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Role of transcription factor yin yang 1 in manganese-induced reduction of astrocytic glutamate transporters: putative mechanism for manganese-induced neurotoxicity

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Abstract

Astrocytes are the most abundant non-neuronal glial cells in the brain. Once relegated to a mere supportive role for neurons, contemporary dogmas ascribe multiple active roles for these cells in central nervous system (CNS) function, including maintenance of optimal glutamate levels in synapses. Regulation of glutamate levels in the synaptic cleft is crucial for preventing excitotoxic neuronal injury. Glutamate levels are regulated predominantly by two astrocytic glutamate transporters, glutamate transporter 1 (GLT-1) and glutamate aspartate transporter (GLAST). Indeed, the dysregulation of these transporters has been linked to several neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD), as well as manganism, which is caused by overexposure to the trace metal, manganese (Mn). Although Mn is an essential trace element, its excessive accumulation in the brain as a result of chronic occupational or environmental exposures induces a neurological disorder referred to as manganism, which shares common pathological features with Parkinsonism. Mn decreases the expression and function of both GLAST and GLT-1.Astrocytes are commonly targeted by Mn, and thus reduction in astrocytic glutamate transporter function represents a critical mechanism of Mn-induced neurotoxicity. In this review, we will discuss the role of astrocytic glutamate transporters in neurodegenerative diseases and Mn-induced neurotoxicity.

Keywords

Astrocytes; Glutamate; GLAST; GLT-1; glutamate transporters; Manganese; Neurotoxicity

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Introduction

Astrocytes, which have been typically relegated as structural and nutritional support for neurons, exert several essential functions to maintain optimal neuronal activity [1]. One of their major functions is to maintain low levels of extracellular glutamate to prevent excitotoxic neuronal injury. The maintenance of optimal synaptic glutamate levels is achieved predominantly by two glutamate transporters which are preferentially expressed in astrocytes: glutamate aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), known respectively as excitatory amino acid transporter (EAAT)1 and EAAT2 in humans [2]. The decreased expression and function of these transporters has been linked to multiple neurodegenerative disorders including amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson disease (PD) and Huntington's disease (HD) [3]. Manganese (Mn) neurotoxicity has been implicated in the development of these neurological disorders [4] along with manganism. Mn induces mitochondrial impairment, oxidative stress, and dysfunction of astrocytic glutamate transporters [5-7].

Astrocyte functions on neuronal survival and protection in the CNS

Astrocytes comprise greater than half of the brain volume, and carry out multiple essential functions, playing an active role in regulating CNS physiology. Astrocytes participate in a wide range of functions from synaptic transmission [8] to adult neurogenesis [9]. Consequently, dysfunction of astrocytes has been associated with a number of neurological disorders, including epilepsy, ALS, schizophrenia and manganese neurotoxicity, to name a few [10]. Astrocytes exert several important roles which are closely related to the prevention of neurotoxicity including antioxidant action, production of growth factors, and regulation of glutamate neurotransmission. For example, neurons are more vulnerable to injury due to their limited anti-oxidant capacity, and rely on astrocytes for productions of anti-oxidant enzymes and substances against neuronal oxidative stress. Astrocytes are a rich source of various anti-oxidants, including glutathione (GSH), ascorbate and superoxide dismutases [11, 12]. Astrocytes are also critically involved in neuronal survival and neuroprotection by producing various neurotrophic factors including brain- and glial- derived neurotrophic factors, nerve growth factor, insulin-like growth factor, basic fibroblast growth factor and transforming growth factor-α and -β [13-16]. Astrocytes are essential in the regulation of neurotransmitter homeostasis, particularly glutamate. During glutamate neurotransmission, astrocytes remove ~80% of glutamate from extracellular synaptic clefts via the glutamate transporters, GLT-1 and GLAST [17, 18].

Astrocytic glutamate transporters

In humans, there are five subtypes of excitatory amino acid transporters (EAATs) that have ~50% sequence identity and ~60% structural similarity among them [19]. These five subtypes also show distinct expression profiles; EAAT1 (GLAST in rodents) and EAAT2 (GLT-1 in rodents) are predominantly expressed in astrocytes, while the other three members, EAAT3, EAAT4 and EAAT5, are expressed in neurons with EAAT3 abundantly expressed throughout the CNS, EAAT4 localized in the cerebellum and EAAT5 in retina [20]. These transporters also show variation in expression and activity during developmental stages, as GLAST is mostly active in the developing CNS, while GLT-1 is predominant in

the adult CNS [21]. Glutamate transport via astrocytic glutamate transporters is energy-dependent, coupled with uptake of three Na^+ ions and one H^+ ion, and the counter transport of one K^+ ion [22, 23]. These transporters normally exist as oligomers, especially trimers, in the plasma membranes with each monomer acting as an independent functional unit [24-26].

Astrocytic glutamate transporters, GLT-1 and GLAST, play a major role in preventing excitotoxic neuronal injury. It has been shown that deletion of GLT-1 increases neuronal susceptibility to cortical injury as well as seizure activity in GLT-1 knockout mice [27]. Mutation of GLAST induces loss of motor coordination and increases the susceptibility of cerebellar neurons to neurotoxic insults in GLAST mutant mice [28]. Increased levels of glutamate in the extracellular space contribute to the development of these pathological symptoms in both studies. Moreover, knock down of GLT-1 and GLAST by their respective antisense oligonucleotides in both in vitro and in vivo settings induces excitotoxicity-related neurodegeneration and progressive paralysis, secondary to elevated extracellular glutamate [18].

Dysfunctions of astrocytic glutamate transporters in neurological diseases

Given the critical role of the glutamate transporters in maintaining glutamate levels below the toxic threshold, impairment of expression and function of these transporters leads to excitotoxic neuronal injury and is linked to numerous neurological disorders.

A decrease in glutamate uptake as well as expression of GLT-1 and GLAST has been noted in cultured cortical astrocytes derived from AD patients [29]. GLT-1 expression is also decreased in animal models of AD [30]. Amyloid beta (Aβ), whose excessive deposition as amyloid plaques in the brain is considered to play a key role in the etiology of AD, has been lined to a reduction in the expression of both GLT-1 and GLAST, as well as glutamate uptake in cultured astrocytes [31, 32]. Moreover, a reduction of GLT-1 expression and glutamate uptake has been noted in ALS patients [33, 34]. The impaired GLT-1 function in ALS is secondary to inflammation and oxidative stress [35]. Expression and function of both GLT-1 and GLAST are also decreased in animal models of seizure [36, 37].

In PD, impairment in astrocytic glutamate transporter function is associated with damage to nigrostriatal dopaminergic neurons [38]. In a PD animal model employing unilateral 6-hydroxydopamine, it has been shown that GLT-1 and GLAST proteins are significantly reduced in the striatum of the lesioned rats [39]. Similarly, *N*-methyl-4-phenylpyridinium (MPP^+), a chemical known to mimic PD-like symptoms in humans and animal models, has been shown to induce dysregulation of glutamate uptake in both *in vitro* and *in vivo* experimental models [40, 41]. Clinically, the role of glutamate transporters in PD is further supported by observations on decreased glutamate uptake in platelets from PD patients [42]. However, the role on glutamate transporters in PD animal models remain controversial as some studies have failed to note changes in mRNA/protein levels of these transporters in 6-hydroxydopamine-lesioned rats [43, 44].

Heavy metal-induced dysfunction of glutamate transporters

Astrocytic glutamate transporters are susceptible to heavy metals, such as lead (Pb) and methylmercury (MeHg), in addition to Mn. Pb has been shown to decrease expression and function of both GLAST and GLT-1 [45]. The effects of Pb on glutamate transporters were region-specific, with the hippocampus being the most vulnerable area, thus correlating with the preponderance of hippocampally-induced cognitive deficits associated with Pb exposure [46]. MeHg exposure has been shown to trigger increased reactive oxygen species, specifically H_2O_2, which inhibited EAAT1/GLAST function as well as EAAT1/GLAST mRNA expression in primary cultures of astrocytes [47]. MeHg also contributes to the dysregulation of glutamate homeostasis by impairing GLAST and GLT-1 function in CHO cells transfected with these transporters [48]. Notably, the MeHg-induced glutamate dyshomeostasis and increased oxidative stress are attenuated by memantine, a *N*-methyl-D-aspartate (NMDA) receptor inhibitor, consistent with MeHg-induced dysregulation of glutamate homeostasis [49].

Mn toxicity associated with dysregulation of glutamate transporters has been a subject of recent studies by our group [50], and it is discussed in the following sections.

Mn neurotoxicity

Mn is an essential trace element that is required for numerous biochemical reactions. It is ubiquitously present in all human tissues and carries out a broad range of functions, including immune response, ATP generation, bone growth, digestion and reproduction [51]. In addition, Mn serves as a cofactor for multiple metalloenzymes, such as glutamine synthetase, mitochondrial superoxide dismutase, arginase and pyruvate decarboxylase [52-54]. However, accumulation of Mn in the brain following chronic exposure to excessive levels of this metal, from either environmental or occupational sources, leads to a neuropathologic sequalae, referred to as manganism. The clinical features of manganism are in large measure analogous to those seen in PD, characterized by cognitive and motor dysfunction [55, 56]. A variety of industries, including welding [57], mining [58], battery production [59], and Mn-alloy plants [60] represent occupational sources of Mn exposures. Environmental sources of Mn exposure include the usage of an Mn-containing gasoline anti-knock additive, methylcyclopentadienyl manganese tricarbonyl (MMT), and fungicidal pesticides, such as maneb [61]. In addition, consumption of soy-based formulas [62], total parenteral nutrition [63] and drinking water contaminated with high levels of Mn [64] represent other potential Mn sources. Mn is absorbed into the human body via inhalation or gastrointestinal absorption, followed by its transport into the brain by various transporters, such as the divalent metal transporter-1 (DMT-1) [65, 66], transferrin [67], and the divalent metal/bicarbonate ion symporters ZIP8 and ZIP14 [4], to name a few. Notably, Mn transport into the brain is enhanced by activation of NMDA receptors [66].

Mn and neurodegenerative disorders

In addition to manganism, which is characterized as a neurological disorder with shared features of PD, a growing body of evidence reveals that Mn overexposure is implicated in multiple neurodegenerative diseases. Chronic exposure to high content of Mn may precipitate PD progression by decreasing striatal dopamine turnover and promoting a-

synuclein misfolding and aggregation [68, 69]. Mn overload has also been suggested to be closely related to ALS as a Mn smelter developed occupational manganism and bulbar ALS in Germany [70]. Moreover, High content of Mn has been reported in ALS cases in the spinal cord [71]. Mn overload has also been implicated in prion disease as Mn triggers misfolding and aggregation of prion protein [72] and elevated Mn levels have been observed in the CNS in human prion disease [73]. Mn overload may play a role in AD as a patient with elevated Mn levels showed dementia and typical pathological signs of AD in the brain such as numerous neuritic plaques and neurofibrillary tangles [74].

Mechanisms of Mn neurotoxicity

Given that Mn neurotoxicity is associated with multiple neurodegenerative diseases [4], numerous studies have been conducted in order to understand the cellular and molecular mechanisms involved in Mn effects in the brain. Oxidative stress, mitochondrial dysfunction, apoptosis, inflammation and excitotoxicity have been posited as the primary molecular and cellular mechanisms of Mn-induced neurotoxicity. Since Mn accumulates in dopamine-rich regions of the brain, such as the globus pallidus, substantia nigra and striatum, Mn-induced dopamine oxidation has also been suggested as a primary mechanism of its neurotoxicity [75, 76]. Moreover, Mn directly induces oxidative stress, as both in rats [77] and primates [78] it decreases glutathione (GSH) levels, and treatment with anti-oxidants (N-acetylcysteine) rescues the Mn-induced pathological phenotype [79].

The preferential sequestration of Mn in mitochondria makes this energy producing organelle vulnerable to Mn toxicity. In mitochondria, Mn interferes with oxidative phosphorylation by inhibiting F_1ATPase at low levels [80], and by inhibiting complex I of the electron transport chain at higher concentrations [81]. Mn-induced apoptosis and inflammation also play an important role in Mn neurotoxicity. During Mn-induced apoptotic cell death, both extrinsic and intrinsic apoptotic pathways are activated both in astrocytes and neurons [82, 83]. Moreover, Mn potentiates the release of several inflammatory molecules, including cytokines, such as TNF-α, IL-6 and IL-1β, prostaglandins, and nitric oxide from activated glial cells, leading to neuroinflammation [84-86]. Excitotoxic neuronal death also contributes to Mn neurotoxicity, as Mn reduces the expression and function of astrocytic glutamate transporters [87, 88]. Inhibition of NMDA receptors with MK 801, an NMDA antagonist, reverses Mn-induced lesions in rat striatum, affirming the involvement of excitotoxic neuronal injury in Mn-induced neurotoxicity [89].

Mn-induced astrocytic dysregulation

Astrocytes preferentially take up Mn, concentrating it up to 50-60 fold higher than in adjacent neurons [90]. Accordingly, astrocytes are considered as the primary site of early damage and dysfunction upon elevated cerebral Mn levels. In addition to manganism, another neuropathological condition that is associated with astrocyte-mediated Mn toxicity is hepatic encephalopathy (HE), which is characterized by brain edema secondary to astrocyte swelling [91]. HE is accompanied by increased levels of Mn in the blood and brain [92], and the development of Alzheimer's type II astrocytes by displaying enlarged pale nuclei and prominent nucleoli [93]. Oxidative/nitrosative stress and mitochondrial dysfunction are involved in Mn-induced astrocyte swelling since pretreatment of astrocytes

with vitamin E (antioxidant), L-NAME (nitric oxide synthase inhibitor) and Cyclosporin A (mitochondrial permeability transition inhibitor) attenuate astrocyte swelling [91]. Mn-induced astrocyte swelling is mediated by enhanced membrane expression of water channel protein aquaporin-4, as knockdown of aquaporin-4 with siRNA significantly attenuates Mn-induced astrocyte swelling [94].

Reactive astrocyte-induced generation of pro-inflammatory molecules with a subsequent neuroinflammation represents a key feature of Mn-induced neurotoxicity. This Mn action in astrocytes might be important because neuroinflammation is also inherent to several neurodegenerative diseases, including ALS and PD [84, 95, 96]. Co-treatment of astrocytes with subtoxic levels of Mn and the inflammatory inducer, lipopolysaccharide, or interferon-γ potentiates production and expression of inflammatory mediators, such as prostaglandin E2 and COX-2 [97]. Notably, the production of inflammatory molecules, especially TNF-α and IL-1β is directly related to the impairment in GLT-1 function [98, 99].

A role for astrocytic nitric oxide synthase 2 (NOS2) has been implicated in Mn-induced neurotoxicity, as genetic deletion of NOS2 (in ducible NOS) attenuates its neurotoxicity [100], and neuronal injury coincides with increased reactive astrocytes expressing NOS2 in Mn-exposed mice [101]. Taken together, astrocytes appear to play a critical role in Mn-induced neurotoxicity by multiple mechanisms, such as astrocyte swelling, inflammation and glutamate transporter dysfunction. Among those, impaired glutamate transporter function might be the most important factor due to its propensity to trigger excitotoxic neuronal injury.

Mn-induced impairment of astrocytic glutamate transporters

Inflammation and oxidative stress are likely involved in Mn-induced dysregulation of astrocytic glutamate transporters since oxidative stress inhibits glutamate transporter function [102]. In astrocytes, oxidative stressors such as peroxynitrite and H_2O_2 inhibit glutamate uptake via EAAT1, EAAT2 and EAAT3, while treatment with reducing agents, such as dithithreotol restores glutamate uptake [103]. The role of Mn-induced neuroinflammation has been implicated in the impairment of glutamate transporter expression and function, as Mn treatment releases inflammatory cytokine TNF-α [104] which reduces expression and function of GLT-1 [99].

The protein kinase C (PKC) pathway might play a critical role in mediating Mn-induced dysfunction of astrocytic glutamate transporters [105, 106]. Mn increases the phosphorylation of both the PKC-α and -δ isoforms in astrocytes [107], whereas inhibition of PKC reverses the Mn-induced decrease in glutamate uptake, as well as GLT-1 and GLAST protein levels [106]. Mn-induced activation of the apoptotic pathway also plays a role in the reduction of astrocytic glutamate transporter expression, since a pan caspase inhibitor, Z-VAD-FMK, efficiently attenuates Mn-induced reduction in glutamate uptake, as well as GLT-1 and GLAST protein levels [108].

Mechanisms of Mn-induced reduction of GLT-1/GLAST at the transcriptional level

Given that the reduction in expression and function of glutamate transporters is inherent to a myriad of neurodegenerative diseases, identifying the molecular target of Mn-induced

reduction in astrocytic glutamate transporter expression at the transcription level would be highly desirable. It may facilitate the development of novel therapeutics to restore impairment in glutamate transporter function. Several studies have shown that NF-κB mediates the stimulatory effects of various positive regulators of GLT-1, including neuronal secreting factors [109], epidermal growth factor, dibutyryl cAMP [110], ceftriaxone [111], as well as estrogenic compounds such as estrogen, tamoxifen and raloxifene [112, 113].

However, the negative regulatory mechanism of GLT-1 at the transcriptional level remains largely unexplored. Recently, findings from our group revealed that the transcription factor yin yang 1 (YY1) is a critical repressor of GLT-1 and also mediates Mn-induced down-regulation of GLT-1 in astrocytes as shown in Figure 1 [104].

YY1 is a critical mediator for Mn-induced reduction of GLT-1 expression and function

YY1 is a multifunctional transcription factor that can initiate, activate or repress gene transcription depending on its interaction with other available cellular factors [114]. It is composed of 414 amino acids with four zinc fingers at the C-terminus in human YY1 [115]. Although the role of YY1 in the physiological as well as pathological conditions has been studied extensively in developmental and cancer biology [116, 117], YY1 has also been recognized to play a critical role in the nervous system such as neural development [118] and developmental myelination [119]. In astrocytes, YY1 is involved in regulation of glutamate homeostatis by modulating glutamate transporters, GLAST and GLT-1. It has been reported that excess glutamate increased YY1 binding to GLAST promoter and decreased glutamate uptake in chick Bergman glia cells [120]. Moreover, astrocyte elevated gene-1 (AEG-1) recruited YY1 to repress GLT-1 promoter activity and glutamate uptake in primary fetal human astrocytes [121]. Recently, our findings established that Mn enhanced YY1 promoter activity, YY1 mRNA and protein levels via NF-κB activation. Mn-induced TNF-α release from astrocytes may mediate the effects of Mn on GLT-1 repression via YY1 as TNF-α increased YY1 promoter activity, mRNA and protein levels, whereas it represses GLT-1 mRNA levels as shown in Fig. 1 [99].

Role of Histone deacetylases (HDACs) in Mn-activated YY modulation on GLT-1

Epigenetically, HDACs classes I and II serve as critical co-repressors of YY1 for GLT-1 promoter activity, and Mn enhances the interaction between YY1 and HDAC1 [104]. Interestingly, YY1 is a dominant factor by overriding the positive action of NF-κB on GLT-1 promoter activity when the two are simultaneously activated. Mn enhances the interaction of YY1 with NF-κB [104], suggesting that Mn activates NF-κB for GLT-1 activity, but decreases GLT-1 expression. HDAC inhibitors increase GLT-1 promoter activity and reverse the Mn- induced repression of GLT-1 promoter activity [104]. These results demonstrate that YY1, using HDACs as co-repressors, is a critical negative transcriptional regulator of GLT-1 and mediates Mn-induced GLT-1 repression. In addition, our findings provide molecular insight into Mn neurotoxicity, as well as neurological disorders associated with impairment of GLT-1 expression.

Summary

Astrocytes play a pivotal role in normal physiological functions of the brain including neuronal synaptic activities through various mechanisms. In addition, as predominant sources of anti-oxidants and numerous growth factors, astrocytes play a critical role in neuroprotection against various forms of toxic stimuli and brain injuries. More importantly, maintaining optimal glutamate levels in the synaptic cleft by removing excess glutamate into astrocytes via glutamate transporters represents one of the most important functions of these cells. Given that various neurological disorders, including manganism, are associated with dysfunction of astrocytic glutamate transporters, elucidation of molecular mechanisms by which Mn decreases expression of these transporters is imperative for identifying molecular targets and the development of potential therapeutics against neurodegenerative diseases. Our findings that YY1 plays a critical role in Mn-induced repression of GLT-1 gene transcription offers new insights for targeting such signaling pathways to treat neurological disorders associated with GLT-1 dysfunction and increased concetrations of synaptic glutamate levels.

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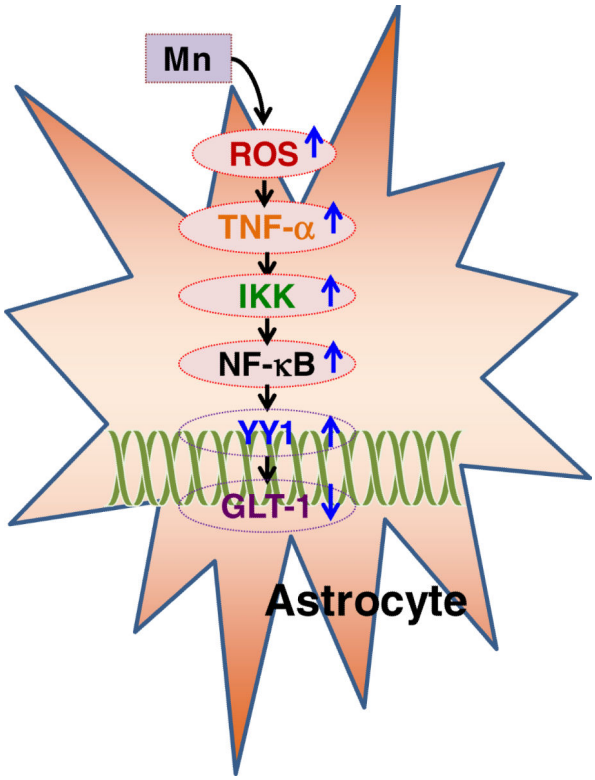

Figure 1.

Mn produces ROS and TNF-α which activate YY1 via the IKK/NF-κB pathway. YY1 is a repressor of the GLT-1 promoter and decreases GLT-1 expression. IKK, IκB kinase; TNF-α: tumor necrosis factor-α; NF-κB, nuclear factor κB.