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Manganese causes neurotoxic iron accumulation via translational repression of amyloid precursor protein and H-Ferritin.

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Abstract

For more than 150 years, it is known that occupational overexposure of **manganese** (Mn) causes movement disorders resembling Parkinson's disease (PD) and PD-like **syndromes**. However, the mechanisms of Mn toxicity are still poorly understood. Here, we demonstrate that Mn dose- and time-dependently blocks the protein translation of amyloid precursor protein (APP) and heavy-chain Ferritin (H-Ferritin), both iron homeostatic proteins with neuroprotective features. APP and H-Ferritin are post-transcriptionally regulated by iron responsive proteins, which bind to homologous iron responsive elements (IREs) located in the 5'-untranslated regions (5'-UTRs) within their mRNA

transcripts. Using reporter assays, we demonstrate that Mn exposure repressed the 5'-UTR-activity of APP and H-Ferritin, presumably via increased iron responsive proteins-iron responsive elements binding, ultimately blocking their protein translation. Using two specific Fe^{2+} -specific probes (RhoNox-1 and IP-1) and ion chromatography inductively coupled plasma mass spectrometry (IC-ICP-MS), we show that loss of the protective axis of APP and H-Ferritin resulted in unchecked accumulation of redox-active ferrous iron (Fe^{2+}) fueling neurotoxic oxidative stress. Enforced APP expression partially attenuated Mn-induced generation of cellular and lipid reactive oxygen species and **neurotoxicity**. Lastly, we could validate the Mn-mediated suppression of APP and H-Ferritin in two rodent in vivo models (C57BL6/N mice and RjHan:SD rats) mimicking acute and chronic Mn exposure. Together, these results suggest that Mn-induced **neurotoxicity** is partly attributable to the translational inhibition of APP and H-Ferritin resulting in impaired iron metabolism and exacerbated neurotoxic oxidative stress. OPEN SCIENCE BADGES: This article has received a badge for *Open Materials* because it provided all relevant information to reproduce the study in the manuscript. The complete Open Science Disclosure form for this article can be found at the end of the article. More information about the Open Practices badges can be found at https://cos.io/our-services/open-science-badges/.

KEYWORDS: H-ferritin; SH-SY5Y neural-like cell line; amyloid precursor protein (APP); iron responsive element (IRE); **manganese** (Mn); reactive oxygen species (ROS)

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