Impairment of glutamine/glutamate-γ-aminobutyric acid cycle in manganese toxicity in the Central Nervous System

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Manganese (Mn) is an essential trace element that is required for maintaining the proper function and regulation of many biochemical and cellular reactions. Despite its essentiality, at excessive levels Mn is toxic to the central nervous system (CNS). The overdose accumulation of Mn in specific brain areas, such as the substantia nigra, the globus pallidus and the striatum, triggers neurotoxicity resulting in a neurological brain disorder, referred to as manganism. Mn toxicity is associated with the disruption of glutamine (Gln)/glutamate (Glu) GABA cycle (GGC). The GGC represents a complex process, since Gln efflux from astrocytes must be met by its influx in neurons. Mn toxicity is associated with the disruption of both of these critical points in the cycle. In cultured astrocytes, pre-treatment with Mn inhibits the initial net uptake of Gln in a concentration-dependent manner. Mn added directly to primary culture of astrocytes induces deregulation in the expression of SNAT3, SNAT2, ASCT2 and LAT2 transporters and significantly decreases in Gln uptake mediated by the transporting Systems N and ASC, and a decrease in Gln efflux mediated by Systems N, ASC and L. Further, Mn disrupts Glu transporting systems leading to both a reduction in Glu uptake and elevation in extracellular Glu levels. Interestingly, there appear to be common signaling targets of Mn in GGC cycling in glial cells. Namely, the PKC signaling is affected by Mn in glutamine and glutamate transporters expression and function. Additionally, Mn deregulates GS expression and activity. Those evidences could triggers depletion of glutamine synthesis/metabolism in glia cells and consequently diminish astrocytic–derived glutamine, while disruption of Glu removal/transport can mediate dyshomeostasis in neurotransmission of functioning neurons. Here we highlight the mechanistic commonalities inherent to Mn- neurotoxicity related to the astrocyte pathology and GGC impairment.