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Manganese Control of Glutamate Transporters' Gene Expression

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Abstract

Manganese (Mn) is an essential trace element, serving as a cofactor for several enzymes involved in various cellular and biochemical reactions in human body. However, chronic overexposure to Mn from occupational or environmental sources induces a neurological disorder, characterized by psychiatric, cognitive, and motor abnormalities, referred to as manganism. Mn-induced neurotoxicity is known to target astrocytes since these cells preferentially accumulate Mn. Astrocytes are the most abundant non-neuronal glial cells in the brain, and they play a critical role in maintaining the optimal glutamate levels to prevent excitotoxic death. The fine regulation of glutamate in the brain is accomplished by two major glutamate transporters – glutamate transporter-1 (GLT-1) and glutamate aspartate transporter (GLAST) that are predominantly expressed in astrocytes. Excitotoxic neuronal injury has been demonstrated as a critical mechanism involved in Mn neurotoxicity and implicated in the pathological signs of multiple neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Recent evidences also establish that Mn directly deregulates the expression and function of both astrocytic glutamate transporters by decreasing mRNA and protein levels of GLT-1 and GLAST. Herein, we will review the mechanisms of Mn-induced gene regulation of glutamate transporters at the transcriptional level and their role in Mn toxicity.

Keywords

Manganese; Astrocytes; Glutamate transporters; GLT-1; GLAST; Yin Yang 1

Conflict of Interest The author declares no conflicts of interest.

1 Introduction

Manganese (Mn) is an abundantly available trace element that is required for normal functioning and development of the central nervous system (CNS) (Takeda 2003). Mn acts as a cofactor for many crucial enzymes such as arginase, pyruvate decarboxylase, superoxide dismutase, and glutamine synthetase (Bentle and Lardy 1976; Stallings et al. 1991; Wedler and Denman 1984; Diez et al. 1992). But, excessive CNS accumulation of Mn may cause toxicity, resembling Parkinson's disease (PD), and is referred to as manganism (Chen et al. 2015; Kwakye et al. 2015). The occupational and environmental sources of Mn exposure include welding, mining, and ferroalloy industries as well as Mn-contaminated drinking water and also from the use of gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) and pesticide maneb (Bast-Pettersen et al. 2004; Bowler et al. 2007; Montes et al. 2008; Williams et al. 2012). Mn is transported into the CNS via multiple transporters including transferrin, divalent metal transporter-1 (DMT-1), *N*-methyl-D-aspartate (NMDA) receptor channel, and the divalent metal/bicarbonate ion symporters ZIP8 and ZIP14 (Aschner and Gannon 1994; Au et al. 2008; Fujishiro et al. 2012; Itoh et al. 2008). Once Mn enters into the brain, astrocytes appear to be more vulnerable to Mn toxicity compared to other cell types since they preferentially accumulate Mn (Morello et al. 2008). One of the critical functions of astrocytes in the CNS is to maintain optimal glutamate levels to prevent the excitotoxic neuronal death (Danbolt 2001). Astrocytes express two glutamate transporters – glutamate transporter-1 (GLT-1) and glutamate aspartate transporter (GLAST), also known as excitatory amino acid transporter (EAAT) 1 and 2 in humans, respectively, which are responsible for uptaking more than 80% of extracellular glutamate. Since among the five subtypes of glutamate transporters, GLT-1/EAAT2 and GLAST/EAAT1 carry out most of the glutamate uptake in the CNS, and these astrocytic isoforms are the primary target of Mn toxicity; herein we will focus on the effects of Mn on these two transporters. Mn is known to interfere with the astrocytic glutamate regulation by inhibiting the gene expression of glutamate transporters (Lee et al. 2009, 2012) which will be discussed in the next sections.

2 Astrocytes and Mn Neurotoxicity

Astrocytes are the principal reservoir for Mn accumulation in the brain with the presence of efficient Mn transport system. Astrocytes contain 50–60-fold higher Mn concentration than their neuron counterparts (Morello et al. 2008; Aschner et al. 1992). Further, the preferential sequestration of Mn in mitochondria makes this energy-producing organelle more prone to Mn toxicity by Mn-induced mitochondrial dysfunction and oxidative stress (Erikson et al. 2004; Chen and Liao 2002; Gavin et al. 1999). Mn directly inhibits the enzymes involved in ATP-generating pathways and also activates mitochondrial apoptotic pathway to exert cytotoxic effects (Gavin et al. 1992; Gonzalez et al. 2008). Furthermore, Mn also induces oxidative stress by inhibiting glutathione synthetase, an astrocyte-specific enzyme that is critical for the synthesis of antioxidant glutathione (Erikson et al. 2004, 2006). More importantly, Mn also interferes with the glutamate-glutamine cycle that leads to the imbalance of neurotransmitters, a common trigger for various neurodegenerative disorders (Sidoryk-Wegrzynowicz and Aschner 2013).

2.1 Glutamate Excitotoxicity in Mn Neurotoxicity

Glutamate is the major excitatory neurotransmitter in the CNS, and it plays an important role in various essential brain functions including cognition, learning, and memory (Danbolt 2001). However, the increased extracellular levels of glutamate, followed by the overstimulation of glutamate receptors, induce excitotoxic neuronal injury. The survival and proper functioning of neurons is regulated by astrocytes given that astrocytes not only provide structural, metabolic, and trophic support for neurons but also produce and supply neuronal growth factors and antioxidants (Seifert et al. 2006). Mn-elicited excitotoxicity could result from the interference with the astrocyte function of glutamate uptake or through the activation of glutamate receptors. The study by Brouillet et al. first established that Mn produces excitotoxic lesions in rat striatum by impairing the ATP generation, and treatment with NMDA receptor antagonist MK-801 ameliorates these injuries (Brouillet et al. 1993). These observations were further confirmed in a later study, which showed that MK-801 prevents Mn-induced neurotoxicity (Xu et al. 2010a, b). The same group also showed that Mn causes neurotoxicity in rats by increasing extracellular glutamate, secondary to the altered expression of NMDA receptors (Xu et al. 2010c). Similarly, the role of glutamate receptor activation in Mn neurotoxicity was evident in Mn-caused neuronal loss in globus pallidus where Mn increased the sensitivity of postsynaptic glutamate receptors to glutamate (Spadoni et al. 2000). However, more severe effects of Mn toxicity may be mediated by impairment of astrocyte function caused by reduced expression and function of astrocytic gluta-mate transporters.

2.2 Mn Inhibition of Glutamate Transporters' Gene Expression

The reduced expression and function of astrocytic glutamate transporters is linked to the pathogenesis of a myriad of neurological disorders including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), stroke, HIV-associated dementia, and glaucoma (Potter et al. 2013; Rao et al. 2001; Robelet et al. 2004; Rothstein et al. 1995; Yanagisawa et al. 2015). Since many of these diseases are also associated with Mn toxicity, it prompted researchers to investigate the effects of Mn on glutamate transporters. The studies revealed that Mn decreases glutamate uptake in astrocytes (Hazell and Norenberg 1997). Mn inhibition of glutamate uptake was further confirmed by another study demonstrating that Mn decreases glutamate uptake in astrocytes by reducing GLAST expression (Erikson and Aschner 2002). Consistently, another study showed that Mn decreases both GLAST and GLT-1-mediated glutamate uptake (Mutkus et al. 2005). A decrease in the expression of GLT-1 and GLAST was also noted in nonhuman primates exposed to Mn although the reduction in expression was dependent on brain areas and exposure duration (Erikson et al. 2007, 2008). Later studies from our group demonstrated that Mn decreases glutamate uptake activity of GLAST by reducing its protein expression and membrane trafficking (Lee et al. 2009). We also showed that Mn decreases the promoter activity, mRNA/protein levels, and activity of GLT-1 in astrocytes (Lee et al. 2012). These studies illustrated that Mn-induced reduction in the expression of transforming growth factor (TGF)-α and -β mediates Mn inhibition of glutamate transporters' expression and function.

3 Mn Induces Glutamate Transporters' Gene Dysregulation

Since Mn reduces the promoter activity as well as mRNA and protein levels of glutamate transporters, it is apparent that Mn acts at the transcription level to exert its repressive effects. However, the mechanism of Mn-induced transcriptional repression of glutamate transporters is not completely known. Multiple intracellular signaling pathways and transcription factors are suggested to mediate the Mn's inhibitory action on glutamate transporters.

3.1 Intracellular Signaling Pathways

Mn is known to activate some intracellular signaling pathways that mediate its effects on glutamate transporters. Among these, protein kinase C (PKC) appears to be one of the major pathways involved in Mn-induced regulation of glutamate transporters. Mn activates PKCα and PKCδ to decrease glutamate uptake, and inhibition of either PKC isoforms reverses Mn-induced reduction of glutamate uptake in astrocytes (Sidoryk-Wegrzynowicz et al. 2011, 2012). Furthermore, inhibition of the PKC pathway also attenuated Mn-induced decrease in protein expression levels of GLT-1 and GLAST (Sidoryk-Wegrzynowicz et al. 2012). These findings established a major role of the PKC pathway in Mn-induced repression of glutamate transporters. The same study also showed that Mn enhances the interaction between GLT-1 and PKCδ and knockdown of PKCδ alleviates the Mn-induced decrease in glutamate uptake (Sidoryk-Wegrzynowicz et al. 2012). The caspase-3-dependent cleavage of PKCδ is also implicated in Mn-induced neurotoxicity (Kitazawa et al. 2005; Latchoumycandane et al. 2005). Corroborating with these findings, inhibition of caspase-3 with Z-Ala-Glu (OMe)-Val-Asp (OMe)-fluoromethyl+ ketone (Z-VAD-FMK) abrogated Mn-induced decrease in GLT-1 and GLAST protein expression as well as glutamate uptake (Sidoryk-Wegrzynowicz et al. 2012). Moreover, caspase-3- mediated cleavage of GLT-1 results in inactivation of the GLT-1 transporter, suggesting that apoptotic signaling also modulates the glutamate transporters' function (Boston-Howes et al. 2006). Mn activation of PKCs might also result in reduced membrane trafficking of glutamate transporters given that phorbol ester-induced PKC activation has been shown to decrease the cell surface expression of GLT-1 (Kalandadze et al. 2002). A similar role of PKC-induced phosphorylation of GLAST leading to its decreased glutamate uptake activity has been reported (Conradt and Stoffel 1997). In addition to PKCs, several in vitro and in vivo studies have shown that Mn activates other signaling kinases such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase, and Akt, but the definitive role of these pathways in Mn-induced downregulation of glutamate transporters remains to be elucidated (Cordova et al. 2012; Ito et al. 2006; Peres et al. 2013; Yin et al. 2008).

3.2 Transcriptional Regulation

Mn-induced inhibition of glutamate transporters starts from promoter levels, so there must be some crucial transcription factors that mediate the repressive effects of Mn on the gene expression of transporters. However, the role of transcription factors in regulating the gene expression of glutamate transporters during Mn toxicity had not been investigated. We recently demonstrated that a transcription factor Yin Yang 1 (YY1) mediates Mn-induced repression of GLT-1 and GLAST (Karki et al. 2014a, 2015). These studies established that

Mn activates YY1 to inhibit the expression and function of astrocytic glutamate transporters. Both GLT-1 and GLAST promoters contain consensus-binding sites for YY1, and Mn increased the binding of YY1 to these sites in the promoters. Previous studies have noted the role of YY1 in repressing glutamate transporters, and our findings illustrated that Mn inhibition of glutamate transporters is mediated by YY1 (Lee et al. 2011; Rosas et al. 2007). Multiple studies have shown that various positive modulators of glutamate transporters such as soluble neuronal factors, ceftriaxone, epidermal growth factor, estrogen, and selective estrogen receptor modulators (SERMs) all activate nuclear factor-κB (NF-κB) to upregulate glutamate transporters (Karki et al. 2013, 2014b, 2015; Ghosh et al. 2011; Lee et al. 2008). We demonstrated that Mn-activated YY1 can completely suppress NF-κB-mediated stimulatory effects on glutamate transporters, indicating that the repressive effects of YY1 can easily surpass the positive regulatory pathways (Karki et al. 2014a, 2015). Our studies also showed that tumor necrosis factor-α (TNF-α) facilitates Mn-induced YY1 activation given that Mn treatment increases TNF-α secretion in astrocytes and TNF-α decreases YY1 expression (Karki et al. 2014a). Earlier studies have established that TNF-α is a repressor of glutamate transporters and Mn increases TNF-α expression (Kim et al. 2003; Sitcheran et al. 2005; Su et al. 2003; Zhao et al. 2009). Furthermore, TNF-α increases YY1 expression as well as its DNA-binding activity (Huerta-Yepez et al. 2006). Accordingly, it appears that Mn-TNFα-YY1 activation cascade is responsible for the transcriptional repression of astrocytic glutamate transporters. Further studies are required to investigate if other repressive transcription factors of glutamate transporters such as nuclear factor of activated T cells (NFAT) and N-myc are also involved in Mn-induced repression of glutamate transporters (Sitcheran et al. 2005; Abdul et al. 2009).

3.3 Epigenetic Regulation

Methylation and acetylation represent two major epigenetic regulatory pathways that modulate the expression of glutamate transporters. For example, methylation of the EAAT2 promoter reduces its activity, and inhibition of DNA methyltransferases increases EAAT2 mRNA levels (Zschocke et al. 2007). The increased expression and activity of various histone deacetylases (HDACs) is linked to neurological disorders, and accordingly several HDAC inhibitors have been shown to be neuroprotective against a wide range of neurotoxic insults including glutamate excitotoxicity (Baltan et al. 2011; Bardai and D'Mello 2011; Janssen et al. 2010; Leng et al. 2010). The epigenetic regulation of glutamate transporters was previously demonstrated by a study where valproic acid, a HDAC inhibitor, increases acetylated histone H4 levels in the GLT-1 promoter (Perisic et al. 2010). Direct evidence for the role of HDACs in repressing glutamate transporters was established by our recent studies where overexpression of various HDAC isoforms resulted in decreased glutamate transporters' promoter activities (Karki et al. 2014a, 2015). Furthermore, HDACs were recruited as corepressors by YY1 to inhibit glutamate transporters, and activation of HDACs suppressed stimulatory effects of NF-κB. Given that recruitment of repressor proteins is one of the mechanisms involved in YY1-mediated gene repressions (Shi et al. 1997), Mn-induced inhibition of glutamate transporters occurs with the formation of YY1-HDAC repressor complex that also sequesters NF-κB rendering it inactive. This was further supported by the findings that Mn increases interactions between HDACs, YY1, and p65, suggesting that Mn exerts its inhibitory actions on glutamate transporters by inducing the

formation of a transcriptional repressor comprised of YY1, HDACs, and NF-κB. Moreover, the involvement of HDACs in negatively regulating glutamate transporters is further corroborated by findings that a wide range of HDAC inhibitors increase the expression and function of glutamate transporters and attenuate Mn-induced impairment of the transporters (Karki et al. 2014a, 2015).

3.4 Attenuation of Mn-Induced Glutamate Transporters' Repression

Mn toxicity is associated with a plethora of neurodegenerative disorders, including AD, PD, HD, and ALS, and current knowledge suggests that Mn-induced impairment of astrocytic glutamate transporters might play a crucial role in triggering the pathogenesis of these diseases (Bowman et al. 2011). The pharmacological compounds that can reverse Mn-induced repression of astrocytic glutamate transporters could be developed as potential therapeutics against the diseases elicited by Mn neurotoxicity and the dysregulation of glutamate transporters. In this regard, the studies from our group have established that estrogen and SERMs could be promising therapeutic candidates to combat Mn toxicity (Lee et al. 2009, 2012; Karki et al. 2014b). The protective effects of estrogen and SERMs might be via production of TGF-α that stimulates transporters expression by activating NF-κB and cAMP response element-binding protein (CREB) pathways (Karki et al. 2013, 2014b). Likewise, activation of the ERK and Akt pathways facilitates the stimulatory effects of estrogenic compounds on glutamate transporters (Lee et al. 2009). The findings that SERMs upregulate glutamate transporters and reverse Mn inhibitory actions have an important clinical significance since these SERMs are already in clinic utilities. For instance, tamoxifen and raloxifene are US Food and Drug Administration (FDA)-approved drugs for breast cancer and osteoporosis, respectively. Given their clinical safety record and ability to attenuate Mn-induced repression of glutamate transporters, the efficacy of SERMs in treating Mn-induced neurological disorders merits further evaluation. It has been shown that riluzole, the only drug for ALS in clinics, exerts protective effects against Mn-induced disruption of expression and function of astrocytic glutamate transporters (Deng et al. 2012). Various HDAC inhibitors are also known to enhance glutamate transporters' expression, and our studies demonstrated that these compounds can attenuate Mn-induced repression of glutamate transporters (Karki et al. 2014a, 2015). As discussed above, the neuroprotective roles of HDAC inhibitors are well appreciated, and with these new findings that they can also offer protection against Mn-caused impairment of glutamate transporters, at least some of these HDAC inhibitors could offer a plausible alternative therapeutics to be developed against glutamate excitotoxicity and Mn toxicity. At the mechanistic level, the protective actions of HDAC inhibitors on Mn toxicity might be due to their ability to interfere with the YY1 pathway. This notion is supported by observations that Mn activates YY1 to repress glutamate transporters and valproic acid, a HDAC inhibitor, decreases YY1 binding to the GLAST promoter, relieving the repressive effects of YY1 on GLAST (Aguirre et al. 2008).

4 Summary

The dysregulation of astrocytic glutamate transporters and ensuing excitotoxicity appears to be one of the major mechanisms involved in Mn neurotoxicity. The accumulating evidences suggest that Mn acts at the transcription level to downregulate glutamate transporters and

epigenetic regulation, especially HDACs, which also play a crucial role in this process. At the cellular level, the increased expression of TNF-α with the subsequent activation of the YY1 pathway mediates Mn-induced impairment of astrocytic glutamate transporters. Pharmacological compounds that effectively attenuate Mn inhibition of glutamate transporters could be potential therapeutics against both Mn neurotoxicity and excitotoxicity. To this end, estrogen, SERMs, riluzole, and HDAC inhibitors might be considered as promising therapeutic candidates against the neurological disorders elicited by Mn toxicity-mediated dysfunction of astrocytic glutamate transporters. Future studies could be profitable directed to provide more precise information on the mechanisms by which Mn regulates glutamate transporters' gene expression, paving the way for exploring critical cellular pathways and novel pharmacological compounds with an ultimate goal of developing effective therapeutics against Mn-caused excitotoxicity.

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