

Manganese neurotoxicity and GABA/glutamate interactions

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Abstract:

Brain extracellular concentrations of amino acids (e.g. aspartate, glutamate, taurine) and divalent metals (e.g. zinc, copper, manganese) are primarily regulated by astrocytes. Adequate glutamate homeostasis is essential for the normal functioning of the central nervous system (CNS). Glutamate is of central importance for nitrogen metabolism and, along with aspartate, is the primary mediator of the excitatory pathways in the brain. Similarly, the maintenance of proper manganese levels is important for normal brain functioning. Several *in vivo* and *in vitro* studies have linked increased manganese concentrations with alterations in the content and metabolism of neurotransmitters, namely dopamine, γ -aminobutyric acid, and glutamate. It has been reported by our laboratory and others, that cultured rat primary astrocytes exposed to manganese displayed decreased glutamate uptake, thereby increasing the excitotoxic potential of glutamate. Furthermore, decreased uptake of glutamate has been associated with decreased gene expression of glutamate: aspartate transporter (GLAST) in manganese-exposed astrocytes. Additional studies have suggested that attenuation of astrocytic glutamate uptake by manganese may be a consequence of reactive oxygen species (ROS) generation. Collectively, these data suggest that excitotoxicity may occur due to manganese-induced altered glutamate metabolism, representing a proximate mechanism for manganese-induced neurotoxicity.

Keywords: Manganese; Glutamate-GABA; Neurotoxicity

Article:

1. Introduction

Manganese (Mn) is an essential trace element that is found in varying amounts in all tissues. Manganese concentrations are highest in tissues rich in mitochondria, where it forms stable complexes with ATP and inorganic phosphate. Manganese functions as a constituent of metalloenzymes and an activator of enzymes. For example, arginase, a manganese containing enzyme, is essential in urea formation; pyruvate carboxylase, the rate-limiting enzyme in gluconeogenesis, and the antioxidant, manganese superoxide dismutase (Mn-SOD), also utilize manganese as a constituent ([Hurley and Keen, 1987](#)). While rare in occurrence, manganese deficiency in humans has been reported, and it is characterized with skeletal abnormalities and seizure activity, probably due to decreased MnSOD and glutamine synthetase (GS) activities ([Critchfield et al., 1993](#)). Exposure to excessive manganese is more widely reported (see below for conditions) and it is associated with psychological and motor disturbances ([Calne et al., 1994](#); [Pal et al., 1999](#)).

Symptoms of chronic manganese neurotoxicity (manganism) are similar to those associated with Parkinson's Disease (PD); however, clinically they are distinct. Similarities between PD and manganism include the presence of generalized bradykinesia and widespread rigidity. Dissimilarities between PD and manganism include (1) a less frequent resting tremor, (2) more frequent dystonia, (3) a particular propensity to fall backwards, (4) failure to detect a reduction in fluorodopa uptake by positron emission tomography (PET; [Calne et al., 1994](#); [Pal et al., 1999](#)) in manganism. Given these clinical differences, it has been proposed that manganese neurotoxicity does not directly damage the nigrostriatal pathway, as in PD, but causes PD-like effects by damaging output pathways downstream from the nigrostriatal dopaminergic pathway (see [Fig. 1 A](#); [Calne et al., 1994](#); [Pal et al., 1999](#); [Verity, 1999](#)). Manganism is linked with increased brain levels of manganese, primarily in those brain regions known to be iron-rich, namely, caudate putamen, globus pallidus, substantia nigra, and subthalamic nuclei. These regions are collectively referred to as the basal ganglia.

Glutamate is the most prevalent excitatory neurotransmitter (Cotman et al., 1981), whereas γ -aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter (Olsen and DeLorey, 1999).

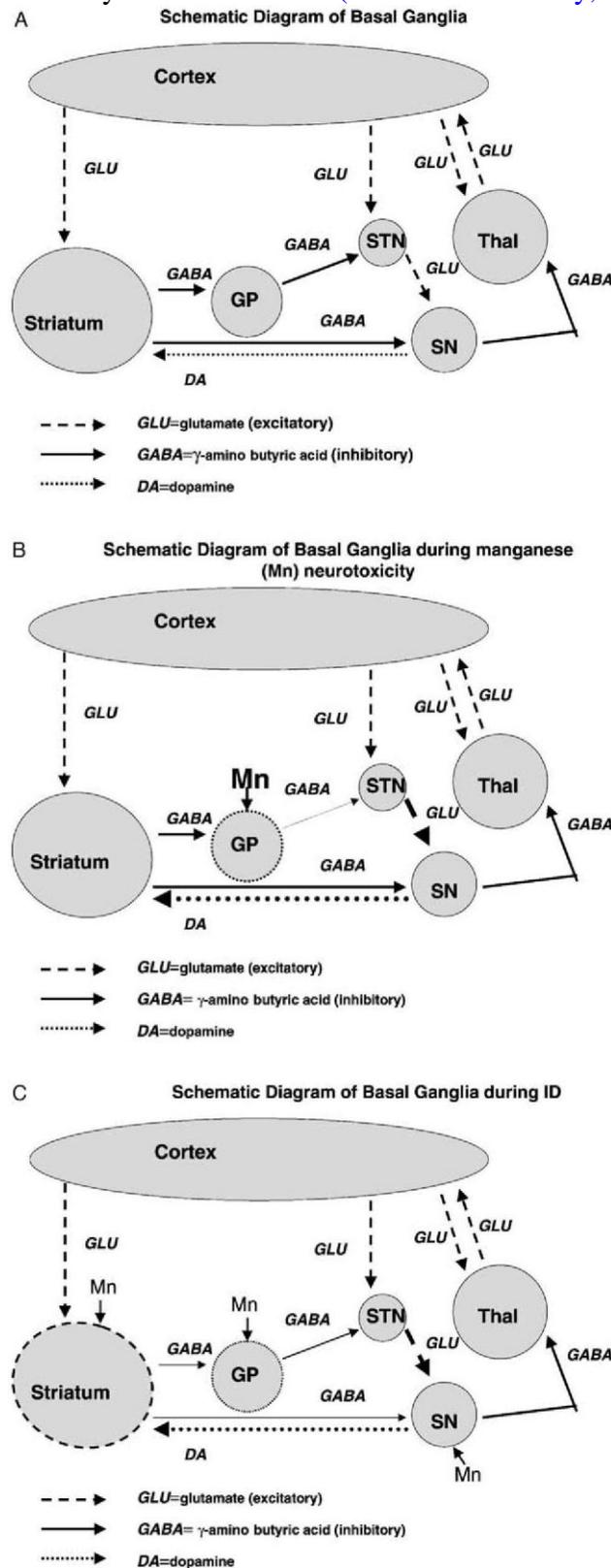


Fig. 1. (A) This simplified schematic diagram of the basal ganglia depicts the primary neurotransmitters required for normal functioning. GP: globus pallidus, STN: subthalamic nuclei, Thal: thalamus, SN: substantia nigra. Adapted from Graybiel (1990) and Verity (1999). (B) During manganism, it is hypothesized that manganese accumulates in the brain, primarily in the globus pallidus. Increased regional manganese causes degeneration leading to decreased GABAergic output into the subthalamic nuclei. Glutamatergic

input into the substantia nigra from the subthalamic nuclei is unregulated leading to dopaminergic dysfunction in the striatum. The thickness of the lines illustrate strength of neurotransmission. GP: globus pallidus, STN: subthalamic nuclei, Thal: thalamus, SN: substantia nigra. Adapted from Graybiel (1990) and Verity (1999). (C) During iron deficiency (ID), several brain regions (striatum, globus pallidus and substantia nigra) significantly accumulate manganese, but to a lesser extent than is reported in manganism. ID-associated manganese accumulation in the striatum is negatively correlated with GABA (Erikson et al., 2002). This relationship may reflect decreased GABAergic firing into the substantia nigra which may contribute to the dopaminergic alterations characterized by ID (see Erikson et al., 2000, 2001). The thickness of the lines illustrate strength of neurotransmission. GP: globus pallidus, STN: subthalamic nuclei, Thal: thalamus, SN: substantia nigra. Adapted from Graybiel (1990) and Verity (1999).

Cortical glutamate afferents project into the striatum where, in concert with GABA and dopamine, motor behaviors are controlled (Carlsson and Carlsson, 1990). Glutamate is converted to GABA by decarboxylation via glutamate decarboxylase (GAD) and is degraded via GABA-transaminase. Altered glutamatergic and GABAergic functioning can contribute to altered striatal dopamine metabolism (Page et al., 2001; Castro and Zigmond, 2001). Therefore, we have postulated that the neurotoxic effects of manganese on striatal dopamine may be indirectly mediated via abnormal striatal glutamate and/or GABA metabolism, and that temporally, changes in areas that are known to avidly accumulate manganese precede the well described effects of manganese on dopaminergic function. Specifically, it is hypothesized that manganese accumulation in the globus pallidus causes decreased GABAergic efferent firing from the globus pallidus into the subthalamic nuclei. Consequently, glutamatergic projections into the substantia nigra that originate from the subthalamic nuclei, will fire in an uncontrolled manner causing dysregulation of dopaminergic output into the striatum from the substantia nigra (see Fig. 1B). This review will discuss some of the latest studies that focus on manganese-induced alterations of glutamate neurochemistry.

2. Susceptible subpopulations to manganese toxicity

In addition to occupational exposures to manganese, liver disease is a known risk factor for increased accumulation of manganese in the brain, both in humans and in animal models (Malecki et al., 1999a; Herynek et al., 2001; Montes et al., 2001). Liver disease is associated with decreased biliary excretion of manganese and those afflicted with biliary atresia display hypermanganesemia and T1-weighted magnetic resonance imaging (MRI) signal hyperintensity in the globus pallidus (Rose et al., 1999; Reimund et al., 2000; Ikeda et al.,

2000a; Ikeda et al., 2000b). Hepatic encephalopathy is a neuropathological complication of cirrhosis, and patients afflicted with the disease display bilateral signal hyperintensities in the globus pallidus thought to be due to manganese deposition. As previously reported, the psychiatric alterations associated with this condition are likely caused by altered glutamate metabolism due to increased brain manganese (Hazell and Norenberg, 1997; Zhou and Norenberg, 1999).

It is estimated that approximately 2 billion people suffer from iron deficiency (ID) throughout the world (ACC/SCN, report, 1992). ID is associated with increased dietary manganese absorption in both humans and animals (Finley, 1999; Davis et al., 1992). In addition, rats exposed to high doses of manganese exhibit altered brain iron metabolism (Zheng et al., 1999). Furthermore, ID is associated with increased manganese accumulation in the brain (Chua and Morgan, 1996; Kwik-Urbe et al., 2000).

Both manganese and iron transport to extrahepatic tissues, including the brain, are dependent upon transferrin-mediated endocytosis (Crowe and Morgan, 1992; Malecki et al., 1999b). Furthermore, ID causes increased brain regional transferrin (Tf) and transferrin receptor (TfR) concentrations in a heterogeneous fashion (Chen et al., 1995; Erikson et al., 1997; Pinero et al., 2000). Recently, our laboratory has shown that ID causes significant manganese accumulation in several brain regions of rats and that this change in manganese levels correlates with neurochemical alterations (Erikson et al., 2002). Specifically, glutamate and GABA levels are significantly lowered (see Section 3).

3. In vivo studies

Reports of glutamate and GABA concentrations in the rat brain upon manganese exposure are inconsistent. For example, exposure to 6 mg Mn/kg per day (\approx 10 times normal intake), led to a significant increase in brain manganese concentrations and significant decrease in GABA concentrations (Lai et al., 1984). Another report showed that rats exposed to 20 mg Mn/kg per day (\approx 30 times normal intake) had significantly increased brain manganese, GABA, and glutamate concentrations (Lipe et al., 1999). Accordingly, it appears that a relationship exists between the severity of manganese exposure and neurotransmitter concentrations, with lower manganese exposure leading to decreased GABA and glutamate, and high manganese-exposure leading to increased GABA and glutamate concentrations.

Our laboratory recently reported manganese associated decreases in glutamate and GABA levels in rat brains (Erikson et al., 2002). These changes were directly related to dietary treatment with semi-purified diets containing varying amounts of iron and manganese. Specifically, weanling rats were fed either a normal diet (3 ppm Fe, 10 ppm Mn), iron deficient (3 ppm Fe, 10 ppm Mn) or iron deficient: manganese supplemented (3 ppm Fe, 100 ppm Mn).

Seven brain regions were analyzed for manganese and amino acids (including glutamate and GABA). ID caused a significant increase in manganese levels in caudate putamen, globus pallidus, hippocampus, thalamus, cortex, cerebellum and substantia nigra. Furthermore, increased dietary manganese did not cause significant increases in regional manganese levels beyond ID, corroborating previous studies which showed that despite severe levels of manganese exposure, brain manganese concentration only increased 2–3-fold (Dorman et al., 2001). In the same experiments (Erikson et al., 2002), GABA concentration was negatively correlated with manganese levels in the striatum, whereas the effects on glutamate concentrations were observed only in the cortex.

Fig. 1C emphasizes the brain regions (striatum, globus pallidus and substantia nigra) where ID-associated manganese accumulation leads to altered neurotransmitter levels. A novel finding from our study was that the manganese concentration in the striatum was negatively correlated with GABA concentration. This relationship is noteworthy for it suggests that the striatum is sensitive to a modest increase in manganese concentration (\approx 40% increase compared to control) which leads to a disturbance in GABA levels. This disturbance in GABAergic inhibitory firing into the substantia nigra may lead to dopaminergic dysfunction in the striatum (e.g. increased striatal dopamine levels). The primary neurobiological symptoms of ID are dopaminergic disturbances (Erikson et al., 2000, 2001). It is possible that some of these alterations in dopamine metabolism observed in ID may be due to abnormal GABAergic functioning due to manganese accumulation. Overall lending credence to the hypothesis that changes in GABA neurobiology may precede changes in dopamine functioning during manganese exposure.

While it is attractive to hypothesize that changes in glutamate and/or GABA precipitate the altered dopamine metabolism seen in manganism, virtually no studies exist to support this notion. A recent study examined the effects of sub-chronic manganese exposure in a pre-Parkinson's rat model (Gwiazda et al., 2002). The study utilized 6-OH dopamine exposed rats as the pre-Parkinson's model. They injected the rats with 4.8 mg Mn/kg body weight for three times a week for 5 weeks. Striatal GABA levels were increased upon manganese exposure, but dopamine levels remained unchanged, suggesting that the GABAergic system may be more sensitive than dopaminergic systems to increased manganese levels, particularly in the striatum. Similar effects may exist for glutamate-related changes due to manganese exposure, but those data are lacking.

4. In vitro studies

It has also been shown that manganese neurotoxicity may be due to an indirect excitotoxic event caused by altered glutamate metabolism (Brouillet et al., 1993). In the brain, both manganese uptake (Aschner et al., 1992) and glutamate uptake predominantly occur in astrocytes. Astrocytes take up glutamate by a Na^+ -dependent mechanism (Hertz, 1979). In the presence of ammonia, glutamate is metabolized to glutamine by the astrocyte-specific enzyme glutamine synthetase (GS; Martinez-Hernandez et al., 1977), maintaining [glutamate]_o at 0.3 μM (Waniewski and Martin, 1986). This represents a 10,000-fold gradient versus [glutamate]_i (3 mM). This

glutamate–glutamine pathway constitutes the source of a glutamate pool in brain (Berl et al., 1961). GS contains eight manganese ions per octamer, and accounts for approximately 80% of total manganese in brain. Unlike neurons, astrocytes have the ability to concentrate manganese at levels 50-fold higher than the culture media (Wedler et al., 1989; Aschner et al., 1992), providing a mechanism by which manganese concentrations in astrocytic cytosol could attain the range required for activation of GS. Recent studies in our laboratory (Erikson and Aschner, 2002; Erikson et al., 2002) and others (Hazell and Norenberg, 1997) have demonstrated that glutamate uptake is significantly attenuated in primary astrocyte cultures upon addition of manganese to the culture medium. Recently, Lafon-Cazal et al. (1993) showed that glutamate receptor (*N*-methyl-D-aspartate; NMDA) stimulation produces significant elevations in both super-oxide and hydroxyl radicals in cultured cerebellar granule cells.

Interference with glutamate transporter function will lead to increased extracellular glutamate concentrations. Potential reactive oxygen species (ROS) generation as a consequence of manganese exposure will further oppose the removal of extracellular glutamate by inhibiting the high affinity glutamate transporters (Trotti et al., 1998). This manganese induced ROS generation is theorized to be due to interference with respiration in the mitochondria, although this remains controversial. Furthermore, decreased [³H]-D-aspartate in astrocytes is attenuated upon antioxidant treatment, suggesting that ROS play a role in altering the glutamate uptake process in astrocytes (Allen et al., 2001). The cumulative sum of these events will trigger an amplifying cycle, potentially contributing to the dysfunction of astrocytes and their inability to maintain optimal control over the extracellular milieu, thereby, indirectly leading to neuronal demise via glutamate receptor activation (NMDA).

Astrocytes are equipped with mechanism(s) for the rapid removal of glutamate from synaptic clefts. This uptake process occurs via sodium/potassium-dependent membrane proteins known as glutamate transporters. While there are several glutamate transporters known to be important for neuronal functioning, GLT-1 (glutamate transporter) and GLAST (glutamate/aspartate transporter) are the prominent astrocytic transporters (see Danbolt, 2001 for review).

GLAST (glutamate and aspartate transporter) is the most prevalent glutamate transporter in cultured astrocytes (Kondo et al., 1995). It is, therefore, probable that the decreased glutamate uptake observed in manganese-exposed astrocytes (250 μM MnCl₂ for 18 h) represents decreased GLAST expression (Erikson and Aschner, 2002). Glutamate transporters are rapidly synthesized, and a cytosolic pool of these proteins is available for plasma membrane insertion as functional proteins in response to changes in extracellular glutamate levels (Davis et al., 1998). Decreased glutamate uptake observed in manganese-exposed astrocytes is, therefore, potentially due to decreased functional glutamate transporters (e.g. GLAST). Although most literature on manganese neurotoxicity and neurotransmitter metabolism focuses on alterations in the dopamine system (see Verity, 1999 for review), these studies lend credence to the possibility of alterations in the glutamatergic system, as well as GABA systems, particularly in striatum where cortical glutamatergic afferents converge.

5. Conclusion

A key neurochemical alteration associated with manganese neurotoxicity is altered extracellular glutamate levels. Attenuated glutamate uptake by astrocytes has been invoked as the primary cause for this disturbance (Hazell and Norenberg, 1997; Erikson and Aschner, 2002). Most likely, manganese affects the regulation of glutamate transporter genes (e.g. GLAST) (Erikson and Aschner, 2002), possibly through ROS generation, although this has not been directly studied. The ensuing increase in extracellular glutamate concentrations is potentially excitotoxic to juxtaposed neurons, representing a proximate cause of manganese neurotoxicity. ID is associated with altered glutamate and GABA metabolism which can partially be attributed to increased brain manganese and/or disturbances in dopamine metabolism (Erikson et al., 2000, 2001). Furthermore, while tissue levels of GABA and glutamate are known consequences of ID-associated manganese increases, potential changes in the extracellular levels of these neurotransmitters upon manganese exposure are yet to be determined. It is these extracellular levels of GABA and glutamate coupled with tissue levels that will elucidate more clearly the neurochemical consequences of manganese neurotoxicity.

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