REVIEW ARTICLE

Manganese Biological Functions and Neurological Impacts: A Narrated Review

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ABSTRACT

Manganese (Mn) is an essential trace mineral critical to variousbiological processes, including metabolism, antioxidant defense, and enzyme activity. It serves as a cofactor in key metabolic pathways, such as carbohydrate and amino acid metabolism, and plays a pivotal role in the function of enzymes like manganese superoxide dismutase (MnSOD), which protects against oxidative stress by neutralizing free radicals. Additionally, Mn is essential for bone formation, wound healing, and maintaining a healthy immune response by interacting with other transition metals. Despite its vital roles, Mn poses significant health risks when consumed in excess, particularly to neurological health. Excessive Mn exposure, whether from occupational settings like mining and welding or non-occupational sources such as contaminated food and water, can lead to manganism—chronic Mn toxicity. This condition is associated with severe neurological impairments, including motor dysfunction, cognitive decline, and behavioral abnormalities that mimic the symptoms of Parkinson's disease. Mn accumulation in the basal ganglia results in oxidative stress and neuroinflammation, which are believed to drive these effects. Children are morevulnerable to Mn intoxication, with elevated levels linked to poor academic performance, memory difficulties, behavioral problems resembling ADHD, and lower IQ. These cognitive and emotional challenges can significantly impair development and long-term mental health. Given the widespread distribution of Mn, both naturally and industrially, it is essential to establish regulatory measures that limit exposure. Understanding individual variability in Mn metabolism and sensitivity is crucial for developing occupational safety guidelines and public health policies. Mn's multifaceted role in human health underscores the need for balanced consumption to maintain its beneficial effects while minimizing potential toxicity. Comprehensive strategies are necessary to safeguard public health and ensure the well-being of future generations.

Keywords:
Manganese: Mineral: Essential; Health impact; Neurological Impact

INTRODUCTION

Manganese (Mn) is an element naturally occurring in rocks, soils, and sediments. It is an essential trace mineral the body requires in small amounts for various biological functions that contribute to overall well-being and optimal performance (Baj, et al., 2023). It serves as a cofactor for numerous enzymes involved in critical processes such as the metabolism of cholesterol, carbohydrates, and amino acids, as well as blood coagulation, antioxidant defense, and bone formation (NIH, 2019). The mineral is predominantly found in the liver, kidneys, pancreas, and bones, where it supports essential physiological activities. The mineral, Mn is especially valued for its role in antioxidant processes, particularly as a component of manganese superoxide dismutase (MnSOD), an enzyme that protects cells from oxidative damage by neutralizing free radicals (Liu et al., 2022). It also contributes to the production of glycosaminoglycans, which is essential for bone and cartilage development. Additionally, it plays a role in the urea cycle and supports the liver in detoxifying ammonia (Caldwell et al., 2018). Despite its vital biological roles, excessive exposure to manganese can have serious health consequences, particularly for the central nervous system (Miah, et al., 2020). Prolonged overexposure, whether through occupational hazards such as welding, mining or environmental sources like contaminated food and water can lead to manganese toxicity, also known as manganism (Banismita, et al., 2023). This neurotoxic condition mirrors Parkinson's disease, manifesting in motor dysfunction, cognitive impairments, and behavioral abnormalities due to the accumulation of Mn in the brain's basal ganglia (Peres et al., 2016). The neurotoxicity is driven by oxidative stress, mitochondrial dysfunction, and disruptions in neurotransmitter balance (Pajarillo et al., 2022). Given the dual nature of manganese as both essential and potentially toxic, regulatory

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agencies have established daily dietary recommendations to balance its benefits and risks. The Recommended Nutrient Intake (RNI) for adults in Malaysia, aligned with the global guidelines, suggests 2.3 mg for men and 1.8 mg for women to support its crucial biological functions such as enzyme activity, while minimizing the risk of toxicity. Common dietary sources of manganese include whole grains, nuts, leafy vegetables, and tea (NIH). However, individual variability in manganese metabolism and excretion underscores the need for more research to fully comprehend its complex roles in health and disease, as well as the importance of ensuring occupational and environmental safety, particularly in regions with inadequate regulatory standards (Baj, et al., 2023).

Manganese (Mn) is a trace mineral that serves as a crucial cofactor for many enzymes. It plays a vital role in supporting a wide range of metabolic activities in our body.The main enzymes that demand manganese in their reactions are Manganese superoxide dismutase (MnSOD), arginase, pyruvate carboxylase, and phosphoenolpyruvate carboxykinase (PEPCK) (Baly, et al., 1985). Fifty years ago, superoxide dismutase (SOD) was originally identified (McCord and Fridovich, 1969). A significant number of species that exist in the presence of oxygen produce at least one SOD, and it has since been widely established that SODs constitute the first line of defense against oxygen-free radicals. In addition, superoxide is a free radical with a negative charge that is created when oxygen receives one electron (Hayyan, et al., 2016). According to Winterbourne, (2008), it is only somewhat reactive on its own, but it takes part in several processes that produce a range of reactive oxygen species (ROS). Research on the bacterium Lactobacillus plantarum, which feeds on Mn-rich fermenting plant materials, suggested that Mn might have an antioxidant role in bacteria (Feng, et al., 2020). The ROS is produced from molecular oxygen because of normal metabolism. These ROS are categorized into two groups which are free radicals and non-radicals. The three main ROS are known as superoxide (O2-.), hydroxyl radical (OH-), and hydrogen peroxide (H2O2) (Birben, et al., 2012). The mitochondria are the principal source of ROS production by oxidative phosphorylation (Andreyev, et al., 2005, Turrens, et al., 2003) and MnSOD is essential for mitochondrial health and functions as a scavenger of free radicles (Miriyala, et al., 2012. MnSOD acts as an antioxidant that reduces superoxide radical levels, which helps to avoid mitochondrial malfunction and apoptosis. MnSOD transforms superoxide anion radicals into hydrogen peroxide and oxygen in mitochondria (Wang et al., 2018). This reaction is important to protect cells from oxidative damage in our body (Dorman, 2023). In metabolic cycle reactions, manganese also plays an important role as a cofactor for several enzymes. This includes influencing carbohydrates, amino acids, and lipid metabolism. Furthermore, the mechanism of pyruvate carboxylase which is known as a biotin-dependent enzyme is activated by the acetyl-Coa. Acetyl CoA binds to the enzyme and enhances the affinity for pyruvate and CO2. Pyruvate carboxylase carries CO2 and the biotin is carboxylated in the presence of ATP and forming carboxybiotin. Then, the carboxyl group is transferred to private cells, forming oxaloacetate (Haddad, 2023). Furthermore, the role of manganese throughout the process is that ions act as cofactors, stabilizing the structure of the enzyme and facilitating the binding of substrates (Robinson, 2015).This reaction is essential for maintaining energy balance and metabolic homeostasis, as it sustains glucose synthesis during fasting and replenishes intermediates in the citric acid cycle (Nakrani, et al 2023). Additionally, glutamine synthetase in nitrogen metabolism involves combining ammonia with glutamine, which is used as a nitrogen donor in several biosynthetic processes, to detoxify it (Zhou, et al., 2020) This enzyme also needs manganese to stabilize the structure of the enzyme and manganese participates in the binding of substrates.

WOUND HEALING

Wound healing is a complex and dynamic process of several stages, including hemostasis, inflammation, proliferation, and remodeling. These include the important phases such as inflammation, new tissue/proliferation, and maturation/remodeling (Gurtner, 2008). To repair injured tissue, this complex process requires the synergetic actions of many varied cells, including the extracellular matrix elements and growth hormones. Again, Mn is involved in several important processes of wound healing. Due to the low cost, abundance, and essential functions as a micronutrient that supports metabolic and enzymatic activities in the human body (Haque et al., 2021), this element is utilized in various studies to demonstrate its significant role in wound healing. Specifically, it has been documented that the existence of manganese ions stimulates the growth of keratinocyte and fibroblast cell lines by promoting integrin expression during the proliferation stage *in vivo* investigations of cell monolayers (TENAUD et al., 1999). Manganese ions also have stronger antioxidant effects in suppressing microsomal lipid peroxidation and peroxyl radical quenching than other transition metals (Coassin et al., 1992). In some studies, manganese is alsoused in therapy for tumors called melanoma and promote wound healing. This treatment has strong photothermal conversion efficiency and biocompatibility to eradicate remaining tumor cells and heal surgically excised wounds (Liu et al., 2018). Silicate bioceramics provide a promising avenue for tissue engineering, encompassing skin applications (Zhou et al., 2018). Besides, Fe, Co, and Mn are transition elements that might be added to silicate bioceramics to improve their photothermal performance.

Thus, it is to hypothesize that Mn-doped silicate biomaterials may possess the ability to kill tumors and promote wound healing, making them extremely beneficial for the treatment of melanoma and other wounds. (Wu et al., 2021). In Wu (2021) study on manganese-doped calcium silicate nanowire-incorporated alginate hydrogels (MCSA hydrogels) for in situ photothermal ablation of melanoma followed by wound healing. Researchers have developed Mn-doped calcium silicate nanowires with photothermal properties, incorporated into an alginate hydrogel (MCSA). This hydrogel combines photothermal therapy and wound healing, gelling under a mild acid environment to release metallic ions. Manganese enhances the photothermal treatment of skin melanoma tumors and, along with other bioactive ions, accelerates wound healing. MCSA hydrogels show promise for combined melanoma therapy and wound healing.

IMMUNE FUNCTIONS

Transition metals, which include iron, zinc, manganese, and copper, are vital to life because they play a variety of biological roles in proteins as structural and catalytic cofactors (Andreini et al., 2008) and immunity (Murdoch, and Skaar, 2022). Protein database analyses highlight the significance of transition metals to cellular function, indicating that over 30% of all proteins interact with a metal cofactor. Therefore, these metals are necessary for healthy immune function following the stringent requirements for metals in several cellular functions (Wintergurst et al., 2007). It has been demonstrated that Mn impacts macrophage activity, and is essential for phagocytosis, pathogen detection, and immune cell activation. A healthy amount of manganese contributes to the ability of macrophages to react to infections and release the inflammatory cytokines required to start and control the immune response (Institute of Medicine, 2001).

MANGANESE TOXICITY AND NEUROLOGICAL DISORDERS

The multifaceted nature of manganese toxicity presents health risks stemming from both occupational and non-occupational exposures. Industries like welding and mining carry significant risks due to workplace exposure, primarily through inhalation. However, non-occupational exposure can also occur through excessive consumption of contaminated food or water. This broadens the scope of individuals susceptible to manganese toxicity beyond just those in direct industrial settings. Miah et al.,2020 reported that individuals living near mining, manufacturing, and welding industries face elevated risks of manganese toxicity. Moreover, studies have reported heightened atmospheric manganese concentrations near manganese-producing factories, further exacerbating the risk of exposure in surrounding communities (Miah et al., 2020). This suggests that proximity to these industrial activities can increase exposure levels, even for those not employed in such sectors (Baj, et al., 2023). On the other hand, the environment is full of metals, which are widely distributed due to both natural and man-made processes. Metals are also abundant in the earth's crust. Due to their potential to bioaccumulate in living things and potentially biomagnified, metals released into the soil, water, and air as a result of this redistribution pose serious risks to the environment and public health (Niampradit, et al., 2024). Due to this, humans continuously interact with the metal exposome.The elements are categorized as essential or non-essential, with metals making up almost two-thirds of all elements found. Essential metals include iron, cobalt, copper, zinc, manganese, sodium, potassium, magnesium, calcium, and molybdenum (Zoroddu, et al., 2019). These elements are necessary for many biological processes, including cell adhesion, redox homeostasis, development, immunity, and neurotransmission. However, the consequences of manganese accumulation in the brain's basal ganglia regions are particularly concerning. The striatum, pallidum, and substantia nigra pars compacta are areas where manganese tends to accumulate. This accumulation renders these brain regions especially vulnerable to damage and oxidative stress, leading to neurotoxic effects and impairment of normal brain function (Miah, et al., 2020). One significant concern is the association between manganese accumulation and the increased risk of Parkinson's disease (PD)-like symptoms, resembling manganism (Kwakye, et al., 2015). Neurological impairments, such as deficits in motor function, have been linked to elevated manganese levels in the basal ganglia (Peres, et al., 2016).

IMPACT ON COGNITIVE DEVELOPMENT AMONG CHILDREN

The cognitive and behavioral health of children is significantly at risk from exposure to elevated levels of manganese. Research has repeatedly demonstrated that elevated Mn levels are linked to lower IQs, memory problems, and poorer academic achievement. Children who are frequently exposed to manganese tend to perform worse on cognitive tests that assess verbal, nonverbal, and overall cognitive function. These deficiencies can manifest in various ways, including difficulties in language acquisition, problem-solving skills, and overall intellectual development. Furthermore, the impact on memory can affect both short-term and long-term retention of information, making it challenging for affected children to keep up with their peers academically (lund, et al., 2017).

Additionally, children exposed to high levels of Mn frequently experience behavioral problems like hyperactivity, attention deficits, and increased aggression. These behavioral issues can severely disrupt their ability to function in school settings, leading to academic underperformance and social difficulties (Aschner, et al., 2042). These kids might exhibit impulsivity and trouble focusing, which are hallmarks of attention deficit hyperactivity disorder (ADHD) (Santiago, et al., 2024).

CONCLUSIONS

In conclusion, manganese is a vital micronutrient essential for numerous physiological functions, including enzyme activity, antioxidant defense, and immune regulation. However, excessive manganese exposure, especially in occupational settings like mining and welding, poses serious neurotoxic risks, particularly for children, affecting cognitive development and long-term mental health. The bioaccumulation of manganese in the environment exacerbates these risks, extending beyond industrial workers to surrounding populations.

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