Manganese[1,2]

Manganese is an essential metal because it is required for proper immune function, regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, blood coagulation, and hemostasis and defense against reactive oxygen species. The beneficial effects of manganese are due to the incorporation of the metal into metalloproteins. The functions carried out by manganese metalloproteins include oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. In addition, manganese is incorporated into arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, pyruvate carboxylase, and manganese superoxide dismutase enzymes. Tissue contents in mammals are in the range of 0.3–2.9 μg Mn/g wet tissue weight (1), making manganese one of the most common metals in tissues.

Deficiencies

Due to its numerous dietary sources, manganese deficiency is exceptionally rare and has not been reported in the literature under nonexperimental settings. Inadequate dietary intake of manganese results in impaired growth, poor bone formation and skeletal defects, abnormal glucose tolerance, and altered lipid and carbohydrate metabolism (1). Men experimentally placed on manganese-depleted diets developed a transient skin rash on their torsos and had decreased serum cholesterol concentrations (1). In addition, blood calcium, phosphorus, and alkaline phosphatase concentrations were also elevated in men following a manganese-deficient diet, which may indicate increased bone remodeling. Insufficient manganese concentrations have been shown to negatively affect reproductive health and development. The consumption of <1 mg Mn/d led to altered mood and increased pain during the premenstrual phase of the estrous cycle (1). Decreased birth weight has been observed in children whose mothers had lower than average blood manganese concentrations (<16.9 μg Mn/L maternal blood) (1). Low concentrations of manganese in children (<8.154 μg/L) have also been associated with lower color scores in the Stroop Color-Word Test, a measure of cognitive flexibility and processing speed (1).

Diet Recommendations

The Institute of Medicine's DRI for manganese cites ~2 mg/d as an adequate intake for adults and 1.2–1.5 mg/d for children (2).

Food Sources

Plant sources have much higher manganese concentrations than animal sources. For a thorough list of food sources and their manganese concentrations, see the review by Freeland-Graves et al. (3). Whole grains (wheat germ, oats, and bran), rice, and nuts (hazelnuts, almonds, and pecans) contain the highest amounts of manganese. Chocolate, tea, mussels, clams, legumes, fruit, leafy vegetables (spinach), seeds (flax, sesame, pumpkin, sunflower, and pine nuts), and spices (chili powder, cloves, and saffron) are also rich in manganese. Dietary supplements and vitamins are another source of manganese, some of which contain ≤20 mg Mn. Manganese is taken as a supplement for a variety of conditions, including osteoarthritis and osteoporosis (1). The concentration of manganese in drinking water varies by location, ranging between 1 and 100 μg/L (but can exceed 200 μg/L in well water; see Toxicity). The US Environmental Protection Agency has set 50 μg/L as the maximum allowable manganese concentration in drinking water.

Clinical Uses

Due to the paramagnetic nature of this element, manganese is an ideal component for contrasting agents used in MRI. Because ionic manganese can be toxic to cells, these contrasting agents are often manganese porphyrins or other chelating compounds (4).

Toxicity

The Tolerable Upper Intake Level for manganese is 9–11 mg/d for adults and 2–6 mg Mn/d for children, varying with age. The absorption of manganese is tightly regulated in the gut and therefore toxicity from dietary exposure has not been reported. Throughout the world, manganese toxicity is due to environmental exposures, including airborne exposure and drinking water. Typical airborne exposure routes are from automobile exhaust and occupational exposure. Methylcyclopentadienyl manganese tricarbonyl is an anti-knock additive in nonleaded gasoline, which contains ~24.4% manganese by weight. Occupations at risk for airborne manganese exposure are welders and workers in the ferroalloy industry and battery manufacturers. To date, most studies point to these exposures not exceeding acceptable airborne levels (5). Toxic amounts of waterborne manganese (>2 times the acceptable level) have been reported from wells in areas in which soil manganese concentrations were found to be exceptionally high. A recent study found that >1 million people who rely on well water living in parts of Virginia, North Carolina, South Carolina, and Georgia reside in an area in which soil manganese concentrations are exceptionally high and most of the wells tested have manganese levels that are considered unhealthy (6). Populations that rely on well water from ground-water sources with a propensity for manganese contamination have reported learning impairment in children consuming unfiltered well water (7).

Recent Research

Current research activities revolve around the mechanisms involved in manganese neurotoxicity, including brain transport and the discovery of biomarkers of exposure. Manganese is

transported via the transferrin/transferrin receptor mechanism and divalent metal transporter, both of which are critical for normal brain iron transport. Recently, the zinc transporters (ZIP-8[5] and ZIP-14, SLC30A10), the cation transporting ATPase (ATP13A2), and the calcium ATPases (SPCA1 and SPCA2) have been shown to play important roles in brain manganese transport. Defects in SLC30A10 have been linked to Parkinson disease and are likely involved in familial manganism (5). With occupational exposure (welders, ferroalloy industry workers) being a primary route of neurotoxic exposure, the discovery of an ideal biomarker(s) is imperative for minimizing exposure. Though not perfect, blood manganese concentrations provide the best estimate for brain manganese levels, but this relationship holds up only when exposure is recent (5).

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[5]Abbreviations used: ATP13A2, cation-transporting ATPase 13A2; SLC30A10, solute carrier family 30 member 10; SPCA, secretory pathway Ca^{2+}-ATPase; ZIP, Zrt-Irt-like protein 14.