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Manganese Efflux in Parkinsonism: Insights from Newly Characterized *SLC30A10* Mutations

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Abstract

Although manganese (Mn) is required for normal cellular function, overexposure to this metal may cause an extrapyramidal syndrome resembling Parkinson's disease (PD). Notably, high whole-blood Mn levels have been reported in patients with idiopathic PD. Because Mn is both essential at low dose and toxic at higher dose; its transport and homeostasis are tightly regulated. Previously, the only protein known to be operant in cellular Mn export was the iron-regulating transporter, ferroportin (Fpn). The causal role for Mn in PD has yet to be fully understood, but evidence of a familial predisposition to PD associated with Mn toxicity is mounting. A recently discovered mutation in *SLC30A10* identified its gene product as putatively involved in Mn efflux. Patients with the *SLC30A10* mutation display Parkinsonian-like gate disturbances and hypermanganesemia. This review will address Mn transport proteins, the newly discovered *SLC30A10* mutations and their implications to Parkinsonism and Mn regulation.

Keywords

manganese; SLC30A10; ferroportin 1; Parkinson's disease; iron

Introduction

Manganese (Mn) is an essential trace element, but at elevated levels it is also a risk factor for Parkinson's disease (PD). Mn homeostasis is required for a variety of cellular processes, and is necessary for normal central nervous system (CNS) functioning, including immune function, carbohydrate metabolism [1,2]. Under normal conditions, Mn functions as a cofactor for a variety of proteins including a subset of Mn-specific proteins, such as glutamate synthetase (GS) and superoxide dismutase 2 (SOD2, Mn-SOD) that are integral to cell detoxification and survival [3]. Mn uptake and distribution is important to normal cellular processes in the brain, including astrocyte morphology and migration, glutamate/γ-aminobutyric acid (GABA) metabolism, and DAergic neuron maintenance [4,5,6,7].

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Overexposure to Mn may be toxic, marked by accumulation of Mn in the basal ganglia as observed with magnetic resonance imaging (MRI) [8,9]. Overexposure may occur in occupational settings, especially from Mn mining dusts and welding fumes [10,11]. Welding fume-exposed workers are much more likely to experience Parkinsonism then matched controls [12]. Occupationally exposed workers have distinct MRI patterns with increased T1-weighted intensities in the basal ganglia, especially the globus pallidus [13]. In addition, exposures to Mn from medically administered parenteral nutrition have been reported [9,14,15], corroborating both inhalation and ingestion represent routes of absorption [16]. These overexposures may lead to manganism, defined as a Parkinsonism-like syndrome [17]. Notably, exposure to Mn has been implicated in idiopathic cases of Parkinsonism, including PD [18,19], and exposures from air or water are correlated with increased risk of PD [2,19,20]. The strongest correlation between any type of environmental exposure and increased PD risk is inherent to occupational exposures to Mn [16,19,21].

Parkinsonism encompasses a group of neurological disorders with the defining feature of marked motor impairment, presenting as tremor, postural instability and hypokinesia. PD is the leading cause of Parkinsonism and is the second leading cause of neurodegenerative diseases, affecting nearly 2% of persons above the age of 60 in the United States. Identified risk factors for PD include age, genetics, as well as environmental exposures. The risk of developing PD doubles every ten years after the age of 70 [22,23]. In the last two decades, 15 loci and 11 genes have been liked to familial inherited PD [24,25,26]. For nearly a century, we have understood that the progressive motor impairment in PD results from the loss of DAergic neurons in the midbrain substantia nigra (SN) [27], but definitive mechanisms for the etiology of PD are still elusive, with a majority of PD cases remaining idiopathic (of unknown origin).

Although idiopathic PD and Mn-induced Parkinsonism share motor impairment symptoms and DAergic cell loss, there are distinct differences between their clinical manifestations. Unlike idiopathic PD, manganism is more likely to present as dystonia without resting tremor, and in general manganism is less responsive to Levadopa therapy [8,17,28]. The average age of onset for Mn-induced parkinsonism after occupational exposures is 46, compared to 63 for idiopathic PD [29].

Genetic predisposition to Mn toxicity has been correlated with *Parkin* (*PARK2*) [30], a gene involved in autosomal recessive PD, and *ATP13A2* (*PARK9*) [31,32], a putative Mn transporter. *Parkin,* most commonly mutated in autosomal recessive PD, encodes an E3 ubiquitin protein ligases thought to be involved in protein degradation and oxidative stress protection [26,33]. *ATP13A2*, mutated in less than five percent of autosomal recessive PD, encodes a cation transporter ATPase that transports Mn [31,34]. Patients carrying autosomal recessive mutations in *Parkin* and *ATP13A2* also seem to be at increased risk for Mn toxicity [30,32,35]. In addition, patients with idiopathic PD have higher whole-blood Mn levels than individuals without the disease in the same population [36], suggesting that brain Mn accumulation may be involved in the etiology of PD. In cases of PD and Mn overexposure, Mn accumulates in the brain regions associated with Parkinsonian motor dysfunction, primarily the globus pallidus and the substantia nigra of the basal ganglia [5].

Mn absorption, transport and excretion are tightly regulated. A number of proteins involved in Mn transport have been identified including the putative uptake proteins divalent metal transporter-1 (DMT1), transferrin receptor (TfR) and ATP13A2 (PARK9), as well as the efflux protein ferroportin (Fpn). For a more comprehensive review Mn transport please refer to Bowman et al. 2010 [1] and Au et al. 2008 [37].

Mutations in a putative Mn exporter gene *SLC30A10* have been recently described. These mutations are associated with marked motor impairment, including a parkinsonism-like syndrome. The following discussion details known mechanisms of Mn transport, with a focus on the *SLC30A10* gene.

DMT1 and TfR: Fe and Mn Absorption

Proteins involved in Mn transport share the characteristic of carrying more than a single metal species, including DMT1 and transferrin receptor (TfR). Dietary Fe and Mn are both absorbed through the intestine by DMT1 and possibly TfR [37,38,39,40]. Neurons express DMT1 and TfR for the uptake of both Fe and Mn [37,41,42]. DMT1 carries divalent Mn [2,37], whilst TfR carries trivalent Mn. A DMT1 haplotype has been identified as a risk factor for PD [43]; association between TfR polymorphism and PD has yet to be identified [44].

Ferroportin: Fe and Mn Efflux

Ferroportin (Fpn), also known as solute carrier family 40 member 1 (SLC40A1) or iron (Fe)-regulated transporter, was originally described as an Fe exporter. Fpn is the only known protein for Fe-efflux [45]. Absorption, efflux, and distribution of Mn appear to be inversely related to stored Fe, with Fe deficiency facilitating Mn absorption [46,47,48]. Fpn is localized in all cells [41,45] and it was the first protein implicated in Mn-efflux [49,50,51]. Yin et al. identified Fpn as a Mn-transport protein, showing that Mn efflux decreases with decreased expression of Fpn [49,51]. Fpn is a transmembrane protein with 9–12 transmembrane domains [45] with both a cytosolic N and C terminus [52]. Fpn may function as a monomer or a dimer in Fe and Mn efflux [45,50]. Mutations in *Fpn* (*SCL40A1*) lead to Fe accumulation called haemochromatosis type 4, also known as Ferroportin disease [53,54,55]. No neurological symptoms are reported from *Fpn* mutation. The effect of *SCL40A1* mutation on Mn accumulation remains unknown.

Fe in PD and Mn distribution

Fe and Mn share many features beyond transport and efflux proteins. Like Mn, Fe is also paradoxically a dietary requirement, as well as neurotoxin upon overexposure. Under normal conditions, Fe is required for heme oxygen transport throughout the body, as well as mitochondrial electron transport chain function [56,57,58]. Fe accumulation, analogous to Mn, has been implicated in PD [59,60,61]; thus an understanding of Fe transport has also become important in better characterizing the etiology of PD [44].

Of particular relevance to this review, Fe accumulation and distribution seems to be inversely related to Mn accumulation and distribution. Dietary Fe deficiency is one of the most common nutritional deficiencies, affecting nearly two million people world wide, unlike Mn deficiency, which is extremely rare [47,62,63]. Fe deficiency (anemia) can be a risk factor for Mn accumulation in the brain [62,64]. Fe deficiency increases expression of *DMT1, TfR,* and *Fpn*, where as Fe overexposure has been shown to decrease expression of *DMT1* and *Fpn* [65,66,67]. In cases of hereditary haemochromatosis, patients experience Fe overload and hepatic cirrhosis, and *DMT1* and *Fpn* expression is uncoupled from the body Fe status [67]. Fe deficiency increases blood and brain Mn levels in exposed humans and animals [68,69,70], whereas repletion with dietary Fe reduces Mn accumulation [70,71]. Furthermore, Mn overexposure promotes release of Fe stores and reduces cellular Fe load [72,73]. Taking into account the prevalence of global Fe deficiency (see above), this clinical condition represents a risk factor for increased Mn accumulation.

SLC30A10 and Mn efflux

Recently, the first example of a familial inherited mutation in Mn metabolism was observed in 10 different families [71,74,75]. Three papers described a disorder of Mn metabolism first identified by Tuschl et al. 2008 [76], with symptoms including hypermanganesemia, dystonia, polycythemia, and often, hepatic cirrhosis.

The cause of flawed Mn metabolism was identified as an autosomal recessive mutation in *SLC30A10* [71]. Tuschl et al. 2012 described eight families with non-symptomatic individuals with heterozygous *SLC30A10* profiles, and symptomatic individuals with homozygous *SLC30A10* mutations that appear to missense or truncation mutations that render a nonexistent or non-functional protein product. Symptom onset for *SLC30A10* mutations range between 2 and 57 years of age, with most cases presenting in childhood [71,74,75], suggesting a diverse environmental or multi-genetic component to the disease.

SLC30A10 was originally thought to be a zinc (Zn) transporter based on sequence analysis, but upon closer examination, SLC30A10 was identified as an Mn efflux protein. SLC30A10 belongs to the cation diffusion facilitator superfamily of metal transporters responsible for transport of Fe, Cu, Zn, and Mn. SLC30A10 is a 485 amino acid membrane embedded protein with 6 purposed transmembrane domains (TMDs) and a cytoplasmic N and C-termini [75]. Quadi et al. made the argument for SLC30A10 as a Mn transporter based on its amino acid sequence, noting that it contains a conserved NxxxD motif replacing the histidine-rich region characteristic of zinc (Zn) transporters and contains a conserved cytosolic cysteine at TMD IV, similar to other Mn specific transporters. Further, Tuschl et al. demonstrated that Mn sensitive yeast can be rescued by expression of human *SLC30A10*, but not mutated human *SLC30A10*, establishing SLC30A10 as an Mn transporter. SLC30A10 is expressed in the liver and neuronal cells of the globus pallidus under normal conditions, and is absent from the liver upon *SLC30A10* mutation. Additionally, SLC30A10 is expressed in the retina and *SLC30A10* is located on chromosome 1q41 near loci thought to influence high myopia.

The hypermanganesemia associated with *SLC30A10* mutation is extreme, with patients having whole blood Mn levels of 1200–6400 nmol/L, compared with normal whole blood Mn (<320 nmol/L). Interestingly, patients with *SLC30A10* mutation also show low Fe and increased total Fe binding capacity (TIBC), suggestive of Fe deficiency [71]. Along with high circulating levels, Mn appears to accumulate in the brains of patients with *SLC30A10* mutations. MRI showed T1-weighted intensities in the basal ganglia, as well as the cerebellum and anterior pituitary [74,75]. This MRI pattern of Mn accumulation is analogous to those seen in occupational exposures to high levels of Mn in welding fumes [2,10,21].

Dystonia or Parkinsonism is found in all cases with *SLC30A10* mutation. Patients with childhood onset of symptoms show primary dystonia, similar to very early onset of PD, where dystonia is the commonly observed motor symptom [26,77]. Childhood *vs.* adult onset differences in neuromotor disorders have been explained by basal ganglia maturity, and could explain the differences in motor symptoms seen in *SLC30A10* mutation. Treatment for patients with *SLC30A10* mutation involved oral Fe supplementation to increase the competition between Mn and Fe at shared transporters, such as DMT1 and TfR. After a month of Fe supplementation, patients showed marked motor improvement.

The pioneer studies on *SLC30A10* mutations have shed new light on the understanding of its product in Mn-induced neurotoxicity. However, additional research is required to better characterize the role of SLC30A10 in Mn homeostasis. To date, the subcellular localization of this protein has yet to be identified. Absent this knowledge, the mechanism(s) of

SLC30A10 regulated Mn export will be hard to decipher. Does it directly export Mn from the cytosol to the extracellular matrix or to organelles, such as the mitochondria or Golgi for later excretion? Moreover, as Fe supplementation alleviates the symptoms caused by *SLC30A10* mutations, does SLC30A10 specifically regulate Mn as well as Fe efflux? Studies addressing these questions will facilitate the understanding on the role of SLC30A10 in preventing Mn accumulation and its parkinsonism-like effect.

In summary, *SLC30A10* mutations highlight a new Mn metabolic disorder and offer a new chance to understand the role of Mn in Parkinsonism. Previously, occupational and environmental exposure to Mn has shown neurological symptoms of Parkinsonism, and Mn accumulation in the basal ganglia. *SLC30A10* mutations are the first example of a genetic cause correlating neurological symptoms directly with Mn accumulation in humans. Symptoms of *SLC30A10* mutations, including Parkinsonism, are improved with oral Fe supplementation, adding weight to the case for Fe deficiency as a risk factor for Mn-accumulation associated Parkinsonism. It is possible that heterozygous mutations or single nucleotide mutations in *SLC30A10* may interact with environmental or occupational exposure to promote and exacerbate the onset of parkinsonism that would have previously been identified as idiopathic. Further research into the role of *SLC30A10* and other potential putative Mn exporters is needed to determine its possible role in broader cases of Mn exposure and Parkinsonism.

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References

1. Bowman AB, Kwakye GF, Hernández EH, Aschner M. Role of manganese in neurodegenerative diseases. Journal of Trace Elements in Medicine and Biology. 2011; 25:191–203. [PubMed: 21963226]
2. Aschner M, Erikson KM, Hernández EH, Tjalkens R. Manganese and its Role in Parkinson's Disease: From Transport to Neuropathology. Neuromolecular medicine. 2009
3. Morello M, Zatta P, Zambenedetti P, Martorana A, D'Angelo V, Melchiorri G, Bernardi G, Sancesario G. Manganese intoxication decreases the expression of manganoproteins in the rat basal ganglia: An immunohistochemical study. Brain Research Bulletin. 2007; 74:406–415. [PubMed: 17920449]
4. Sidoryk-Wegrzynowicz M, Lee E, Albrecht J, Aschner M. Manganese disrupts astrocyte glutamine transporter expression and function. Journal of neurochemistry. 2009; 110:822–830. [PubMed: 19457077]
5. Stanwood GD, Leitch DB, Savchenko V, Wu J, Fitsanakis VA, Anderson DJ, Stankowski JN, Aschner M, McLaughlin B. Manganese exposure is cytotoxic and alters dopaminergic and GABAergic neurons within the basal ganglia. Journal of neurochemistry. 2009; 110:378–389. [PubMed: 19457100]
6. Kern C, Smith D. Preweaning Mn exposure leads to prolonged astrocyte activation and lasting effects on the dopaminergic system in adult male rats. Synapse. 2010; 65:532–544. [PubMed: 20963817]
7. Yokoyama H, Uchida H, Kuroiwa H, Kasahara J, Araki T. Role of glial cells in neurotoxin-induced animal models of Parkinson's disease. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011; 32:1–7. [PubMed: 21107876]
8. Kim Y, Kim JW, Ito K, Lim HS, Cheong HK, Kim JY, Shin YC, Kim KS, Moon Y. Idiopathic parkinsonism with superimposed manganese exposure: utility of positron emission tomography. Neurotoxicology. 1999; 20:249–252. [PubMed: 10385888]

9. Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. Neurotoxicology. 2006; 27:340–346. [PubMed: 16325915]
10. Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology. 2001; 56:8–13. [PubMed: 11148228]
11. Sriram K, Lin GX, Jefferson AM, Roberts JR, Chapman RS, Chen BT, Soukup JM, Ghio AJ, Antonini JM. Dopaminergic neurotoxicity following pulmonary exposure to manganese-containing welding fumes. Archives of toxicology. 2010; 84:521–540. [PubMed: 20224926]
12. Racette BA, Criswell SR, Lundin JI, Hobson A, Seixas N, Kotzbauer PT, Evanoff BA, Perlmutter JS, Zhang J, Sheppard L, Checkoway H. Increased risk of parkinsonism associated with welding exposure. NeuroToxicology. 2012; 33:1356–1361. [PubMed: 22975422]
13. Criswell SR, Perlmutter JS, Huang JL, Golchin N, Flores HP, Hobson A, Aschner M, Erikson KM, Checkoway H, Racette BA. Basal ganglia intensity indices and diffusion weighted imaging in manganese-exposed welders. Occupational and Environmental Medicine. 2012; 69:437–443. [PubMed: 22447645]
14. Manganese Intoxication and Parenteral Nutrition. 2001:1–5.
15. Chalela JA, Bonillha L, Neyens R, Hays A. Manganese Encephalopathy: An Under-Recognized Condition in the Intensive Care Unit. Neurocritical Care. 2010; 14:456–458. [PubMed: 21174173]
16. Normandin L, Panisset M, Zayed J. Manganese neurotoxicity: behavioral, pathological, and biochemical effects following various routes of exposure. Reviews on environmental health. 2002; 17:189–217. [PubMed: 12462483]
17. Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic parkinsonism: similarities and differences. Neurology. 1994; 44:1583–1586. [PubMed: 7936278]
18. Gorell JM, Rybicki BA, Cole Johnson C, Peterson EL. Occupational metal exposures and the risk of Parkinson's disease. Neuroepidemiology. 1999; 18:303–308. [PubMed: 10545782]
19. Hudnell HK. Effects from environmental Mn exposures: a review of the evidence from non-occupational exposure studies. Neurotoxicology. 1999; 20:379–397. [PubMed: 10385898]
20. Finkelstein M, Jerrett M. 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. 2007; 104:420–432. [PubMed: 17445792]
21. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 1999; 20:239–247. [PubMed: 10385887]
22. Pienaar IS, Götz J, Feany MB. Parkinson's disease: insights from non-traditional model organisms. Progress in neurobiology. 2010; 92:558–571. [PubMed: 20851733]
23. Forno LS. Neuropathology of Parkinson's disease. Journal of neuropathology and experimental neurology. 1996; 55:259–272. [PubMed: 8786384]
24. Kumar KR, Lohmann K, Klein C. Genetics of Parkinson disease and other movement disorders. Current opinion in neurology. 2012; 25:466–474. [PubMed: 22772876]
25. Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Human mutation. 2010
26. Bonifati V. Genetics of Parkinson's disease. Minerva medica. 2005; 96:175–186. [PubMed: 16175160]
27. Lees AJ, Selikhova M, Andrade LA, Duyckaerts C. The black stuff and Konstantin Nikolaevich Tretiakoff. Movement disorders : official journal of the Movement Disorder Society. 2008; 23:777–783. [PubMed: 18383531]
28. Lu CS, Huang CC, Chu NS, Calne DB. Levodopa failure in chronic manganism. Neurology. 1994; 44:1600–1602. [PubMed: 7936281]
29. Erikson K, Aschner M. Increased manganese uptake by primary astrocyte cultures with altered iron status is mediated primarily by divalent metal transporter. NeuroToxicology. 2006; 27:125–130. [PubMed: 16140386]

30. Aboud AA, Tidball AM, Kumar KK, Neely MD, Ess KC, Erikson KM, Bowman AB. Genetic risk for Parkinson's disease correlates with alterations in neuronal manganese sensitivity between two human subjects. NeuroToxicology. 2012:1–7.

31. Gitler A, Chesi A, Geddie M, Strathearn K, Hamamichi S, Hill K, Caldwell K, Caldwell G, Cooper A, Rochet J, Lindquist S. Alpha-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity. Nature Genetics. 2009; 41:308–315. [PubMed: 19182805]

32. Tan J, Zhang T, Jiang L, Chi J, Hu D, Pan Q, Wang D, Zhang Z. Regulation of Intracellular Manganese Homeostasis by Kufor-Rakeb Syndrome-associated ATP13A2 Protein. Journal of Biological Chemistry. 2011; 286:29654–29662. [PubMed: 21724849]

33. Yang H, Zhou HY, Li B, Niu GZ, Chen SD. Downregulation of parkin damages antioxidant defenses and enhances proteasome inhibition-induced toxicity in PC12 cells. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2007; 2:276–283. [PubMed: 18040862]

34. Schneider SA, Bhatia KP. Rare causes of dystonia parkinsonism. Current neurology and neuroscience reports. 2010; 10:431–439. [PubMed: 20694531]

35. Roth JA, Singleton S, Feng J, Garrick M, Paradkar PN. Parkin regulates metal transport via proteasomal degradation of the 1B isoforms of divalent metal transporter 1. Journal of Neurochemistry. 2010; 113:454–464. [PubMed: 20089134]

36. Fukushima T, Tan X, Luo Y, Kanda H. Relationship between Blood Levels of Heavy Metals and Parkinson’s Disease in China. Neuroepidemiology. 2010; 34:18–24. [PubMed: 19893325]

37. Au C, Benedetto A, Aschner M. Manganese transport in eukaryotes: The role of DMT1. NeuroToxicology. 2008; 29:569–576. [PubMed: 18565586]

38. He Q, Du T, Yu X, Xie A, Song N, Kang Q, Yu J, Tan L, Xie J, Jiang H. DMT1 polymorphism and risk of Parkinson’s disease. Neuroscience Letters. 2011; 501:128–131. [PubMed: 21777657]

39. Settivari R, Levora J, Nass R. The divalent metal transporter homologues SMF-1/2 mediate dopamine neuron sensitivity in caenorhabditis elegans models of manganism and parkinson disease. The Journal of biological chemistry. 2009; 284:35758–35768. [PubMed: 19801673]

40. Aschner M, Guilarte TR, Dydak U, Criswell SR, Zheng W. NeuroToxicology. 2012; 33:881–886. [PubMed: 22202748]

41. Moos T, Rosengren Nielsen T. Ferroportin in the Postnatal Rat Brain: Implications for Axonal Transport and Neuronal Export of Iron. Seminars in Pediatric Neurology. 2006; 13:149–157. [PubMed: 17101453]

42. Benedetto A, Au C, Aschner M. Manganese-Induced Dopaminergic Neurodegeneration: Insights into Mechanisms and Genetics Shared with Parkinson's Disease. Chemical reviews. 2009

43. He Q, Du T, Yu X, Xie A, Song N, Kang Q, Yu J, Tan L, Xie J, Jiang H. DMT1 polymorphism and risk of Parkinson’s disease. Neuroscience Letters. 2011; 501:128–131. [PubMed: 21777657]

44. Greco V, De Marco EV, Rocca FE, Annesi F, Civitelli D, Provenzano G, Tarantino P, Scornaienchi V, Pucci F, Salsone M, Novellino F, Morelli M, Paglionico S, Gambardella A, Quattrone A, Annesi G. Association study between four polymorphisms in the HFE, TF and TFR genes and Parkinson's disease in southern Italy. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011; 32:525–527. [PubMed: 21384276]

45. Ward DM, Kaplan J. Ferroportin-mediated iron transport: Expression and regulation. BBA - Molecular Cell Research. 2012; 1823:1426–1433. [PubMed: 22440327]

46. Manganese Accumulatesin Iron-Deficient Rat Brain Regions in a Heterogeneous Fashion and Is Associated with Neurochemical Alterations. 2002:1–14.

47. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and Iron (Fe): Interdependency of Transport and Regulation. Neurotoxicity Research. 2009; 18:124–131. [PubMed: 19921534]

48. Wang X, Li GJ, Zheng W. Efflux of Iron from the Cerebrospinal Fluid to the Blood at the Blood-CSF Barrier: Effect of Manganese Exposure. Experimental Biology and Medicine. 2008; 233:1561–1571. [PubMed: 18849539]

49. Yin Z, Jiang H, Lee E-SY, Ni M, Erikson KM, Milatovic D, Bowman AB, Aschner M. Ferroportin is a manganese-responsive protein that decreases manganese cytotoxicity and accumulation. Journal of Neurochemistry. 2010; 112:1190–1198. [PubMed: 20002294]
50. De Domenico I, Ward DM, Musci G, Kaplan J. Evidence for the multimeric structure of ferroportin. Blood. 2007; 109:2205–2209. [PubMed: 17077321]
51. Madejczyk MS, Ballatori N. The iron transporter ferroportin can also function as a manganese exporter. BBA - Biomembranes. 2012; 1818:651–657. [PubMed: 22178646]
52. Liu X-B, Yang F, Haile DJ. Functional consequences of ferroportin 1 mutations. Blood Cells, Molecules, and Diseases. 2005; 35:33–46.
53. Mayr R, Griffiths WJH, Hermann M, McFarlane I, Halsall DJ, Finkenstedt A, Douds A, Davies SE, Janecke AR, Vogel W, Cox TM, Zoller H. Identification of Mutations in SLC40A1 That Affect Ferroportin Function and Phenotype of Human Ferroportin Iron Overload. Gastroenterology. 2011; 140:2056–2063. e2051. [PubMed: 21396368]
54. Mayr R, Griffiths WJH, Hermann M, McFarlane I, Halsall DJ, Finkenstedt A, Douds A, Davies SE, Janecke AR, Vogel W, Cox TM, Zoller H. Identification of Mutations in SLC40A1 That Affect Ferroportin Function and Phenotype of Human Ferroportin Iron Overload. YGAST. 2011; 140:2056–2063. e2051.
55. Speletas M, Kioumi A, Loules G, Hytiroglou P, Tsitouridis J, Christakis J, Germenis AE. Analysis of SLC40A1 gene at the mRNA level reveals rapidly the causative mutations in patients with hereditary hemochromatosis type IV. Blood Cells, Molecules, and Diseases. 2008; 40:353–359.
56. Hoppe, M.; Brün, B.; Larsson, MP.; Moraeus, L.; Hulthén, L. Nutrition. Vol. 29. Burbank, Los Angeles County, Calif: 2013. Heme iron-based dietary intervention for improvement of iron status in young women; p. 89-95.
57. Hider, RC.; Kong, X. Dalton transactions. Cambridge, England: 2012. Iron speciation in the cytosol: an overview. 2003
58. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and Iron (Fe): Interdependency of Transport and Regulation. Neurotoxicity Research. 2010; 18:124–131. [PubMed: 19921534]
59. Mochizuki H, Yasuda T. Iron accumulation in Parkinson's disease. Journal of Neural Transmission. 2012
60. Moos T, Nielsen TR, Skjørringe T, Morgan EH. Iron trafficking inside the brain. Journal of Neurochemistry. 2007; 103:1730–1740. [PubMed: 17953660]
61. Dexter DT, Wells FR, Lees AJ, Agid F, Agid Y, Jenner P, Marsden CD. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. Journal of neurochemistry. 1989; 52:1830–1836. [PubMed: 2723638]
62. Erikson KM, Syversen T, Aschner JL, Aschner M. Interactions between excessive manganese exposures and dietary iron-deficiency in neurodegeneration. Environmental toxicology and pharmacology. 2005; 19:415–421. [PubMed: 21783506]
63. Beard J, Erikson K, Jones BC. Neonatal iron deficiency results in irreversible changes in dopamine function in rats. The Journal of nutrition. 2003; 133:1174–1179. [PubMed: 12672939]
64. Aschner M, Shanker G, Erikson K, Yang J, Mutkus LA. The uptake of manganese in brain endothelial cultures. Neurotoxicology. 2002; 23:165–168. [PubMed: 12224757]
65. Erikson KM, Jones BC, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. The Journal of nutrition. 2000; 130:2831–2837. [PubMed: 11053528]
66. Erikson KM, Pinero DJ, Connor JR, Beard JL. Regional brain iron, ferritin and transferrin concentrations during iron deficiency and iron repletion in developing rats. The Journal of nutrition. 1997; 127:2030–2038. [PubMed: 9311961]
67. Zoller H, Koch RO, Theurl I, Obrist P, Pietrangelo A, Montosi G, Haile DJ, Vogel W, Weiss G. Expression of the duodenal iron transporters divalent-metal transporter 1 and ferroportin 1 in iron deficiency and iron overload. Gastroenterology. 2001; 120:1412–1419. [PubMed: 11313311]
68. Nam H, Knutson MD. Effect of dietary iron deficiency and overload on the expression of ZIP metal-ion transporters in rat liver. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine. 2012; 25:115–124.
69. Brna P, Gordon K, Dooley JM, Price V. Manganese toxicity in a child with iron deficiency and polycythemia. Journal of child neurology. 2011; 26:891–894. [PubMed: 21596707]

70. Kim Y, Lee BK. Iron deficiency increases blood manganese level in the Korean general population according to KNHANES 2008. Neurotoxicology. 2011; 32:247–254. [PubMed: 21182864]

71. Tuschl K, Clayton PT, Gospe SM Jr, Gulab S, Ibrahim S, Singhi P, Aulakh R, Ribeiro RT, Barsottini OG, Zaki MS, Del Rosario ML, Dyack S, Price V, Rideout A, Gordon K, Wevers RA, Chong WKK, Mills PB. Syndrome of Hepatic Cirrhosis, Dystonia, Polycythemia, and Hypermanganesemia Caused by Mutations in SLC30A10, a Manganese Transporter in Man. The American Journal of Human Genetics. 2012; 90:457–466.

72. Kwik-Uribe C, Smith D. Temporal responses in the disruption of iron regulation by manganese. Journal of neuroscience research. 2006; 83:1601–1610. [PubMed: 16568477]

73. Crooks DR, Ghosh MC, Braun-Sommargren M, Rouault TA, Smith D. Manganese targets m-aconitase and activates iron regulatory protein 2 in AF5 GABAergic cells. Journal of neuroscience research. 2007; 85:1797–1809. [PubMed: 17469137]

74. Stamelou M, Tuschl K, Chong WK, Burroughs AK, Mills PB, Bhatia KP, Clayton PT. Dystonia with brain manganese accumulation resulting from SLC30A10mutations: A new treatable disorder. Movement Disorders. 2012; 27:1317–1322. [PubMed: 22926781]

75. Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, Severijnen L-A, Di Toro Mammarella L, Mignarri A, Monti L, Sanna A, Lu P, Punzo F, Cossu G, Willemsen R, Rasi F, Oostra BA, van de Warrenburg BP, Bonifati V. Mutations in SLC30A10 Cause Parkinsonism and Dystonia with Hypermanganesemia, Polycythemia, and Chronic Liver Disease. The American Journal of Human Genetics. 2012; 90:467–477.

76. Tuschl K, Mills PB, Parsons H, Malone M, Fowler D, Bitner-Glindzicz M, Clayton PT. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—A new metabolic disorder. Journal of Inherited Metabolic Disease. 2008; 31:151–163. [PubMed: 18392750]

77. Baquer NZ, Taha A, Kumar P, McLean P, Cowsik SM, Kale RK, Singh R, Sharma D. A metabolic and functional overview of brain aging linked to neurological disorders. Biogerontology. 2009; 10:377–413. [PubMed: 19381858]

- Manganese (Mn) is required for normal cellular function.
- Excessive Mn may cause a disease resembling Parkinson's disease (PD).
- Mn and Fe homeostasis is regulated by shared transporters.
- SLC30A10 is putatively involved in Mn efflux.
- Patients with the *SLC30A10* mutation display Parkinsonian-like symptoms.