Genetic factors and manganese-induced neurotoxicity

Pan Chen, Nancy Parmalee and Michael Aschner*

Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, USA

INTRODUCTION

Manganese (Mn) is a trace metal required for normal physiological processes in humans. Mn levels are tightly regulated, as high levels of Mn result in accumulation in the brain and cause a neurological disease known as manganism. Manganism shares many similarities with Parkinson's disease (PD), both at the physiological level and the cellular level. Exposure to high Mn-containing environments increases the risk of developing manganism. Mn is absorbed primarily through the intestine and then released in the blood. Excessive Mn is secreted in the bile and excreted in feces. Mn enters and exits cells through a number of non-specific importers localized on the cell membrane. Mutations in one of the Mn exporters, SLC30A10 (solute carrier family 30, member 10), result in Mn induced toxicity.

Keywords: manganese, manganism, Parkinson's disease, neurotoxicity

NEUROTOXICITY INDUCED BY Mn EXPOSURE

HISTORY AND SYMPTOMS OF MANGANISM

Manganese toxicity was first described by Couper (1837) reporting his observations of five manganese ore crushers with muscular weakness, paraplegia, tremor, whispering speech, and a tendency to lean forward while walking. In two of the workers, symptoms progressed even after removal from the Mnore crushing operations. The remaining three workers were removed from Mn exposure at the first signs of muscle weakness in the lower extremities. In these workers, onset of symptoms occurred after months to years of work. In contrast, Racette (2013) noted that contemporary exposures are much lower, and onset of symptoms tends
to occur after years or decades of exposure. Mena described Mn turnover in patients compared to healthy miners using injected 54Mn radioisotope and found significantly faster turnover rates in the healthy miners as compared to miners diagnosed with manganism. Huang described six patients who worked in a factory with inadequate ventilation. Follow up studies on these patients indicate that after removal from Mn exposure, their symptoms continued to worsen for approximately ten years, after which their condition remained constant with severe extrapyramidal dysfunction (Huang et al., 1993, 1998, 2007). Early features of manganism include weakness, anorexia, behavioral, and psychiatric disturbances, difficulty sleeping, impotence, and attention disorders. This early stage is characterized by emotional liability that has been termed “manganese madness.” Patients have described an awareness that their behavior is unusual or abnormal, but an inability to control their outward affect. There is some evidence that if Mn exposure is discontinued at an early stage, these symptoms may revert. However, with acute exposure, progression often occurs even after Mn exposure has ceased. MRI shows clearing of Mn from the globus pallidus (GP) in three to six months (Roth, 2009). In some patients with severe exposure, neurodegenerative signs progress even after removal from exposure. Later symptoms include extrapyramidal deficits including bradykinesia, rigidity, difficulty with gait, specifically a dystonic movement of the foot known as “cock walk,” and a tendency to fall backward. Masked facial expressions and micrographia are also present in manganism, as in PD (Couper, 1837; Rodier, 1955; Mena et al., 1967). Tremor in manganism tends to be slight or absent as compared to PD. Manganism patients do not typically respond therapeutically to L-DOPA (Shinotoh et al., 1997; Koller et al., 2004).

MANGANISM AND PARKINSON’S DISEASE: SIMILARITY AND DIFFERENCES

There is evidence that genes involved in susceptibility to PD are also involved in Mn uptake and homeostasis (discussed in more detail below), leading to the hypothesis that there are common mechanisms of neurodegeneration to manganism and PD. In each cohort, only a subset of exposed individuals developed signs of manganism. It is unknown why some individuals are apparently able to maintain Mn homeostasis in the presence of high exposures, while others accumulate toxic levels of the metal leading to neurodegeneration, or why some individuals improve following cessation of exposure, while others progress. The distinction between manganism and PD is typically made based on exposure history, however, in areas with high levels of naturally or industrially occurring Mn, PD prevalence is higher than in surrounding regions or national registries (Lucchini et al., 2007), indicating that the distinction between PD and manganism may not be entirely clear, especially for chronic, long-term exposures. Understanding the molecular genetics of Mn transport and toxicity may lead to a new understanding of the mechanisms underlying PD.

FACTORS REGULATING Mn TRANSPORT AND TOXICITY

ENVIRONMENTAL FACTORS

As the 5th most abundant metal and the 12th most abundant element on the earth, Mn is present in air, soil, and water. Mn is taken up primarily through the intestine and then circulated in the blood (Davis et al., 1993; Finley et al., 1994). Excessive Mn is secreted via the bile, returning to the intestine and excreted in feces (Davis et al., 1993; Malecki et al., 1996). Mn may also enter the human body by inhalation of fumes containing the metal (Jorge da Silva et al., 2008). It is also secreted through urine and sweat, but in smaller amounts (vs. bile; Cohn and Emmett, 1978; Davis et al., 1993).

Given the abundance of Mn in the environment, humans are exposed to different levels of Mn. Rice, nuts, whole grains, and legumes, as well as green vegetables, tea, and certain fruits contain high Mn levels (ATSDR, 2012). Food-borne Mn levels generally supply the basic dietary requirement for humans without causing disease. However, excessive exposure to environmental Mn results in toxicity. Workers in mining, welding, and smelting industries may be potentially exposed to high Mn levels (Criswell et al., 2012; Racette et al., 2012), as well as individuals residing in the vicinity of Mn associated industries. Exposures to high Mn levels have been associated with greater risk for PD (Racette et al., 2012; Smith et al., 2012). Additional exposures to Mn have been documented from gasoline, steel, fireworks, batteries, leather, glass, ceramics, cosmetics, and textiles, as well as certain pesticides and fungicides (such as Maneb and Mancozeb; ATSDR, 2012). In addition to exposure in high Mn containing environments, patients with dysfunctional biliary system (e.g., those requiring parenteral nutrition) are also more susceptible to Mn induced toxicity, as optimal liver function is required for Mn secretion. In addition, infants and children that receive Mn-containing supplements may be at risk to Mn toxicity, as younger individuals tend to absorb and maintain higher Mn levels compared to adults reflecting a greater requirement for Mn in cellular activities (Keen et al., 1986; Zlotkin et al., 1995). Iron (Fe)-deficient individuals are also at a greater risk for Mn poisoning, as the two metals compete for shared transporters (see below). In recent years, Methcathinone abuse has been linked to manganism, due to the presence of Mn as an impurity (derived from potassium permanganate; Sikk et al., 2013).

GENETIC FACTORS

Transports importing extracellular Mn (Table 1)

Mn enters cells by various transporters (importers) located at the plasma membrane. These transporters are tightly regulated, maintaining optimal Mn levels in cells. The divalent metal transporter 1 (DMT1) is the primary divalent Mn (Mn2+) transporter. It is localized at the plasma membrane (Burdo et al., 2001a) and functions to import Mn2+ from the extracellular matrix into cells (Bell et al., 1989; Aschner and Gannon, 1994; Erikson and Aschner, 2002; Garrick et al., 2003; Au et al., 2009). DMT1 is highly expressed in basal ganglia, such as SN, GP, hypothalamic nucleus, and striatum (Williams et al., 2000; Burdo et al., 2001b; Huang et al., 2004), areas that are known to accumulate high Mn levels (Suzuki et al., 1975; Newland et al., 1989; Rose et al., 1999; Ikeda et al., 2000; Jorge da Silva et al., 2008). In addition to DMT1, other transmembrane proteins also import Mn2+, including the citrate transporter (Crossgrove et al., 2003), zinc transporters ZIP8 (He et al., 2006; Himeno et al., 2009; Fujishiro et al., 2011), calcium channels (Mason, 1993; Lucaciu et al., 1997; Finley, 1998), the choline transporter (Lockman et al., 2001), dopamine transporter
Table 1 | Different types of Mn transporters in a cell.

| Types of Mn transporters | Name | Localization | Roles in Mn transportation |
|--------------------------|------|--------------|---------------------------|
| Importers                | DMT1, ZIP8, citrate transporter, calcium channels, choline transporter, DAT, ATP13A2, TIR | Plasma membrane | Import extracellular Mn into cytoplasm |
| Exporters                | Fpn, SLC30A10 | Plasma membrane | Export cytosolic Mn to extracellular matrix |
| Intracellular transporters | Ca2+-uniporter | Mitochondrial membrane | Export cytosolic Mn into the mitochondria lumen |
|                          | Na+ -independent mechanisms | Mitochondrial membrane | Export mitochondrial Mn to cytosol |
|                          | SPCA1 | Golgi membrane | Import cytosolic Mn into the Golgi lumen |

(DAT; Ingersoll et al., 1999), and a cation-transporting ATPase 13A2 (ATP13A2 or Park9; Gitler et al., 2009; Tan et al., 2011). Trivalent Mn (Mn3+) enters cells primarily via the transferrin receptor (TfR) mechanism (Morris et al., 1992). Notably, none of these proteins is a specific Mn transporter, and they transport additional metals, such as iron, calcium, zinc, etc. Currently, few human diseases are known to be associated with mutations in these importers, with the exception of Park9 and DMT1. Park9 represents a well-known risk factor for PD. High levels of Fe were found in brain due to altered DMT1 expression (Urrutia et al., 2013). Mutations in DMT1 that impair Fe transport protect rodents against parkinsonism-inducing neurotoxins, such as MPTP and 6-hydroxydopamine (Salazar et al., 2008), consistent with a role for DMT1 in Fe-mediated neurodegeneration in PD. He et al. (2011) reported that the CC haplotype in the DMT1 gene is a possible risk factor for PD in the Han Chinese population. Whether mutations in DMT1 alter Mn levels in the brains of these individuals has yet to be determined.

Transports exporting intracellular Mn (Table 1)
Cells export excessive Mn from the cytoplasm to the extracellular matrix, as high Mn levels result in cellular toxicity. Recently, ferroportin (Fpn) was recognized as putative Mn exporter. It transports extracellularly both Fe2+ and Mn2+ (Yin et al., 2010; Madejczyk and Ballatori, 2012). To date, no human diseases have been ascribed to mutations or dysfunction of this protein, indicating that Fpn is unlikely to be the primary Mn exporter. Recently, a gene named SLC30A10 (solute carrier family 30 member 10) was identified in patients with hepatic cirrhosis, dystonia, polycthemia, and hypermanganesemia, concomitant with high Mn brain levels (Quadri et al., 2012; Stamelou et al., 2012; Tuschl et al., 2012). SLC30A10 is localized at the cell membrane, and mutations in this gene either result in early truncation of this protein or amino acid substitution (Quadri et al., 2012; Stamelou et al., 2012; Tuschl et al., 2012). Interestingly, none of the patients were exposed to excessive Mn, yet they displayed symptoms consistent with PD (Quadri et al., 2012; Stamelou et al., 2012; Tuschl et al., 2012). SLC30A10 is the only protein known to cause Mn toxicity when mutated, indicating it may be a primary and a key regulator of Mn export. Our recent data have shown that the wildtype (WT) SLC30A10 protein when expressed in Caenorhabditis elegans (C. elegans), protects against Mn2+ induced lethality and DAergic neurodegeneration, as well as locomotion deficits (basal slowing response, which is regulated by DAergic neurons; unpublished data). It remains unclear whether SCL30A10 is a specific Mn exporter or if it also transports additional metals. Notably, it was originally posited to be a specific zinc transporter (Seve et al., 2004; Bosomworth et al., 2012). Further research is needed to better understand its function and a compound screen could be profitably directed at identifying specific modulators of this transporter, potentially leading to novel therapies in patients with manganese.

Intracellular Mn transporters (Table 1)
Once inside the cell, Mn is transported into various organelles to fulfill its function, thus limiting its potential toxicity from accumulating at high levels in the cytosol. The mitochondria contain the highest Mn levels (Gavin et al., 1999). Mitochondrial SOD requires Mn as a cofactor for optimal function (Borgstahl et al., 1992). The calcium (Ca2+) uniporter imports cytosolic Mn2+ into the mitochondria lumen (Drahota et al., 1969; Gunter and Puskin, 1972; Gunter et al., 1975), and excessive Mn2+ is exported out of mitochondria through sodium (Na+) -independent mechanisms (Gavin et al., 1990). The Golgi apparatus can store excessive Mn2+ and this is mediated by Ca2+/Mn2+ ATPase isofrm 1 (SPCA1). SPCA1 is localized at the Golgi membrane and imports Mn2+ from the cytosol to the Golgi lumen (Murin et al., 2006). Mn in the Golgi is secreted extracellularly through a secretary pathway. Although the nucleus also contains high levels of Mn, the transporters localized to the nuclear membrane remain unknown and future studies are needed to identify these Mn transporters.

PD-associated proteins involved in Mn-induced toxicity (Table 2)
As described above, manganese shares many similar symptoms with PD. ATP13A2 and DAT both are able to transport Mn. Notably mutations in ATP13A2 cause a parkinsonian-like syndrome, Kufor-Rakeb syndrome (KRS). KRS is an autosomal recessive disorder characterized by subacute, juvenile-onset,
Table 2 | PD-associated proteins involved in Mn-induced toxicity.

| PD-associated proteins | Cellular activity | Roles in Mn toxicity |
|------------------------|-------------------|----------------------|
| ATP13A2                | Inorganic cation transporter | Importing extracellular Mn into cytoplasm |
| DAT                    | DA transporter     | Importing extracellular Mn into cytoplasm |
| Parkin                 | E3 ubiquitin ligase | Enhancing Mn accumulation when mutated |
| DJ-1                   | Antioxidant peptidase | Enhancing Mn accumulation when mutated |
| α-synuclein            | Presynaptic protein in synaptic vesicle trafficking and recycling | Reducing Mn accumulation in parkin and DJ-1 mutants |
| UCH-L1                 | Ubiquitin ligase   | Unknown |
| NURR1                  | Transcription factor | Unknown |
| PINK1                  | Serine/threonine kinase | Unknown |
| LRRK2                  | Protein kinase     | Unknown |

and is levodopa-responsive. It is unknown whether mutations in ATP13A2 change its affinity for different cations, specifically Mn, resulting in increased Mn accumulation in the brain. DAT removes synaptic dopamine into the presynaptic membrane for recycling. In PD patients, DAT activity is significantly decreased (Sossi et al., 2007). In C. elegans, dat knockout mutants are resistant to DAergic neurodegeneration induced by Mn exposure, but show a lower survival rate (Benedetto et al., 2010). Mutations in α-synuclein, parkin, and DJ-1, all of which are associated with early onset PD, have also been shown to alter Mn transport (Bornhorst et al., 2014). α-synuclein encodes a presynaptic protein involved in synaptic vesicle trafficking and recycling (Gitler et al., 2008; Ben Gedalya et al., 2009). Point mutations (A30P and A53T) or duplication of α-synuclein result in loss of DAergic neurons concomitant with oxidative stress, protein aggregation, and Lewy bodies formation (Narhi et al., 1999; Hsu et al., 2000; Masliah et al., 2000; Kuwahara et al., 2006), the hallmarks of PD. Parkin encodes an E3 ubiquitin ligase (Shimura et al., 2000) responsible for degradation of abnormal proteins. Mutations in parkin result in DAergic neurodegeneration with increased oxidative stress, yet in the absence of Lewy bodies (Yang et al., 2006). It is known that overexpression of parkin is able to decrease α-synuclein protein aggregation (Petrucelli et al., 2002; Yang et al., 2003). DJ-1 encodes a protein of the peptidase C56 family. It functions as a peroxidase (Andres-Mateos et al., 2007), a chaperone (Shendelman et al., 2004), a metal binding protein (Björkblom et al., 2013), and a regulatory subunit of an RNA binding complex (Hod et al., 1999), thus protecting cells from oxidative stress (Mitsumoto and Nakagawa, 2001; Mitsumoto et al., 2001), α-synuclein aggregation (Zhou et al., 2009), and metal induced cell death (Björkblom et al., 2013). It also regulates androgen receptor-dependent transcription (Takahashi et al., 2001). Mutations in DJ-1 result in increased oxidative stress and DAergic neurodegeneration. Recently, Chakraborty and colleagues found that pdr-1 (worm homolog of parkin) and dfr-1.1 (worm homolog of DJ-1) mutants show enhanced Mn accumulation and increased oxidative stress in C. elegans and these effects may be reduced by expression of WT human α-synuclein (Bornhorst et al., 2014).

Interestingly, WT α-synuclein also protected against DAergic neurodegeneration induced by Mn exposure in pdr-1 (the homolog of mammalian parkin/PARK2) mutant worms (Bornhorst et al., 2014).

In addition to the above proteins, there are other PD-associated proteins whose effect on Mn-induced toxicity remains unknown. These PD genes include ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), NUR-Related factor 1 (NURR1), Pten-Induced Kinase 1 (PINK1) and Leucine-Rich Repeat Kinase 2 (LRRK2). UCH-L1 (or PARK5) is an enzyme expressed in neurons throughout the brain that hydrolyzes C-terminal ubiquitinyl esters to recycle ubiquitin after degradation of misfolded proteins (Wilkinson, 2000; Meray and Lansbury, 2007). Similar to parkin, it also functions as an ubiquitin ligase to prevent protein aggregation (Liu et al., 2002; Gong et al., 2006; Lansbury, 2006). NURR1 is a transcription factor predominantly expressed in central DAergic neurons (Bäckman et al., 1999; Jankovic et al., 2005). It is critical for development and maintenance of the DAergic system as it regulates the expression of tyrosine hydroxylase (TH; Sakurada et al., 1999), DAT (Sacchetti et al., 2001), vesicular monoamine transporter 2 (VMAT2), and aromatic L-amino acid decarboxylase (AADC; Hermanson et al., 2003). PINK1 (or PARK6) is a mitochondrial targeted serine/threonine kinase, with substrates in the cytosol (Zhou et al., 2008). Recent studies indicate that PINK1, together with parkin, is involved in a mitochondrial quality control system to regulate mitochondrial dynamics and function, and protects against cellular stress (Valente et al., 2004; Clark et al., 2006). LRRK2 or PARK8 is a protein kinase expressed preferentially in DAergic neurons (Han et al., 2008). It interacts with parkin in the cytosol and overexpression of either WT LRRK2 or gain-of-function mutants results in DAergic neurodegeneration (Smith et al., 2005). Together, these proteins either interact with parkin or have similar function to parkin. Given that parkin is involved in regulation of Mn toxicity, these PD-related proteins may play a role in Mn-induced toxicity. Future studies could be profitably directed at the studies on how mutations in these genes enhance basal ganglia Mn accumulation.
CONCLUSION
Mn is required for multiple physiological processes. It is a cofactor for various enzymes and plays important roles in mediating oxidative stress responses, regulation of immune responses, carbohydrate metabolism, energy production, cell adhesion and protein modification (Benedetto et al., 2009). Although Mn deficiency results in birth defects and poor bone development, given its abundant and ubiquitous presence in the environment, Mn overexposure represents a more critical contemporary concern. Excessive accumulation of Mn in the brain may cause DAergic neurodegeneration and manganism, the latter sharing a clinical picture analogous to PD. At the cellular level, excessive Mn levels have been associated with increased oxidative stress, impaired ATP production, protein aggregation and mitochondrial dysfunction. α-synuclein aggregation or Lewy bodies are absent in the brains of manganism patients. Given the similarities between manganism and PD, Mn is considered an important environmental factor in causing sporadic PD, especially given recent discoveries that certain PD genes (ATP13A2, parkin, DJ-1, and α-synuclein) are involved in Mn transport and/or toxicity.

Genetic factors associated with Mn toxicity remain to be explored. Several Mn importers have been identified; however, none have mutations associated with Mn related diseases. Compared to the plethora of Mn importers, knowledge about Mn exporters is limited. Fpn and SCL30A10 are the only two exporters compared to the plethora of Mn importers, knowledge about Mn transporters is limited. Fpn and SCL30A10 are the only two exporters identified to date. Among all known Mn transporters, SLC30A10 appears to be a key regulator of Mn homeostasis, given that mutations in this gene can result in manganism in the absence of overexposure to this metal. SLC30A10 localizes at the cell membrane, exports Mn from cells and affords protection in various experimental models.

Several PD associated genes, namely, either transport Mn (ATP13A2; Gitler et al., 2009; Tan et al., 2011) or mediate Mn-induced toxicity (parkin, DJ-1, and α-synuclein; Bornhorst et al., 2014). These results tightly correlate PD with Mn toxicity, supporting the idea of Mn as an environmental factor of PD. It will be of particular interest to study brain Mn levels in PD patients carrying mutations in these genes. Given the similarity between manganism and PD, it is possible that other well known PD genes (UCH-L1, NURR1, PINK1, and LRRK2) also play a role in regulating Mn homeostasis. Future studies should be focused on the relationship between PD-associated proteins and their potential to alter Mn transport and/or toxicity.

ACKNOWLEDGMENT
The manuscript was supported by NIH grant NIEHS R01 10563.

REFERENCES
Andres-Mateos, E., Perier, C., Zhang, L., Blanchard-Fillion, B., Greco, T. M., Thomas, B., et al. (2007). DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase. Proc. Natl. Acad. Sci. U.S.A. 104, 14807–14812. doi: 10.1073/pnas.0703219104
Armstrong, R. A. (2011). Visual symptoms in Parkinson’s disease. Parkinsonism Dis. 2011:908306. doi: 10.4061/2011/908306
Aschner, M. (2000). Manganese: brain transport and emerging research needs. Environ. Health Perspect. 108(Suppl. 3), 429–432. doi: 10.1289/ehp.001083429
Aschner, M. (2002). Open issues from the 15th International Conference on Manganese. Neurotoxicology 23, 123–125. doi: 10.1016/S0161-813X(01)00097-3
Aschner, M., and Gannon, M. (1994). Manganese (Mn) transport across the rat blood-brain barrier: saturable and transferrin-dependent transport mechanisms. Brain Res. Bull. 33, 345–349. doi: 10.1016/0361-9230(94)90204-6
ATSDR. (2012). Toxicological Profile for Manganese. Atlanta, GA: U.S. Department of Health and Human Services, Public Service.
Au, C., Benedetto, A., Anderson, J., Labrousse, A., Erikson, K., Ewbank, J. I., et al. (2009). S1MF-1, S1MF-2, and S1MF-3 DMT1 orthologues regulate and are regulated differentially by manganese levels in C. elegans. PLoS ONE 4:e7792. doi: 10.1371/journal.pone.007792
Bäckman, C., Perlmann, T., Wallén, Å., Hoffer, B. J., and Morales, M. (1999). A selective group of dopaminergic neurons express Nurr1 in the adult mouse brain. Brain Res. 851, 125–132. doi: 10.1016/S0006-8993(99)02149-6
Bell, J. G., Keen, C. L., and Lonnerdal, B. (1989). Higher retention of manganese in suckling than in adult rats is not due to maturational differences in manganese uptake by rat small intestine. J. Toxicol. Environ. Health 26, 387–398. doi: 10.1080/15287398909531263
Benedetto, A., Au, C., and Aschner, M. (2009). Manganese-induced dopaminergic neurodegeneration: insights into mechanisms and genetics shared with Parkinson’s disease. Chem. Rev. 109, 4862–4884. doi: 10.1021/cr800536y
Benedetto, A., Au, C., Avila, D. S., Milatovic, D., and Aschner, M. (2010). Extracellular dopamine potentiates Mn-induced oxidative stress, lifespan reduction, and dopaminergic neurodegeneration in a B10.C–dependent manner in Caenorhabditis elegans. PLoS Genet. 6:e1001084. doi: 10.1371/journal.pgen.1001084
Ben Gedalya, T., Loeb, Y., Israeli, E., Altschuler, Y., Selkoe, D. J., and Sharon, R. (2009). α-synuclein and polyunsaturated fatty acids promote clathrin-mediated endocytosis and synaptic vesicle recycling. Traffic 10, 218–234. doi: 10.1111/j.1600-0854.2008.00853.x
Bjorkblom, B., Adibayeva, A., Maple-Grudem, J., Piston, D., Okvist, M., Xu, X. M., et al. (2013). Parkinson disease protein DJ-1 binds metals and protects against metal-induced cytotoxicity. J. Biol. Chem. 288, 22809–22820. doi: 10.1074/jbc.M113.482091
Borgstahl, G. E., Parge, H. E., Hickey, M. J., Beyer, W. F. Jr., Hallewell, R. A., and Tainer, J. A. (1992). The structure of human mitochondrial manganese superoxide dismutase reveals a novel tetrameric interface of two-4-helix bundles. Cell 71, 107–118. doi: 10.1016/0092-8674(92)90270-M
Bornhorst, J., Chakraborty, S., Meyer, S., Lohren, H., Brinkhaus, S. G., Knight, A. L., et al. (2014). The effects of pdr1, djr1.1 and pink1 loss in manganese-induced toxicity and the role of α-synuclein in C. elegans. Metallomics 6, 476–490. doi: 10.1039/C3MT00325F
Bosomworth, H. J., Thornton, J. K., Coneyworth, L. J., Ford, D., and Valentine, R. A. (2012). Efflux function, tissue-specific expression and intracellular trafficking of the Zn transporter ZnT10 indicate roles in adult Zn homeostasis. Metallomics 4, 771–779. doi: 10.1039/C2MT00888K
Burdo, J. R., Menzies, S. L., Simpson, I. A., Garrick, L. M., Garrick, M. D., Dolan, K. G., et al. (2001a). Distribution of divalent metal transporter 1 and metal transport protein 1 in the normal and Belgrade rat. J. Neurosci. Res. 66, 1198–1207. doi: 10.1002/jnr.1256
Burdo, J. R., Menzies, S. L., Simpson, I. A., Garrick, L. M., Garrick, M. D., Dolan, K. G., et al. (2001b). Distribution of divalent metal transporter 1 and metal transport protein 1 in the normal and Belgrade rat. J. Neurosci. Res. 66, 1198–1207. doi: 10.1002/jnr.1256
Butterworth, R. F., Spahr, L., Fontaine, S., and Layrargues, G. P. (1995). Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metab. Brain Dis. 10, 259–267. doi: 10.1007/BF02109357
Clark, I. E., Dodson, M. W., Jiang, C., Cao, J. H., Huh, J. R., Seol, J. H., et al. (2006). Drosophila pank1 is required for mitochondrial function and interacts genetically with parkin. Nature 441, 1162–1166. doi: 10.1038/nature04779
Cohn, J. R., and Emmett, E. A. (1978). The excretion of trace metals in human sweat. Ann. Clin. Lab. Sci. 8, 270–275.
Couper, J. (1837). On the effects of black oxide manganese when inhaled into the lungs. Brit. Ann. Med. Pharm. Vital Stat. Gen. Sci. 1, 41–42.
Crishell, S. R., Perlmutter, J. S., Huang, J. L., Golchin, N., Flores, H. P., Hobson, A., et al. (2012). Basal ganglia iron indices and diffusion weighted imaging in manganese-exposed welders. Occup. Environ. Med. 69, 437–443. doi: 10.1136/oemед-2011-100119
Crossgrove, J. S., Allen, D. D., Bukaveckas, B. L., Rhineheimer, S. S., and Yokel, R. A. (2003). Manganese distribution across the blood-brain barrier. I. Evidence for carrier-mediated influx of manganese citrate as well as manganese
He, Q., Zech, L., and Greger, I. L. (1993). Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. Proc. Soc. Exp. Biol. Med. 202, 103–108. doi: 10.3838/psebm.202.2.43518

Drahoza, Z., Gazzotti, P., Carafoli, E., andRossi, C. S. (1969). A comparison of the effects of different divalent cations on a number of mitochondrial reactions linked to ion translocation. Arch. Biochem. Biophys. 130, 267–273. doi: 10.1016/0002-9941(69)90033-2

Erikson, K., and Aschner, M. (2002). Manganese causes differential regulation of glutamate transporter (GLAST) taurine transporter and metallothionein in cultured rat astrocytes. Neurotoxicology 23, 595–602. doi: 10.1016/S0161-813X(02)00112-8

Finley, J. W. (1998). Manganese uptake and release by cultured human hepatocarcinoma (Hep-G2) cells. Biol. Trace Elem. Res. 64, 101–118. doi: 10.1007/BF02783328

Finley, J. W., Johnson, P. E., and Johnson, L. K. (1994). Sex affects manganese absorption and retention by humans from a diet adequate in manganese. Am. J. Clin. Nutr. 60, 949–955.

Friberg, L., Nordberg, G., and Vouk, V. B. (1979). Handbook on the Toxicology of Metals. Amsterdam: Elsevier/North-Holland Biomedical Press.

Frost, G., Asling, C. W., and Nelson, M. M. (1959). Skeletal deformities and manganese transferrin. Neurotoxicology 64, 101–105.

Fujishiro, H., Doi, M., Enomoto, S., and Himeno, S. (2011). High sensitivity of RBL-2H3 cells to cadmium and manganese: an implication of the role of ZIP8. Metallomics 3, 710–718. doi: 10.1039/c1mt00020a

Garrick, M. D., Dolan, K. G., Horbinski, C., Ghio, A. J., Higgins, D., Porubcin, M., et al. (2003). DMT1: a mammalian transporter for multiple metals. Biometals 16, 41–54. doi: 10.1023/A:1020702213099

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

Gavin, C. E., Gunter, K. K., and Gunter, T. E. (1999). Manganese and calcium transport in mitochondrial implications for manganese toxicity. Neurotoxicology 20, 445–453.

Gitter, A. D., Bevis, B. I., Shorter, J., Strathearn, K. E., Hamamichi, S., Su, L., et al. (2008). The Parkinson’s disease protein α-synuclein disrupts cellular Rab homoeostasis. Proc. Natl. Acad. Sci. U.S.A. 105, 145–150. doi: 10.1073/pnas.0710685105

Gitter, A. D., Chesi, A., Greddie, M. L., Strathearn, K. E., Hamamichi, S., Hill, K. J., et al. (2009). α-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity. Nat. Genet. 41, 308–315. doi: 10.1038/ng.300

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Ubiquitin hydrolase Uch-L1 rescues α-synuclein-induced decreases in synaptic function and contextual memory. Cell 126, 625–635. doi: 10.1016/S0092-8674(06)00018-X

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Uch-L1 gene encodes two opposing enzymatic activities that affect α-synuclein degradation and Parkinson’s disease susceptibility. Cell 111, 209–218. doi: 10.1016/j.cell.2006.08.011

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Familial Parkinson mutant α-synuclein disrupts cerebrospinal fluid flow and increases the penetrance of the disease. Neurology 66, 730–733. doi: 10.1212/01.wnl.0000196331.16660.67

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Familial Parkinson mutant α-synuclein causes dopamine neuron dysfunction in transgenic Caenorhabditis elegans. J. Biol. Chem. 281, 334–340. doi: 10.1074/jbc.M504682002

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Familial Parkinson mutant α-synuclein causes dopaminergic neuron degeneration and Parkinson’s disease susceptibility. Cell 111, 209–218. doi: 10.1016/j.cell.2006.08.011

Gong, B., Cao, Z., Zheng, P., Vitolo, O. V., Liu, S., Staniszewski, A., et al. (2006). Familial Parkinson mutant α-synuclein causes dopaminergic neuron degeneration and Parkinson’s disease susceptibility. Cell 111, 209–218. doi: 10.1016/j.cell.2006.08.011

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782

Huang, C. C., Chen, S., and Le, W. D. (2005). The role of Nurr1 in the development and contextual memory. J. Cell Sci. 126, 655–657. doi: 10.1242/jcs.022782
Lucia, C. M., Drago, C., Copaescu, L., and Moraria, V. V. (1997). Manganese transport through human erythrocyte membranes. An EPR study. Biochim. Biophys. Acta 1328, 90–98. doi: 10.1016/S0006-2973(97)00039-4

Lucini, R., Albini, E., Placidi, D., Gasparotti, R., Pigozzi, M. G., Montani, G., et al. (2000). Brain magnetic resonance imaging and manganese exposure. Neurotoxicology 21, 769–775.

Lucini, R. G., Albini, E., Benedetti, L., Borghesi, S., Cucaglio, R., Malarza, E. C., et al. (2007). High prevalence of Parkinsonian disorders associated to manganese exposure in the vicinities of ferroalloy industries. Am. J. Ind. Med. 50, 788–800. doi: 10.1002/ajim.20494

Madejczyk, M. S., and Ballatori, N. (2012). The iron transporter ferroportin can also function as a manganese exporter. Biochim. Biophys. Acta 1818, 651–657. doi: 10.1016/j.bjba.2011.12.002

Malecki, E. A., Racette, B. A., Criswell, S. R., Lundin, J. I., Hobson, A., Seixas, N., Kozbauer, P. T., et al. (2012). Increased risk of parkinsonism associated with welding exposure. Neurotoxicology 33, 1356–1361. doi: 10.1016/j.neuro.2012.08.011

Racette, B. A., Mcgee-Minnich, L., Moelten, S. M., Mink, J. W., Videen, T. O., and Perlmutt, J. S. (2011). Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology 56, 8–13. doi: 10.1212/WNL.56.1.8

Rodier, J. (1955). Manganese poisoning in Morrocan miners. Br. J. Ind. Med. 12, 21–35. doi: 10.1136/ob.12.1.21

Roholt, O. A. Jr., and Greenberg, D. M. (1956). Liver arginase. IV. Effect of pH on brain arginase. J. Biol. Chem. 214, 222–223. doi: 10.1002/jbc.214223

Rutkowska, K., Ohshima-Sakurada, M., Palmer, T. D., and Gage, F. H. (1999). Nurr1 enhances transcription of the human dopamine transporter gene through a novel mechanism. J. Neurochem. 76, 1565–1572. doi: 10.1046/j.1471-4159.1999.01018.x

Rutkowska, K., Shirako, Y., and Uehara, S. (2012). Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia and chronic liver disease. J. Neuropsychiatry Clin. Neurosci. 24, 223–236; discussion 222. doi: 10.1176/appi.neuropsych.14.2.223

Sandstead, H. H. (1986). A brief history of the influence of trace elements on brain function. Am. J. Clin. Nutr. 43, 293–298.

Seve, M., Chimenti, F., Ferragina, S., and Favier, A. (2004). In silico identification and expression of SLC30A10 family genes: an expressed sequence tag data mining strategy for the characterization of zinc transporters’ tissue expression. BMC Genomics 5:32. doi: 10.1186/1471-2164-5-32

Shemshed, S., Jonason, A., Martinat, C., Leete, T., and Abeleivich, O. (2004). DJ-1 is a redox-dependent molecular chaperone that inhibits α-synuclein aggregation. PLoS Biol. 2:e63. doi: 10.1371/journal.pbio.0020362

Shinotoh, H., Kawashita, N., 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. doi: 10.1212/WNL.48.4.1053

Sikk, K., Haldre, S., Aquilonius, S. M., Asser, A., Paris, M., Roose, Ä., et al. (2013). SLC30A10 mutations: a new treatable disorder. Mol. Genet. Metab. 117, 640–644. doi: 10.1016/j.ymgme.2013.06.005

Sossi, V., De La Fuente-Fernandez, R., Schulzer, M., Troiano, A. R., Ruth, T. I., and Stoessl, A. J. (2007). Dopamine transporter relation to dopamine turnover in Parkinson’s disease: a positron emission tomography study. Ann. Neurol. 62, 468–474. doi: 10.1002/ana.21204

Stamelou, M., Tuschl, K., Chong, W. K., Burroughs, A. K., Mills, P. B., Bhatia, K. P., et al. (2012). Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder. Mov. Disord. 27, 1317–1322. doi: 10.1002/mds.25138
Suzuki, N., Nakamura, Y., Kobayashi, N., and Sato, T. (1975). On metal elements in pure pigment gallstones. *Tohoku J. Exp. Med.* 116, 233–240. doi: 10.1620/tjem.116.233

Takahashi, K., Taira, T., Niki, T., Seino, C., Iguchi-Ariga, S. M. M., and Ariga, H. (2001). DJ-1 positively regulates the androgen receptor by impairing the binding of PIASxα to the receptor. *J. Biol. Chem.* 276, 37556–37563. doi: 10.1074/jbc.M101730200

Tan, J., Zhang, T., Jiang, L., Chi, J., Hu, D., Pan, Q., et al. (2011). Regulation of intracellular manganese homeostasis by Kufor-Rakeb syndrome-associated ATP13A2 protein. *J. Biol. Chem.* 286, 29654–29662. doi: 10.1074/jbc.M111.233874

Tuschl, K., Clayton, P. T., Gospe, S. M. Jr., Gulab, S., Ibrahim, S., Singh, P., et al. (2012). Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. *Am. J. Hum. Genet.* 90, 457–466. doi: 10.1016/j.ajhg.2012.01.018

Urrutia, P., Aguirre, P., Esparza, A., Tapia, V., Mena, N. P., Arredondo, M., et al. (2013). Inflammation alters the expression of DMT1, FPN1 and hepcidin, and it causes iron accumulation in central nervous system cells. *J. Neurochem.* 126, 541–549. doi: 10.1111/jnc.12244

Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M. K., Harvey, K., Gispert, S., et al. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 304, 1158–1160. doi: 10.1126/science.1096284

Wedler, F. C., and Denman, R. B. (1984). Glutamine synthetase: the major Mn(II) enzyme in mammalian brain. *Curr. Top. Cell. Regul.* 24, 153–169. doi: 10.1016/B978-0-12-152824-9.50021-6

Weissenborn, K., Ehrenheim, C., Hori, A., Kubicka, S., and Manns, M. P. (1995). Pallidal lesions in patients with liver cirrhosis: clinical and MRI evaluation. *Metab. Brain Dis.* 10, 219–231. doi: 10.1007/BF02081027

Wilkinson, K. D. (2000). Ubiquitination and deubiquitination: targeting of proteins for degradation by the proteasome. *Semin. Cell Dev. Biol.* 11, 141–148. doi: 10.1006/scdb.2000.0164

Williams, K., Wilson, M. A., and Bressler, J. (2000). Regulation and developmental expression of the divalent metal-ion transporter in the rat brain. *Cell. Mol. Biol. (Noisy-le-grand)* 46, 563–571.

Yang, Y., Gehrke, S., Imai, Y., Huang, Z., Ouyang, Y., Wang, J.-W., et al. (2006). Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of *Drosophila* Pink1 is rescued by Parkin. *Proc. Natl. Acad. Sci. U.S.A.* 103, 10793–10798. doi: 10.1073/pnas.0602493103

Yang, Y., Nishimura, L., Imai, Y., Takahashi, R., and Lu, B. (2003). Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in drosophila. *Neuron* 37, 911–924. doi: 10.1016/S0896-6273(03)00143-0

Yin, Z., Jiang, H., Lee, E. S., Ni, M., Erikson, K. M., Milatovic, D., et al. (2010). Ferroportin is a manganese-responsive protein that decreases manganese cytotoxicity and accumulation. *J. Neurochem.* 112, 1190–1198. doi: 10.1111/j.1471-4159.2009.06534.x

Zhou, C., Huang, Y., Shao, Y., May, J., Prou, D., Perier, C., et al. (2008). The kinase domain of mitochondrial PINK1 faces the cytoplasm. *Proc. Natl. Acad. Sci. U.S.A.* 105, 12022–12027. doi: 10.1073/pnas.0802814105

Zhou, Z. D., Kerk, S. Y., Xiong, G. G., and Lim, T. M. (2009). Dopamine autooxidation aggravates non-apoptotic cell death induced by over-expression of human AS3T mutant alpha-synuclein in dopaminergic PC12 cells. *J. Neurochem.* 108, 601–610. doi: 10.1111/j.1471-4159.2008.05795.x

Zlotkin, S. H., Atkinson, S., and Lockitch, G. (1995). Trace elements in nutrition for premature infants. *Clin. Perinatol.* 22, 223–240.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 21 April 2014; accepted: 18 July 2014; published online: 04 August 2014.

Citation: Chen P, Parmalee N and Aschner M (2014) Genetic Factors and Manganese-Induced Neurotoxicity. *Front. Genet.* 5:265. doi: 10.3389/fgene.2014.00265

This article was submitted to Toxicogenomics, a section of the journal Frontiers in Genetics.

Copyright © 2014 Chen, Parmalee and Aschner. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.