Abstract

Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder and is the most common cause of dementia. The progression of this multifactorial disease begins many years prior to the onset of cognitive impairment, suggesting the involvement of chronic and/or environmental factors in its pathogenesis. As the fifth most abundant metal on the Earth’s crust, manganese (Mn) is ubiquitously found in the environment and may enter the human body via natural and anthropogenic activities. In contrast to its omnipresence, Mn homeostasis relies on a narrow and delicate balance between its essentiality and toxicity. Chronic exposure to Mn is known to cause disabling neurological effects and studies in animals have shown decreased cognitive function and neurodegeneration. As the brain’s principal excitatory neurotransmitter, glutamate homeostasis is under tight regulation as well. Its extracellular accumulation and prolonged presence in the synaptic cleft is known to cause excitotoxicity, a common denominator in various neurodegenerative diseases, including AD. Taken together, we hypothesize that chronic exposure to elevated Mn disrupts glutamate homeostasis and may be a factor for cognitive decline and AD. To address this hypothesis, we utilized human induced pluripotent stem cells (hiPSC) derived from healthy and AD patients to generate cortical glutamatergic (GLUergic) neurons. Cells were grown for approximately 150 days and heterogeneous cultures of neurons and astrocytes were exposed to 5, 50, and 500 μM Mn for 24 hours. Following exposure, cells were treated with [14C]labeled glutamate for 30 minutes to evaluate glutamate uptake. Our preliminary data displayed decreased uptake of radiolabeled glutamate, further strengthening our hypothesis. Future studies will focus on chronic exposure to a more physiologically relevant concentration of Mn and alterations in glutamate transporters to delineate the mechanism by which Mn induces glutamate dysfunction in AD.

Introduction

- Mn is a naturally occurring essential trace element that can be found in soil, water and the atmosphere. Overexposure to Mn can cause neurotoxicity.
- Glutamate excitotoxicity is implicated in a variety of neurodegenerative disorders including AD, Parkinson’s Disease (PD), and amyotrophic lateral sclerosis (ALS).
- Chronic Mn exposure has been associated with cognitive impairment and diffuse amyloid beta plaques in studies in non-human primates.
- Studies have shown that Mn can decrease the expression of glutamate transporters and reduce the uptake of extracellular glutamate.
- Despite such evidence, the link between Mn and AD remains unclear, warranting further investigation.
- The goal of the present research was to investigate whether exposure to Mn alters glutamate uptake in cortical (CTX) GLUergic neurons/astrocytes generated from healthy or AD patient-derived iPSCs.

Hypothesis

Experimental Design

Results

Conclusions:

- Acute Mn exposure induces an overall decreasing trend in glutamate uptake.
- Preliminary data suggests there may be AD subtype-dependent difference in sensitivity to Mn exposure and altered glutamate homeostasis.
- Our results provide further support for Mn-induced glutamate dysfunction in AD.

Future Directions:

- Multiple cohorts of CTX differentiations are underway and will be further evaluated for:
  - Expression changes in glutamate transporters over time.
  - Sub-cellular localization of glutamate transporters following Mn exposure.
  - Glutamate uptake following chronic Mn exposure at physiologically relevant concentrations.
- Evaluate expression of aquaporin-4 (AQP4) and astrocytic swelling following Mn exposure along with other pertinent cellular/molecular markers of AD pathology.

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References


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