Involvement of APL-1 in Manganese-induced toxicity in *Caenorhabditis elegans* and possible mitigation using Iron Chelators

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Manganese (Mn) is an essential element that participates in several biological processes. However, overexposure to Mn may induce neurotoxicity and contribute to the development of neurodegenerative diseases such as Alzheimer's disease (AD). While the pathophysiology of AD is still unclear, aggregation of misfolded β-amyloid (Aβ) plaques in the brain due to changes in amyloid precursor protein (APP) processing has been postulated to contribute to development of AD. Environmental exposure to Mn have been implicated in the etiology of Alzheimer's disease. Here, we used *Caenorhabditis elegans* (*C. elegans*) as a model to explore putative mechanisms of neurodegeneration secondary to exposure to Mn and mitigation using 3 iron chelators: deferoxamine mesylate (DFO), salicylaldehyde isonicotinoyl hydrazone (SIH) and deferoxamine-caffeine (DFCAF). Specifically, APL-1, the *C. elegans* orthologue of mammalian APP, was studied to evaluate its role in neurotoxicity. Studies were carried out in wild-type N2 and APL-1 (yn5) strains to assess sensitivity to reactive oxygen species (ROS) generation, as well as in BY200 worms, where dopaminergic neurons are labeled with green fluorescent protein (GFP) for the evaluation of neurodegeneration. The results showed that the APL-1 strain was more sensitive to Mn than wild-type worms. Moreover, we observed increased levels of ROS upon exposure to Mn (50 mM) in N2 and APL-1 worms compared to controls. Worms exposed to Mn showed increased dopaminergic neurodegeneration, which was rescued iron chelator treatments. Our results show that Mn causes APL-1-dependent increases in ROS levels and neurodegeneration and that treatment with iron chelators can mitigate the Mn-induced effects.