960; Wynter 1962).

Some studies, mostly involving extremely high occupational exposures as those found in the past or those still occurring in rapidly developing countries, reported a lack of clinical amelioration

with these chelators (Crossgrove and Zheng 2004; Huang et al. 1989; Yamada et al. 1986). In some cases (Cook et al. 1974), amelioration was observed, but not maintained. Established irreversible neuronal damage, inadequate treatment duration and/or follow-up period could explain these unsatisfactory results. Several studies (Discalzi et al. 2000; Herrero Hernández et al. 2003; Herrero Hernandez et al. 2006; Ky et al. 1992; Ono et al. 2002; Penalver 1957) have showed that CaNa2EDTA is clinically effective in the treatment of overt manganism in humans. These observations are consistent with recent therapeutic success in a severe case of genetic hypermanganesemia with extrapyramidal syndrome, polycythemia, and hepatic cirrhosis (Tuschl et al. 2008) and possibly in ephedrone-manganic syndrome cases (Selikhova et al. 2008). Early studies lacked detailed information on treatment and biomarkers, and other drugs were co-administered, thus potentially confounding the results. Recent work (Hazell et al. 2006) has also shown that the Mn chelator 1,2-cyclohexylenedinitrilotetraacetic acid (CDTA) blocked the development of pathological changes in glial cells of rats treated with MnCl2PAS-Na, an antitubercular and antiinflammatory drug, has also been suggested to be useful in occupational manganism (Jiang et al. 2006; Ky et al. 1992), but the patient with the longest follow-up was also previously treated with CaNa2EDTA (Jiang et al. 2006). PAS-Na has been reported to actually increase brain Mn concentrations in MnCl2 poisoned rodents (Sánchez et al. 1995). Large controlled clinical trials are still lacking and would be needed to establish the most efficient and less toxic treatment strategies.

Conclusions

Understanding of the pathogenesis of Mn neurotoxicity and its role in PD will have to incorporate a number of considerations/mechanisms. Future consideration should further be directed at (1) factors controlling Mn2+ uptake and distribution into the brain with emphasis on the relationship between Mn uptake and efflux in other divalent metals, in addition to Fe; (2) the apparent selectivity of dopaminergic neurons; nevertheless, it should also be considered that other neurotransmitter systems are targeted by Mn. Furthermore, on a temporal scale these systems (norepinephrine, GABA, etc.) may be more vulnerable than the dopaminergic system itself; (3) the mechanistic effects of Mn at the molecular level, improving the understanding on altered signal transduction pathways and cross talk between various neural cells; (4) the interaction between Mn exposure and genetics, vis-à-vis transport as well as the interaction between Mn and wild-type or mutant alleles of PD-associated proteins; and, finally, (5) the development of more effective diagnosis and treatments for Mn poisoning.

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References

ACGIH. (2009). Threshold limit values (TLVs®) for chemical substances and physical agents and biological exposure indices (BEIs®) Cincinnati, OH.

Alessio, L., Campagna, M., & Lucchini, R. (2007). From lead to manganese through mercury: Mythology, science, and lessons for prevention. American Journal of Industrial Medicine, 50, 779–787.

Anderson, J. G., Cooney, P. T., & Erikson, K. M. (2007). Brain manganese accumulation is inversely related to gamma-amino butyric acid uptake in male and female rats. Toxicological Sciences, 95, 188–195.

Anderson, J. G., Fordahl, S. C., Cooney, P. T., Weaver, T. L., Colyer, C. L., & Erikson, K. M. (2008). Manganese exposure alters extracellular GABA, GABA receptor and transporter protein and mRNA levels in the developing rat brain. Neurotoxicology, 29, 1044–1053.

Anderson, J. G., Fordahl, S. C., Cooney, P. T., Weaver, T. L., Colyer, C. L., & Erikson, K. M. (2009). Manganese exposure alters extracellular norepinephrine, norepinephrine receptor and transporter protein and mRNA levels in the developing rat brain. Brain Research, Submitted.

Apostoli, P., Lucchini, R., & Alessio, L. (2000). Are current biomarkers suitable for the assessment of manganese exposure in individual workers? American Journal of Industrial Medicine, 37, 283–290.

Aschner, M., & Dorman, D. C. (2007). Manganese: Pharmacokinetics and molecular mechanisms of brain uptake. Toxicological Reviews, 25, 147–154.

Aschner, M., Gannon, M., & Kimelberg, H. K. (1992). Manganese uptake and efflux in cultured rat astrocytes. Journal of Neurochemistry, 58, 730–735.

Aschner, M., Guilarte, T. R., Schneider, J. S., & Zheng, W. (2007). Manganese: Recent advances in understanding its transport and neurotoxicity. Toxicology and Applied Pharmacology, 221, 131–147.

Ashizawa, R. (1927). Uber einen sektionsfall von chronischer manganvergiftung. Jap J Med Sci Trans, Sect VIII-Int Med Pediat Psychiat, 1, 173–191.

Autissier, N., Rochette, L., Dumas, P., Beley, A., Loireau, A., & Bralet, J. (1982). Dopamine and norepinephrine turnover in various regions of the rat brain after chronic manganese chloride administration. Toxicology, 24, 175–182.

Baek, S. Y., Cho, J. H., Kim, E. S., Kim, H. J., Yoon, S., Kim, B. S., et al. (2004). CDNA array analysis of gene expression profiles in brain of mice exposed to manganese. Industrial Health, 42, 315–320.

Bant, R. G., & Markesbery, W. R. (1977). Elevated manganese levels associated with dementia and extrapyramidal signs. Neurology, 27, 213.

Barhoumi, R., Faske, J., Liu, X., & Tjalkens, R. B. (2004). Manganese potentiates lipopolysaccharide-induced expression of NOS2 in C6 glioma cells through mitochondrial-dependent activation of nuclear factor kappaB. Brain Research Molecular Brain Research, 122, 167–179.

Bertinet, D. B., Tinivella, M., Balzola, F. A., de Francesco, A., Davini, O., Rizzo, L., et al. (2000). Brain manganese deposition and blood levels in patients undergoing home parenteral nutrition. JPEN. Journal of Parenteral and Enteral Nutrition, 24, 223–227.

Bikashvili, T. Z., Shukakidze, A. A., & Kiknadze, G. I. (2001). Changes in the ultrastructure of the rat cerebral cortex after oral doses of manganese chloride. Neuroscience and Behavioral Physiology, 31, 385–389.

Bock, N. A., Paiva, F. F., Nascimento, G. C., Newman, J. D., & Silva, A. C. (2008). Cerebrospinal fluid to brain transport of manganese in a non-human primate revealed by MRI. Brain Research, 1198, 60–170.

Boojar, M. M., Goodarzi, F., & Basedaghat, M. A. (2002). Long-term follow-up of workplace and well water manganese effects on iron status indexes in manganese miners. Archives of Environmental Health, 57, 519–528.

Bouchard, M., Mergler, D., Baldwin, M., Panisset, M., Bowler, R., & Roels, H. A. (2007). Neurobehavioral functioning after cessation of manganese exposure: A follow-up after 14 years. American Journal of Industrial Medicine, 50, 831–840.

Bowman, A., Erikson, K. M., & Aschner, M. (2009). Manganese: The Two faces of essentiality and neurotoxicity. In Huang S, Ed. Metals and neurodegeneration. Kerala, India: Research Signpost.

Brouillet, E. P., Shinobu, L., McGarvey, U., Hochberg, F., & Beal, M. F. (1993). Manganese injection into the rat striatum produces excitotoxic lesions by impairing energy metabolism. Experimental Neurology, 120, 89–94.

Burton, N. C., Schneider, J. S., Syversen, T., & Guilarte, T. S. (2009). Effects of chronic manganese exposure on glutamatergic and GABAergic neurotransmitter markers in the non-human primate brain. Toxicological Sciences [Epub ahead of print]. PMID: 19520674.

Calne, D. B., Chu, N. S., Huang, C. C., Lu, C. S., & Olanow, W. (1994). Manganism and idiopathic parkinsonism: Similarities and differences. Neurology, 44, 1583–1586.

CDC-MMWR. (2006). Deaths associated with hypocalcemia from chelation therapy-Texas, Pennsylvania and Oregon, 2003-2005. 55, 204–207.

Cersosimo, M. G., & Koller, W. C. (2006). The diagnosis of manganese-induced parkinsonism. Neurotoxicology, 27, 340–346.

Chandra, S. V., Murthy, R. C., Husain, T., & Bansal, S. K. (1984). Effect of interaction of heavy metals on (Na+-K+) ATPase and the uptake of 3H-DA and 3H-NA in rat brain synaptosomes. Acta pharmacologica et toxicologica, 54, 210–213.

Chang, J. Y., & Liu, L. Z. (1999). Manganese potentiates nitric oxide production by microglia. Brain Research. Molecular Brain Research, 68, 22–28.

Chen, C. J., Ou, Y. C., Lin, S. Y., Liao, S. L., Chen, S. Y., & Chen, J. H. (2006). Manganese modulates pro-inflammatory gene expression in activated glia. Neurochemistry International, 49(1), 62–71.

Cook, D. G., Fahn, S., & Brait, K. A. (1974). Chronic manganese intoxication. Archives of Neurology, 30, 59–64.

Cotzias, G. C., & Greenough, J. J. (1958). The high specificity of the manganese pathway through the body. Journal of Clinical Investigation, 37, 1298–1305.

Couper, J. (1837). On the effects of black oxide of manganese when inhaled into the lungs. British Annals Medical Pharma, 1, 41–42.

Crossgrove, J. S., Allen, D. D., Bukaveckas, B. L., Rhineheimer, S. S., & Yokel, R. A. (2003). Manganese distribution across the blood-brain barrier. I. Evidence for carrier-mediated influx of manganese citrate as well as manganese and manganese transferrin. Neurotoxicology, 24, 3–13.

Crossgrove, J., & Zheng, W. (2004). Manganese toxicity upon overexposure. NMR in Biomedicine, 17, 544–553.

da Silva, C. J., da Rocha, A. J., Jeronymo, S., Mendes, M. F., Milani, F. T., Maia, A. C., Jr., et al. (2007). A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: Manganism symptoms and T1 hyperintense changes in the basal ganglia. American Journal of Neuroradiology, 28, 1474–1479.

de Bie, R. M., Gladstone, R. M., Strafella, A. P., Ko, J. H., & Lang, A. E. (2007). Manganese-induced Parkinsonism associated with methcathinone (Ephedrone) abuse. Archives of Neurology, 64, 886–889.

De Paris, P., & Caroldi, S. (1994). In vivo inhibition of serum dopamine-beta-hydroxylase by CaNa2EDTA injection. Human and Experimental Toxicology, 13, 253–256.

Deitmer, J. W., Broer, A., & Broer, S. (2003). Glutamine efflux from astrocytes is mediated by multiple pathways. Journal of Neurochemistry, 87, 127–135.

Deng, Y., Xu, Z., Xu, B., Tian, Y., Deng, X., Xin, X., & Gao, J. (2009). Excitotoxicity in rat's brain induced by exposure of manganese and neuroprotective effects of pinacidil and nimodipine. Biological Trace Element Research [Epub ahead of print]. PMID: 19300915.

Discalzi, G., Pira, E., Herrero Hernández, E., Valentini, C., Turbiglio, M., & Meliga, F. (2000). Occupational Mn parkinsonism: Magnetic resonance imaging and clinical patterns following CaNa2-EDTA chelation. Neurotoxicology, 21, 863–866.

Eide, D. J. (2004). The SLC39 family of metal ion transporters. Pflugers Archives. European Journal of Physiology, 447, 796–800.

Ejima, A., Imamura, T., Nakamura, S., et al. (1992). Manganese intoxication during total parenteral nutrition. Lancet, 339, 426.

Embden, H. (1901). Zur kenntiss der metallischen nervendgifte. Deutsche medizinische Wochenschrift, 27, 795–796.

Erikson, K., & Aschner, M. (2002). Manganese causes differential regulation of glutamate transporter (GLAST) taurine transporter and metallothionein in cultured rat astrocytes. Neurotoxicology, 23, 595–602.

Erikson, K. M., Dorman, D. C., Lash, L. H., & Aschner, M. (2008). Duration of airborne-manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. Neurotoxicology, 29, 377–385.

Fairhall, L. T., & Neal, P. A. (1943). Industrial manganese poisoning. National Institute of Health Bulletin No. 182, Washington DC, US Govt. Print. Off., 1–24.

Fell, J. M., Reynolds, A. P., Meadows, N., Khan, K., Long, S. G., Quaghebeur, G., et al. (1996). Manganese toxicity in children receiving long-term parenteral nutrition. Lancet, 347, 1218–1221.

Filipov, N. M., Seegal, R. F., & Lawrence, D. A. (2005). Manganese potentiates in vitro production of proinflammatory cytokines and nitric oxide by microglia through a nuclear factor kappa B-dependent mechanism. Toxicological Sciences, 84, 139–148.

Finkelstein, M. M., & Jerrett, M. (2007). A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. Environmental Research, 104, 420–432.

Fitsanakis, V. A., Zhang, N., Anderson, J. G., Erikson, K. M., Avison, M. J., Gore, J. C., et al. (2008). Measuring brain manganese and iron accumulation in rats following 14 weeks of low-dose manganese treatment using atomic absorption spectroscopy and magnetic resonance imaging. Toxicological Sciences, 103, 116–124.

Fitsanakis, V. A., Zhang, N., Avison, M. J., Gore, J. C., Aschner, J. L., & Aschner, M. (2006). The use of magnetic resonance imaging (MRI) in the study of manganese neurotoxicity. Neurotoxicology, 27, 798–806.

Foglieni, C., Fulgenzi, A., Ticozzi, P., Pellegatta, F., Sciorati, C., Belloni, D., et al. (2006). Protective effect of EDTA preadministration on renal ischemia. BMC Nephrology, 7, 5.

Foulkes, E. C., & McMullen, D. M. (1987). Kinetics of transepithelial movement of heavy metals in rat jejunum. American Journal of Physiology, 253, G134–G138.

Galindo, A., Del Arco, A., & Mora, F. (1999). Endogenous GABA potentiates the potassium-induced release of dopamine in striatum of the freely moving rat: A microdialysis study. Brain Research Bulletin, 50, 209–214.

Gao, G., Wu, Y., & Guo, Y. (2003). Survey on chronic occupational hazards in welders. Chinese Journal Industrial Medicine, 16, 107.

Garcia, S. J., Gellein, K., Syversen, T., & Aschner, M. (2006). A manganese-enhanced diet alters brain metals and transporters in the developing rat. Toxicological Sciences, 92, 516–525.

Garcia, S. J., Gellein, K., Syversen, T., & Aschner, M. (2007). Iron deficient and manganese supplemented diets alter metals and transporters in the developing rat brain. Toxicological Sciences, 95, 205–214.

Gavin, C. E., Gunter, K. K., & Gunter, T. E. (1990). Manganese and calcium efflux kinetics in brain mitochondria. Relevance to manganese toxicity. The Biochemical Journal, 266, 329–334.

Gavin, C. E., Gunter, K. K., & Gunter, T. E. (1992). Mn2+ sequestration by mitochondria and inhibition of oxidative phosphorylation. Toxicology and Applied Pharmacology, 115, 1–5.

Gerson, R. J., & Shaikh, Z. A. (1984). Differences in the uptake of cadmium and mercury by rat hepatocyte primary cultures. Role of a sulfhydryl carrier. Biochemical Pharmacology, 33, 199–203.

Girijashanker, K., He, L., Soleimani, M., Reed, J. M., Li, H., Liu, Z., et al. (2008). Slc39a14 gene encodes ZIP14, a metal/bicarbonate symporter: Similarities to the ZIP8 transporter. Molecular Pharmacology, 73, 1413–1423.

Graham, D. G. (1984). Catecholamine toxicity: A proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson’s disease. Neurotoxicology, 5, 83–95.

Guilarte, T. R., Burton, N. C., McGlothan, J. L., et al. (2008a). Impairment of nigrostriatal dopamine neurotransmission by manganese is mediated by pre-synaptic mechanism(s): Implications to manganese-induced parkinsonism. Journal of Neurochemistry, 107, 1236–1247.

Guilarte, T. R., Burton, N. C., Verina, T., Prabhu, V. V., Becker, K. G., Syversen, T., et al. (2008b). Increased APLP1 expression and neurodegeneration in the frontal cortex of manganese-exposed non-human primates. Journal of Neurochemistry, 105, 1948–1959.

Guilarte, T. R., McGlothan, J. L., Degaonkar, M., Chen, M. K., Barker, P. B., Syversen, T., et al. (2006). Evidence for cortical dysfunction and widespread manganese accumulation in the nonhuman primate brain following chronic manganese exposure: A 1H-MRS and MRI study. Toxicological Sciences, 94, 351–358.

Gunter, T. E., Gavin, C. E., Aschner, M., & Gunter, K. K. (2006). Speciation of manganese in cells and mitochondria: a search for the proximal cause of manganese neurotoxicity. Neurotoxicology, 27, 765–776.

Gupta, S. K., Murthy, R. C., & Chandra, S. V. (1980). Neuromelanin in manganese-exposed primates. Toxicology Letters, 6, 17–20.

Gwiazda, R. H., Lee, D., Sheridan, J., & Smith, D. R. (2002). Low cumulative manganese exposure affects striatal GABA but not dopamine. Neurotoxicology, 23, 69–76.

Haest, C. W., Kamp, D., Plasa, G., & Deuticke, B. (1977). Intra- and intermolecular cross-linking of membrane proteins in intact erythrocytes and ghosts by SH-oxidizing agents. Biochimica et Biophysica Acta, 469, 226–230.

HaMai, D., Rinderknecht, A. L., Guo-Sharman, K., Kleinman, M. T., & Bondy, S. C. (2006). Decreased expression of inflammation-related genes following inhalation exposure to manganese. Neurotoxicology, 27, 395–401.

Hauser, R. A., Zesiewicz, T. A., Rosemurgy, A. S., Martinez, C., & Olanow, C. W. (1994). Manganese intoxication and chronic liver failure. Annals of Neurology, 36, 871–875.

Haydon, P. G., & Carmignoto, G. (2006). Astrocyte control of synaptic transmission and neurovascular coupling. Physiological Reviews, 86, 1009–1031.

Hazell, A. S., Normandin, L., Nguyen, B., & Kennedy, G. (2003). Upregulation of ‘peripheral-type’ benzodiazepine receptors in the globus pallidus in a sub-acute rat model of manganese neurotoxicity. Neuroscience Letters, 349, 13–16.

Hazell, A. S., Normandin, L., Norenberg, M. D., Kennedy, G., & Yi, J. H. (2006). Alzheimer type II astrocytic changes following sub-acute exposure to manganese and its prevention by antioxidant treatment. Neuroscience Letters, 396, 167–171.

He, L., Girijashanker, K., Dalton, T. P., et al. (2006). ZIP8, member of the solute-carrier-39 (SLC39) metal-transporter family: characterization of transporter properties. Molecular Pharmacology, 70, 171–180.

Hearn, A. S., Stroupe, M. E., Cabelli, D. E., Ramilo, C. A., Luba, J. P., Tainer, J. A., et al. (2003). Catalytic and structural effects of amino acid substitution at histidine 30 in human manganese superoxide dismutase: Insertion of valine C gamma into the substrate access channel. Biochemistry, 42, 2781–2789.

Henriksson, J., & Tjalve, H. (2000). Manganese taken up into the CNS via the olfactory pathway in rats affects astrocytes. Toxicological Sci, 55, 392–398.

Herrero Hernández, E., Discalzi, G., Dassi, P., Jarre, L., & Pira, E. (2003). Manganese intoxication: the cause of an inexplicable epileptic syndrome in a 3 year old child. Neurotoxicology, 24, 633–639.

Herrero Hernández, E., Discalzi, G., Valentini, C., Venturi, F., Chiò, A., Carmellino, C., et al. (2006). Follow-up of patients affected by manganese-induced Parkinsonism after treatment with CaNa2EDTA. Neurotoxicology, 27, 333–339.

Herrero Hernández, E., Valentini, M. C., & Discalzi, G. (2002). T1-weighted hyperintensity in basal ganglia at brain magnetic resonance imaging: are different pathologies sharing a common mechanism? Neurotoxicology, 23, 669–674.

Hirsch, E. C., Hunot, S., Damier, P., & Faucheux, B. (1998). Glial cells and inflammation in Parkinson's disease: A role in neurodegeneration? Annals of Neurology, 44, S115–S120.

Holbrook, Jr. D. J. (1976). Assessment of the toxicity of automotive emissions, Vol. II. EPA 6001-76-010b.

HSBC. (2003). "BOC group-litigation a real risk". Personal injury litigation against welding rod manufacturers. Hazardous Times GeneralCologneRe. http://www.facworld.com/WebLib.NSF/Object/HazardTimesApril2003.pdf/$File/HazardTimesApril2003.pdf.

Huang, C. C., Chu, N. S., Lu, C. S., Chen, R. S., Schulzer, M., & Calne, D. B. (2007). The natural history of neurological manganism over 18 years. Parkinsonism Related Disorders, 13, 143–145.

Huang, C. C., Chu, N. S., Lu, C. S., Wang, J. D., Tsai, J. L., Tzeng, J. L., et al. (1989). Chronic manganese intoxication. Archives of Neurology, 46, 1104–1106.

Huang, C. C., Lu, C. S., Chu, N. S., et al. (1993). Progression after chronic manganese exposure. Neurology, 43, 1479–1483.

Jiang, Y. M., Mo, X. A., Du, F. Q., Hochberg, F., Lilienfeld, D., Olanow, W., et al. (2006). Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: A case of 17-year follow-up study. Journal of Occupational and Environmental Medicine, 48, 644–649.

Kawamura, R., Ikuta, H., Fukuzumi, S., Yamadaa, R., Tsubaki, S., Kodama, T., et al. (1941). Intoxication by manganese in well water. The Kitasato Archives Experimental Medicine, 18, 145–169.

Keen, C. L., Ensunsa, J. L., & Clegg, M. S. (2000). Manganese metabolism in animals and humans including the toxicity of manganese. Metal Ions in Biological Systems, 37, 89–121.

Keen, C. L., & Leach, R. M. (1987). In H. G. Seiler, H. Sigel, & A. Sigel (Eds.), Handbook on toxicity of inorganic compounds (pp. 405–415). New York: Marcel Dekker.

Kessler, K. R., Wunderlich, G., Hefter, H., & Seitz, R. J. (2003). Secondary progressive chronic manganism associated with markedly decreased striatal D2 receptor density. Movement Disorders, 18, 217–219.

Kim, Y. (2006). Neuroimaging in manganism. Neurotoxicology, 27, 369–372.

Kim, Y., Kim, J. W., Ito, K., Lim, H. S., Cheong, H. K., Kim, J. Y., et al. (1999). Idiopathic parkinsonism with superimposed manganese exposure: Utility of positron emission tomography. Neurotoxicology, 20, 249–252.

Kim, Y., Kim, J. M., Kim, J. W., Yoo, C. I., Lee, C. R., Lee, J. H., et al. (2002). Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure: what does it mean? Movement Disorders, 17, 568–575.

Kim, Y., Park, J. K., Choi, Y., Yoo, C. I., Lee, C. R., Lee, H., et al. (2005). Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology, 26, 107–111.

Klos, K. J., Ahlskog, J. E., Kumar, N., Cambern, S., Butz, J., Burritt, M., et al. (2006). Brain metal concentrations in chronic liver failure patients with pallidal T1 MRI hyperintensity. Neurology, 67, 1984–1989.

Koller, W. C., Lyons, K. E., & Truly, W. (2004). Effect of levodopa treatment for parkinsonism in welders: A double-blind study. Neurology, 62, 730–733.

Komaki, H., Maisawa, S., Sugai, K., Kobayashi, Y., & Hashimoto, T. (1999). Tremor and seizures associated with chronic manganese intoxication. Brain and Development, 21, 122–124.

Koos, T., & Tepper, J. M. (1999). Inhibitory control of neostriatal projection neurons by GABAergic interneurons. Nature Neuroscience, 2, 467–472.

Kosai, M. F. & Boyle, A. J. (1956). Ethylenediaminetetraacetic acid in manganese poisoning of rats. Industrial Medicine and Surgery, 25(1), 1–3.

Kowaltowski, A. J., Castilho, R. F., & Vercesi, A. E. (1995). Ca(2+)-induced mitochondrial membrane permeabilization: Role of coenzyme Q redox state. American Journal of Physiology, 269, 141–147.

Krachler, M., & Rossipal, E. (2000). Concentrations of trace elements in extensively hydrolysed infant formulae and their estimated daily intakes. Annals of Nutrition and Metabolism, 44, 68–74.

Krieger, D., Krieger, S., Jansen, O., Gass, P., Theilmann, L., & Lichtnecker, H. (1995). Manganese and chronic hepatic encephalopathy. Lancet, 346, 270–274.

Kruman, I. I., & Mattson, M. P. (1999). Pivotal role of mitochondrial calcium uptake in neural cell apoptosis and necrosis. Journal of Neurochemistry, 72, 529–540.

Ky, S. Q., Deng, H. S., Xie, P. Y., & Hu, W. (1992). A report of two cases of chronic serious manganese poisoning treated with sodium para-aminosalicylic acid. British Journal of Industrial Medicine, 49, 66–69.

Lai, J. C., Lim, L., & Davison, A. N. (1982). Effects of Cd2+, Mn2+, and Al3+ on rat brain synaptosomal uptake of noradrenaline and serotonin. Journal of Inorganic Biochemistry, 17, 215–225.

Lategan, A. J., Marien, M. R., & Colpaert, F. C. (1990). Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. Brain Research, 523, 134–138.

Levin, O. S. (2005). “Ephedron” encephalopathy. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova, 105, 12–20.

Liang, Y., & Xiang, Q. (2004). Occupational health services in PR China. Toxicology, 198, 45–54.

Liu, X., Buffington, J. A., & Tjalkens, R. B. (2005). NF-kappaB-dependent production of nitric oxide by astrocytes mediates apoptosis in differentiated PC12 neurons following exposure to manganese and cytokines. Brain Research. Molecular Brain Research, 141, 39–47.

Liu, X., Sullivan, K. A., Madl, J. E., Legare, M., & Tjalkens, R. B. (2006). Manganese-induced neurotoxicity: The role of astroglial-derived nitric oxide in striatal interneuron degeneration. Toxicological Sciences, 91, 521–531.

Lloyd, R. V. (1995). Mechanism of the manganese-catalyzed autoxidation of dopamine. Chemical Research in Toxicology, 8, 111–116.

Lonnerdal, B. (1994). Nutritional aspects of soy formula. Acta Paediatrica. Supplement, 402, 105–108.

Lu, C. S., Huang, C. C., Chu, N. S., & Calne, D. B. (1994). Levodopa failure in chronic manganism. Neurology, 44, 1600–1602.

Marien, M. R., Colpaert, F. C., & Rosenquist, A. C. (2004). Noradrenergic mechanisms in neurodegenerative diseases: A theory. Brain Research. Brain Research Reviews, 45, 38–78.

Martel, A. E., Smith, R. M., & Motekaitis, R. J. (1998). NIST critically selected stability constants of metal complexes. NIST standard references database. P. 46.

Martinez-Hernandez, A., Bell, K. P., & Norenberg, M. D. (1977). Glutamine synthetase: Glial localization in brain. Science, 195, 1356–1358.

Meral, H., Kutukcu, Y., Atmaca, B., Ozer, F., & Hamamcioglu, K. (2007). Parkinsonism caused by chronic usage of intravenous potassium permanganate. Neurologist, 13, 92–94.

Meyer, J. S., & Quenzer, L. F. (2005). Psychopharmacology: Drugs, the brain, and behavior (pp. 132–137). Sunderland, MA: Sinauer Associates.

Moreno, J. A., Sullivan, K. A., Carbone, D. L., Hanneman, W. H., & Tjalkens, R. B. (2008). Manganese potentiates nuclear factor-kappaB-dependent expression of nitric oxide synthase 2 in astrocytes by activating soluble guanylate cyclase and extracellular responsive kinase signaling pathways. Journal of Neuroscience Research, 86, 2028–2038.

Nachtman, J. P., Delor, S., & Brennan, C. E. (1987). Manganese neurotoxicity: Effects of varying oxygen tension and EDTA on dopamine auto-oxidation. Neurotoxicology, 8, 249–253.

Nelson, K., Golnick, J., Korn, T., & Angle, C. (1993). Manganese encephalopathy: Utility of early magnetic resonance imaging. British Journal of Industrial Medicine, 50, 510–513.

Newland, M. C., Ceckler, T. L., Kordower, J. H., & Weiss, B. (1989). Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. Experimental Neurology, 106, 251–258.

Normandin, L., Ann Beaupre, L., Salehi, F., St-Pierre, A., Kennedy, G., Mergler, D., et al. (2004). Manganese distribution in the brain and neurobehavioral changes following inhalation exposure of rats to three chemical forms of manganese. Neurotoxicology, 25, 433–441.

Ohtake, T., Negishi, K., Okamoto, K., Oka, M., Maesato, K., Moriya, H., et al. (2005). Manganese-induced Parkinsonism in a patient undergoing maintenance hemodialysis. American Journal of Kidney Diseases, 46, 749–753.

Olanow, C. W. (2004). Manganese-induced parkinsonism and Parkinson’s disease. Annals of the New York Academy of Sciences, 1012, 209–223.

Olanow, C. W., Good, P. F., Shinotoh, H., Hewitt, K. A., Vingerhoets, F., Snow, B. J., et al. (1996). Manganese intoxication in the rhesus monkey: A clinical, imaging, pathologic, and biochemical study. Neurology, 46, 492–498.

Ono, K., Komai, K., & Yamada, M. (2002). Myoclonic involuntary movement associated with chronic manganese poisoning. Journal of the Neurological Sciences, 199, 93–96.

Pal, P. K., Samii, A., & Calne, D. B. (1999). Manganese neurotoxicity: A review of clinical features, imaging and pathology. N eurotoxicology, 20, 227–238.

Parenti, M., Rusconi, L., Cappabianca, V., Parati, E. A., & Groppetti, A. (1988). Role of dopamine in manganese neurotoxicity. Brain Research, 473, 236–240.

Park, J. D., Chung, Y. H., Kim, C. Y., Ha, C. S., Yang, S. O., Khang, H. S., et al. (2007). Comparison of high MRI T1 signals with manganese concentration in brains of cynomolgus monkeys after 8 months of stainless steel welding-fume exposure. Inhalation Toxicology, 19, 965–971.

Penalver, R. (1957). Diagnosis and treatment of manganese intoxication; report of a case. AMA Archives of Industrial Health, 16, 64–66.

Pentschew, A., Ebner, F. F., & Kovatch, R. M. (1963). Experimental manganese encephalopathy in monkeys. A preliminary report. Journal of Neuropathology and Experimental Neurology, 22, 488–499.

Perl, D. P., & Olanow, C. W. (2007). The neuropathology of manganese-induced Parkinsonism. Journal of Neuropathology and Experimental Neurology, 66, 675–682.

Racette, B. A., McGee-Minnich, L., Moerlein, S. M., Mink, J. W., Videen, T. O., & Perlmutter, J. S. (2001). Welding-related parkinsonism: Clinical features, treatment, and pathophysiology. Neurology, 56, 8–13.

Reardan, D. T., Meares, C. F., Goodwin, D. A., McTigue, M., David, G. S., Stone, M. R., et al. (1985). Antibodies against metal chelates. Nature, 316, 265–268.

Ritter, J., & Marti-Feced, C. (1960). Trials and results of the treatment of patients with manganese poisoning and of the prevention of manganese poisoning by EDTA calcium or calcitetracemate disodium. Archives des maladies professionnelles, 21, 115–130.

Rodier, J. (1955). Manganese poisoning in Moroccan miners. British Journal of Industrial Medicine, 12, 21–35.

Rodier, J., Mallet, R., & Rodi, L. (1954). Detoxicating effects of ethylenediamine tetraacetate of calcium in experimental manganese poisoning. Archives des maladies professionnelles, 15, 210–223.

Roels, H., Sarhan, M. J., Hanotiau, I., de Fays, M., Genet, P., Bernard, A., et al. (1985). Preclinical toxic effects of manganese in workers from a Mn salts and oxides producing plant. Science of the Total Environment, 42, 201–206.

Rommelfanger, K. S., & Weinshenker, D. (2007). Norepinephrine: The redheaded stepchild of Parkinson's disease. Biochemical Pharmacology, 74, 177–190.

Rosenstock, H. A., Simons, D. G., & Meyer, J. S. (1971). Chronic manganism. Neurologic and laboratory studies during treatment with levodopa. JAMA, 217, 1354–1358.

Roth, J. A., & Garrick, M. D. (2003). Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese. Biochemical Pharmacology, 66, 1–13.

Salazar, J., Mena, N., Hunot, S., Prigent, A., Alvarez-Fischer, D., Arredondo, M., et al. (2008). Divalent metal transporter 1 (DMT1) contributes to neurodegeneration in animal models of Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America, 105, 18578–18583.

Sánchez, D. J., Gómez, M., Domingo, J. L., Llobet, J. M., & Corbella, J. (1995). Relative efficacy of chelating agents on excretion and tissue distribution of manganese in mice. Journal of Applied Toxicology, 15, 285–288.

Sanotsky, Y., Lesyk, R., Fedoryshyn, L., Komnatska, I., Matviyenko, Y., & Fahn, S. (2007). Manganic encephalopathy due to "ephedrone" abuse. Movement Disorders, 22, 1337–1343.

Sata, F., Araki, S., Murata, K., & Aono, H. (1998). Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: Observations in metal workers. Journal of Toxicology and Environmental Health. Part A, 54, 167–178.

Scholten, J. M. (1953). On manganese encephalopathy; description of a case. Folia psychiatrica, neurologica et neurochirurgica Neerlandica, 56, 878–884.

Selikhova, M., Fedoryshyn, L., Matviyenko, Y., Komnatska, I., Kyrylchuk, M., Krolicki, L., et al. (2008). Parkinsonism and dystonia caused by the illicit use of ephedrone—a longitudinal study. Movement Disorders, 23, 2224–2231.

Sengupta, A., Mense, S. M., Lan, C., Zhou, M., Mauro, R. E., Kellerman, L., et al. (2007). Gene expression profiling of human primary astrocytes exposed to manganese chloride indicates selective effects on several functions of the cells. Neurotoxicology, 28, 478–489.

Seth, P. K., & Chandra, S. V. (1984). Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese poisoning. Neurotoxicology, 5, 67–76.

Seth, P. K., & Chandra, S. V. (1988). Neurotoxic effects of manganese. III Neuropathological changes in manganese intoxication. In S. C. Bondy & K. N. Prasad (Eds.), Metal neurotoxicity (pp. 22–23). Boca Raton, FL: CRC Press Inc.

Shinotoh, H., Snow, B. J., Chu, N. S., Huang, C. C., Lu, C. S., Lee, C., et al. (1997). Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: A positron emission tomography study. Neurology, 48, 1053–1056.

Shinotoh, H., Snow, B. J., Hewitt, K. A., Pate, B. D., Doudet, D., Nugent, R., et al. (1995). MRI and PET studies of manganese-intoxicated monkeys. Neurology, 45, 1199–1204.

Shishova, E. Y., Di Costanzo, L., Emig, F. A., Ash, D. E., & Christianson, D. W. (2009). Probing the specificity determinants of amino acid recognition by arginase. Biochemistry, 48, 121–131.

Sikk, K., Taba, P., Haldre, S., Bergquist, J., Nyholm, D., Zjablov, G., et al. (2007). Irreversible motor impairment in young addicts—ephedrone, manganism or both? Acta Neurologica Scandinavica, 115, 385–389.

Singh, J., Husain, R., Tandon, S. K., Seth, P. K., & Chandra, S. V. (1974). Biochemical and histopathological alterations in early manganese toxicity in rats. Environmental Physiology and Biochemistry, 4, 16–23.

Smith, A. D., & Bolam, J. P. (1990). The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends in Neurosciences, 13, 259–265.

Smith, D., Gwiazda, R., Bowler, R., Roels, H., Park, R., Taicher, C., et al. (2007). Biomarkers of Mn exposure in humans. American Journal of Industrial Medicine, 50, 801–811.

Snyder, R. M., Mirabelli, C. K., & Crooke, S. T. (1986). Cellular association, intracellular distribution, and efflux of auranofin via sequential ligand exchange reactions. Biochemical Pharmacology, 35, 923–932.

Sonnewald, U., Westergaard, N., Krane, J., Unsgård, G., Petersen, S. B., & Schousboe, A. (1991). First direct demonstration of preferential release of citrate from astrocytes using [13C]NMR spectroscopy of cultured neurons and astrocytes. Neuroscience Letters, 128, 235–239.

Spranger, M., Schwab, S., Desiderato, S., Bonmann, E., Krieger, D., & Fandrey, J. (1998). Manganese augments nitric oxide synthesis in murine astrocytes: A new pathogenetic mechanism in manganism? Experimental Neurology, 149, 277–283.

Struve, M. F., McManus, B. E., Wong, B. A., & Dorman, D. C. (2007). Basal ganglia neurotransmitter concentrations in rhesus monkeys following subchronic manganese sulfate inhalation. American Journal of Industrial Medicine, 50, 772–778.

Takeda, A. (2003). Manganese action in brain function. Brain Research. Brain Research Reviews, 41, 79–87.

Tandon, S. K., & Khandelwal, S. (1982). Chelation in metal intoxication. XII. Antidotal efficacy of chelating agents on acute toxicity of manganese. Archives of Toxicology, 50, 19–25.

Tekkok, S. B., Brown, A. M., Westenbroek, R., Pellerin, L., & Ransom, B. R. (2005). Transfer of glycogen-derived lactate from astrocytes to axons via specific monocarboxylate transporters supports mouse optic nerve activity. Journal of Neuroscience Research, 81, 644–652.

Tjalkens, R. B., Liu, X., Mohl, B., Wright, T., Moreno, J. A., Carbone, D. L., et al. (2008). The peroxisome proliferator-activated receptor-gamma agonist 1, 1-bis(3′-indolyl)-1-(p-trifluoromethylphenyl)methane suppresses manganese-induced production of nitric oxide in astrocytes and inhibits apoptosis in cocultured PC12 cells. Journal of Neuroscience Research, 86, 618–629.

Tjalkens, R. B., Zoran, M. J., Mohl, B., & Barhoumi, R. (2006). Manganese suppresses ATP-dependent intercellular calcium waves in astrocyte networks through alteration of mitochondrial and endoplasmic reticulum calcium dynamics. Brain Research, 1113, 210–219.

Troadec, J. D., Marien, M., Darios, F., Hartmann, A., Ruberg, M., Colpaert, F., et al. (2001). Noradrenaline provides long-term protection to dopaminergic neurons by reducing oxidative stress. Journal of Neurochemistry, 79, 200–210.

Tuschl, K., Mills, P. B., Parsons, H., Malone, M., Fowler, D., Bitner-Glindzicz, M., et al. (2008). Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—a new metabolic disorder. Journal of Inherited Metabolic Disease, 31, 151–163.

von Jaksch, R. (1907). Uber mangantoxikosen und manganophobie. Münchener medizinische Wochenschrift, 20, 969–972.

Voss, H. (1939). Progressive bulbarparalyse und amyotrophische lateralsklerose nach chronischer manganvergiftung. Archives of Bewerbepath Bewerbehyg, 9, 464–476.

Walsh, M. P. (2007). The global experience with lead in gasoline and the lessons we should apply to the use of MMT. American Journal of Industrial Medicine, 50, 853–860.

Wang, X. (2003). Analysis of health conditions of 1160 welders. Occupation and Health. 19.

Wang, D., Zhou, W., & Wang, S. (2001). Hazard of manganese exposure to the welders. Chinese Journal of Industrial Medicine, 14, 114–115.

Wasserman, G. A., Liu, X., Parvez, F., et al. (2006). Water manganese exposure and children’s intellectual function in Araihazar, Bangladesh. Environmental Health Perspectives, 114, 124–129.

Wedler, F. C., Ley, B. W., & Grippo, A. A. (1989). Manganese(II) dynamics and distribution in glial cells cultured from chick cerebral cortex. Neurochemical Research, 14, 1129–1135.

Woolf, A., Wright, R., Amarasiriwardena, C., & Bellinger, D. (2002). A child with chronic manganese exposure from drinking water. Environmental Health Perspectives, 110, 613–616.

Wynter, J. E. (1962). The prevention of manganese poisoning. Industrial Medicine and Surgery, 31, 308–310.

Xu, B., Xu, Z. F., & Deng, Y. (2009). Protective effects of MK-801 on manganese-induced glutamate metabolism disorder in rat striatum. Experimental and Toxicologic Pathology [Epub ahead of print]. PMID: 19540097.

Yamada, M., Ohno, S., Okayasu, I., Okeda, R., Hatakeyama, S., Watanabe, H., et al. (1986). Chronic manganese poisoning: A neuropathological study with determination of manganese distribution in the brain. Acta Neuropathologica, 70, 273–278.

Zecca, L., Stroppolo, A., Gatti, A., Tampellini, D., Toscani, M., Gallorini, M., et al. (2004). The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. Proceedings of the National Academy of Sciences of the United States of America, 101, 9843–9848.

Zhang, S., Zhou, Z., & Fu, J. (2003). Effect of manganese chloride exposure on liver and brain mitochondria function in rats. Environmental Research, 93, 149–157.

Zheng, W., Ren, S., & Graziano, J. H. (1998). Manganese inhibits mitochondrial aconitase: A mechanism of manganese neurotoxicity. Brain Research, 799, 334–342.

Zwingmann, C., Leibfritz, D., & Hazell, A. S. (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. Journal of Cerebral Blood Flow and Metabolism, 23, 756–771.

Zwingmann, C., Leibfritz, D., & Hazell, A. S. (2004). Brain energy metabolism in a sub-acute rat model of manganese neurotoxicity: An ex vivo nuclear magnetic resonance study using [1–13C]glucose. Neurotoxicology, 25, 573–587.