Mn Neurotoxic Mechanism and its Effects on Human Health: Acute Versus Chronic

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Short Communication

Numerous theories have been put forward to define the biological basis of Mn-induced neurotoxicity since a large body of evidence supports the neurotoxic effects of acute Mn overload. Despite the fact that neurological illnesses and Mn toxicity share some clinical characteristics and/or pathways, as well as evidence of disturbed Mn homeostasis in human patients, our knowledge of how chronic Mn exposure may cause or worsen CNS morbidities is still limited. There is a gap in our knowledge regarding the extent to which chronic low-dose metal exposures contribute to neurological disease in comparison to other risk factors. Then, if so, do they accomplish this through the same pathways that lead to their acute neurotoxicity? This is crucial to comprehend the mechanisms underlying the latent and/or chronic effects of neurotoxic metals. We now lack a framework in order to accurately establish a probabilistic and mechanical connection between chronic metal exposure and long-term neurological consequences. The following crucial characteristics of Mn, and more generally, metal toxicity, need to be taken into account in order to close this knowledge gap.

Depending on the length of exposure, toxicity can be either acute or chronic. The former describes unfavourable reactions that happen in response to one or more exposures over a brief period of time (hours to days), with modest variations depending on the model system [1]. It often entails quantifying a certain biological outcome and establishing a dose-effect connection. It's important to note that acute in vitro Mn toxicity studies frequently use concentrations that are far higher (even lethal) than ambient values, and the endpoint measurements are taken nearly immediately after the exposure window has closed. Even though such studies can disclose the immediate effects of overload and offer valuable mechanistic insight, they do not fully reflect actual exposures or compensatory adjustments made in response to chronic overload.

It is crucial to keep in mind that actual human exposures take place over a long period of time, ranging from months to years, and involve lower extracellular or intracellular Mn levels that are not linked to cell death in acute neurotoxicity studies. In addition, higher chronic Mn exposures, which are frequently linked to occupational settings and the development of manganism, are associated with distinct pathologies that are at least partially unrelated to those seen with lower chronic Mn exposures, according to environmental epidemiological studies involving both adults and children who have received excessive Mn exposure from tainted drinking water, air, or infant formula [2]. Additionally, Mn neurotoxicity does not immediately show neurological symptoms; instead, they may develop slowly over years or at subclinical levels, accompanied by modest structural changes in the brain. These lines of evidence imply that chronic Mn poisoning involves a latent phase that is consistent with the progressive emergence of neurological problems [3].

Further research is necessary because the mechanisms underlying the cellular alterations brought on by chronic Mn poisoning remain obscure. Furthermore, there is a strong likelihood that sex, age, persistence and latency of effect interact in complex ways. Ageing does enhance vulnerability to Mn toxicity and is the main risk factor for neurological diseases [4]. In contrast, due to their immature excretion mechanisms and developing brains, children may experience a different course of Mn-induced neurotoxicity. Additionally, there is a developing understanding of potential sex-dependent susceptibility differences [5].

Even though there is an urgent need for a thorough description of the molecular concepts causing chronic Mn neurotoxicity, data from recent literature offers some fascinating insights. By using RNA sequencing for a transcriptome analysis on the human neuroblastoma SH5-SY5Y cell line, it was shown that distinct patterns of gene expression were induced after 5-hour exposures to physiological (10 M) and hazardous (100 M) levels of MnCl2, respectively, compared to controls. At normal and hazardous Mn levels, respectively, genes involved in the Endoplasmic Reticulum (ER)-Golgi secretory pathway and mitochondrial oxidative phosphorylation were elevated. Similar to this, a prior metabolomic investigation conducted by the same team utilising the same exposure paradigm and model demonstrated significant alterations in energy and fatty acid metabolites at 100 M and neuroprotective amino acid metabolites at 10 M [6]. Another study that examined the effects of various acute Mn exposure levels on mitochondria and cellular energetic metabolism using a mouse striatal neuronal cell line was unable to find any proof of Mn-dependent mitochondrial malfunction at exposures below the acute lethal threshold. These findings imply that low-level Mn exposures may not directly affect mitochondrial and energy processes. On the other hand, transcriptome research on male mice fed a diet deficient in Mn for two weeks revealed a transcriptional profile that was different from controls. It is interesting to notice that the differentially expressed genes from the cells with high Mn levels from the aforementioned study and the authors' Mn-deficient mice were not at odds with one another. Although in vitro-in vivo extrapolation makes it difficult to meaningfully compare the aforementioned studies linearly, they all point to the existence of a cellular adaptive/compensatory mechanism that may serve as a buffer system to handle changes in Mn level. Future research should investigate whether a comparable coping mechanism is present under chronic MN stress and identify the crucial metabolic pathways that are changed.

Acute and chronic Mn poisoning may share certain comparable molecular pathological processes, according to studies. Male Sprague-Dawley rats were given intraperitoneal injections of either 3.6 mg/kg or 18 mg/kg MnCl2 for 150 days at 10-day intervals. These treatments caused signs of Mn-induced neuroinflammation, such as microgliosis and increased gene expression of inflammatory cytokines like tumour necrosis factor-alpha, especially at high Mn concentrations [7]. Interestingly, the number of hepatic Mn transporter genes increased as well, indicating a physiological reaction to deal with the increased Mn burden. A different interpretation, however, that contends that neuroinflammation is not a direct result of Mn per se but rather a secondary impact brought on by other molecular pathologies, such as cellular redox imbalance, is equally worth taking into account. Further in-depth mechanistic studies are therefore required to reveal the linearity in molecular disease and determine if inflammation can be an initial primary impact brought on by chronic low-dose Mn exposure.

Finally, it is important to note that all endpoint measurements were taken within a short temporal window after the conclusion of the exposure, even though the results from the research listed above presented useful information and suggested new areas to investigate. Additionally, since only male animals were used in rodent experiments, it was unable to be determined whether there would be sexual

dimorphism associated with chronic Mn poisoning. In order to advance our understanding of the precise mechanisms underlying Mn neurotoxicity, future studies should, to the best of our ability, address the potential interaction between Mn toxicity and sex, take chronicity into account, and take various temporal endpoint assessments into consideration.

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