Biochemical and Biophysical Research Communications 432 (2013) 1–4

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Manganese efflux in Parkinsonism: Insights from newly characterized *SLC30A10* mutations

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ARTICLE INFO

Article history:
Received 28 December 2012
Available online 26 January 2013

Keywords:
Manganese
SLC30A10
Ferroportin 1
Parkinson's disease
Iron

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.

1. 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 [4–7].

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 [24–26]. 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

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0006-291X/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2013.01.058

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. [1] and Au et al. [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.

1.1. 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 [37–40]. 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 [38]; association between TfR polymorphism and PD has yet to be identified [43].

1.2. 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 [44]. Absorption, efflux, and distribution of Mn appear to be inversely related to stored Fe, with Fe deficiency facilitating Mn absorption [45–47]. Fpn is localized in all cells [41,44] and it was the first protein implicated in Mn-efflux [48–50]. Yin et al. identified Fpn as a Mn-transport protein, showing that Mn efflux decreases with decreased expression of Fpn [48,50]. Fpn is a transmembrane protein with 9–12 transmembrane domains [44] with both a cytosolic N and C terminus [51]. Fpn may function as a monomer or a dimer in Fe and Mn efflux [44,49]. Mutations in *Fpn* (*SCL40A1*) lead to Fe accumulation called haemochromatosis type 4, also known as Ferroportin disease [52,53]. No neurological symptoms are reported from *Fpn* mutation. The effect of *SCL40A1* mutation on Mn accumulation remains unknown.

1.3. 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 [54–56]. Fe accumulation, analogous to Mn, has been implicated in PD [57–59]; thus an understanding of Fe transport has also become important in better characterizing the etiology of PD [43].

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 [46,60,61]. Fe deficiency (anemia) can be a risk factor for Mn accumulation in the brain [60,62]. Fe deficiency increases expression of *DMT1*, *TfR*, and *Fpn*, where as Fe overexposure has been shown to decrease expression of *DMT1* and *Fpn* [63–65]. In cases of hereditary haemochromatosis, patients experience Fe overload and hepatic cirrhosis, and *DMT1* and *Fpn* expression is uncoupled from the body Fe status [65]. Fe deficiency increases blood and brain Mn levels in exposed humans and animals [66–68], whereas repletion with dietary Fe reduces Mn accumulation [68,69]. Furthermore, Mn overexposure promotes release of Fe stores and reduces cellular Fe load [70,71]. Taking into account the prevalence of global Fe deficiency (see above), this clinical condition represents a risk factor for increased Mn accumulation.

1.4. SLC30A10 and Mn efflux

Recently, the first example of a familial inherited mutation in Mn metabolism was observed in 10 different families [69,72,73]. Three papers described a disorder of Mn metabolism first identified by Tuschl et al. [74], 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* [69]. 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 [69,72,73], 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 [73]. 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 [69]. 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 [72,73]. 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 [26,75]. 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.

Acknowledgments

The authors wish to acknowledge partial support from grants from the National Institutes of Environmental Health Sciences (R01 ES10563, P30 ES000267, and T32 ES007028).

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