MANGANESE

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Introduction

Manganese is a transition metal with multiple valencies (1, 2, 3, 4, 6 and 7), widely distributed throughout the earth's crust and present in most plant and animal tissue. As a metal, it is similar to iron and is used industrially in the manufacture of steel, batteries and ceramics. Manganese toxicity among workers in these industries, and in manganese ore miners, is well documented. In addition to its potential for toxicity, manganese is also an essential nutrient. In the human body, it is stored in tissues rich in mitochondria (e.g. the liver and pancreas) and is required for the metabolism of amino acids, proteins, and lipids. Manganese salts have also been used therapeutically, for example in the treatment of psoriasis.

Homeostasis of manganese is by faecal elimination with relatively little appearing in the urine. Hence cholestatic liver disease is associated with manganese retention and toxicity [1].

In excess manganese can be a potent neurotoxicant [2]. "Manganism" describes the Parkinsonian syndrome and psychiatric symptoms that develop in the course of its toxicity (during which Mn is deposited in the basal ganglia of the brain). Consequent neurobehavioral deficits in these cases have been shown to correlate with manganese deposition in the brain [3].

Physiological actions of manganese

Adequate levels of manganese, like zinc and copper, are essential for normal human pre-natal and neonatal development. The physiological functions of manganese are widespread through the body and include [1]:

- Normal skeletal growth and development

- Normal connective tissue growth and development

- Glucose utilization

- Protein and nucleic acid metabolism

- Lipid metabolism

- Pancreatic function

- Reproductive function

- Enzyme activation

Manganese is a component of the antioxidant enzyme superoxide dismutase (SOD), which is present in all aerobic cells, where it is required for the de-toxification of oxygen metabolites. Manganese is also a co-factor for the enzymes hexokinase, pyruvate carboxylase, PEP carboxylase, glutamine synthetase, and xanthine oxidase (among others). It is required for the action of vitamin B1 (thiamine) and for normal brain function (due to its role as an activator of brain enzymes); manganese deficiency can be associated with epilepsy [4,5]. Mn is also required for bone and cartilage formation; low levels are often associated with

joint surface diseases, e.g. arthritis [6,7]. Manganese has a hypoglycaemic activity by virtue of its effect on gluconeogenesis and low manganese concentrations may be found in diabetes mellitus. In the thyroid gland, Mn^{2+} stimulates conversion of MIT (mono-iodotyrosine) to DIT (diiodo-tyrosine) during thyroid hormone synthesis.

Food sources of manganese

The daily requirement for manganese in man is c. 3 mg and the Mn content of current multi-mineral supplements is probably slightly in excess of requirements. The average UK dietary intake of Mn is 8.2 mg/day and the estimated upper limit is 12.2 mg/day. Manganese is present in many foods, particularly green vegetables (2 mg/kg), nuts (14.9 mg/kg), bread (8 mg/kg) and other cereals (6.81 mg/kg). Tea is a rich source of manganese, containing 2.7 mg/kg and is often the largest contributor to manganese intake [8].

Manganese is commonly found in groundwater because of the weathering and leaching of manganese-bearing minerals and rocks into the aquifers; concentrations in drinking water can vary by several orders of magnitude. In the UK the maximum concentration of manganese permitted in drinking water is 50 µg/L [9] but the usual level recorded is below 1.0 µg/L. These figures suggest that manganese intake from water is very small compared to the amount ingested in food.

However, while manganese is widely distributed in unrefined food, excessive reliance on a diet based on refined grains may result in a deficient intake.

Manganese in supplements

Manganese is present in some medicines, in combination with other substances, in use for the prevention and treatment of nutritional deficiencies. Manganese is also present in a number of multi-vitamin and/or mineral food supplements at levels up to 10 mg [8]. Manganese supplements can be taken as tablets or capsules, usually along with other vitamins and minerals in the form of a multivitamin. However, the content of some multi-supplements may in the past have exceeded safe levels of manganese intake.

Manganese is available in a wide variety of forms, including manganese salts (sulfate and gluconate) and manganese chelates (aspartate, picolinate, fumarate, malate, succinate, citrate, and amino acid chelate).

Manganese deficiency

There is some evidence that human diseases such as amylotrophic lateral sclerosis, acromegaly and epilepsy are associated with low tissue levels of manganese and that the manganese intake of many people is below the estimated safe, adequate dietary intake [1]. Reported deficiency symptoms include ataxia, fainting, hearing loss, weakness in tendons and ligaments and, possibly, type 2 diabetes mellitus (since low levels of manganese reduce insulin production and impair glucose metabolism).

Manganese deficiency might also develop from failure to absorb the metal, which normally takes place in the small intestine via a carrier-mediated mechanism. Manganese and iron compete for sites of absorption in the gut, while fibre, phytates, calcium, phosphorus and excessive intake of magnesium may also interfere with manganese absorption.

Absorption of ingested manganese is generally low but appears to be relatively higher in infants than in adults. Bioavailability of manganese from different food types is variable, but is generally low, due to poor solubility of manganese salts. Once absorbed, Mn in the hepatic portal blood binds to albumin and alpha-2 macroglobulin. A small proportion of Mn in the systemic circulation is bound to transferrin. [8]

Use of manganese supplementation to treat fatigue, nervousness and irritability (possibly by enhancing brain enzyme activity) and poor memory (by inducing SOD and protecting brain tissue) was originally reported by Carl Pfeiffer in his book "Mental and Elemental Nutrients" [10]. Pfeiffer suggested that manganese, along with zinc, will help decrease copper levels by both decreasing absorption and increasing urinary losses. He claimed that copper, in physiological but higher than normal amounts, can cause psychological problems and even schizophrenia [11], and that this reflects an underlying tissue manganese deficiency.

Toxic effects of manganese

Manganese is a metal with a relatively low acute toxicity, but many adverse effects from prolonged excess exposure [1]. The brain is the primary target of its toxicity, but the lung, the cardiovascular and the endocrine systems are also affected. In addition, excess manganese has immunological, genotoxic and carcinogenic effects.

Manganese and iron are thought to share absorptive and metabolic pathways. Manganese can interfere with the absorption of dietary iron and long-term exposure to excess levels may result in iron-deficiency anemia. This can be one of the effects of industrial pollution, with workers in the manganese processing industry most at risk. Manganese poisoning has been found among workers making batteries. Symptoms of toxicity also mimic those of Parkinson's disease (tremors, stiff muscles) with hypertension in subjects older than 40 years. In this respect the toxicant effect of manganese is thought to be related to depletion of brain dopamine, with a syndrome of motor dysfunction and memory loss resembling Parkinson disease [12].

While excess manganese exposure can produce neurological symptoms similar to those of Parkinson's disease, there are important differences between the two conditions: for example, Parkinson's is associated with a persistent, resting tremor, whereas manganism is associated with an intentional or kinetic tremor. Blood pressure is also significantly higher in chronic manganese exposure than in Parkinson's and there are other pathological differences between the two conditions [13]. However, exposure to excess manganese (or copper) is thought to increase the risk of developing Parkinson's disease [14]

The carbamate pesticide "Mancozeb" is a wide spectrum anti-fungal containing manganese which may significantly increase the Mn content of ingested fruit and field crops [1]. Reported symptoms of human direct exposure to Mancozeb include skin rash, fatigue, headache, blurred vision and nausea [15].

Environmental exposure to airborne manganese has been associated with neurobehavioral deficits in adults and in children [16,17]. In exposed workers, neurobehavioral deficits have been shown to correlate with manganese deposition in the brain observed by magnetic resonance imaging [3].

Manganese in clinical samples

The Biolab reference intervals for manganese are as follows:

Urine Mn	<5.00 μmol/mol of creatinine
Plasma Mn	9.0 – 40.0 nmol/L
Whole blood Mn	80 - 200 nmol/L
Hair Mn	0.20 – 2.00 μg/gm of hair
Drinking water Mn	< 50 μg/L

Elevated hair manganese with normal blood manganese level has been reported in cases of chronic Mn toxicity [18], emphasizing the fact that some toxic metals may be preferentially excreted in the hair. Hair concentrations of manganese are thought to be the more accurate reflection of chronic exposure than blood manganese which, at lower levels, can vary somewhat in the short term according to dietary intake and thus may not reflect long-term intake or exposure. In contrast, the manganese content of hair will reflect the metal uptake averaged over the duration of the follicle formation [19]. The mechanism of manganese uptake into hair is not well understood, but its affinity for melanin, a coloured protein present in hair and skin, could be involved [20].

However, the concentration of manganese in whole blood is nearly 10 times that in serum, so analysis of whole blood is less likely to suffer from sample contamination (the concentration of Mn in plasma is close to the current ICPMS detection limit). The higher levels of manganese in whole blood as compared to plasma reflect the sequestration of the metal into haemoglobin, which is a de-toxifying action of the erythrocytes. However, nutritional deficiency of manganese is more likely to be apparent from its concentration in plasma than that of whole blood.

Age-related reference ranges have been proposed for blood manganese concentrations in neonates and infants, e.g. <1 year 120 – 325 nmol/L, ≥ 1 year 73 – 210 nmol/L, but we have not been able to confirm this.

Patient preparation:

The patient should discontinue taking nutritional supplements for 48 hours before the collection of blood or urine for manganese determination.

Specimen requirements

For blood or plasma manganese measurement, blood should be collected into an 8 ml trace element-free potassium EDTA tube. Collection tubes and needles can be supplied by Biolab. If a number of blood tubes are being taken at the same collection, the trace element-free tube should be filled first to avoid cross-contamination. Postal samples (overnight delivery) are acceptable.

A 24 hour urine collection is preferred for urine manganese determination, but a 6 hour urine collection is acceptable. The total volume of urine collected should be recorded and, after mixing, 15 mL of urine should be sent to Biolab in a plastic, screw cap container. A postal sample kit can be supplied.

For hair analysis, hair should be cut from the nape of the neck, as close to the scalp as possible. At least 0.5gm of hair is required, which is about one heaped tablespoon full. Only hair up to 1½" (4cm) from scalp can be used. Please allow for this when the hair is long by sending in a larger total sample, for example 2 tablespoons-full of hair.

For water analysis, 20 mL of water should be sent in a plastic, screw cap container (available from Biolab). If the domestic water supply is being tested, water should be taken from the initial run of the tap first thing in the morning (i.e. after the water has been in contact with the fixtures and fittings for more than 6 hours).

Turn around time: 5 working days.

References:

1. Saric M, Lucchini R. Manganese. In: Handbook of the toxicology of metals eds Nordberg GF, Fowler BA, Nordberg M, Friberg LT, pub Academic Press, Elsevier, London 2007; ISBN 978-0-12-369413-3, pp 645- 674.

2. Mergler D, Baldwin M. Early manifestations of manganese neurotoxicity in humans: an update. Environ Res 1997;73:92-100.

3. Chang Y, Kim Y, Woo ST et al. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. Neurotoxicology 2009;30:555–5.

4. Claus HB, Ettinger AS, Schwartz J et al. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology 2010; 21:433-439.

5. Hori H, Ohmari O, Shinkai T et al. Manganese superoxide dismutase gene polymorphism and schizophrenia: relation to tardive dyskinesia. Neuropsychopharm 2000;23:170-177.

6. Palacios C. The role of nutrients in bone health, from A to Z. Crit Rev Food Sci Nutr 2006;46:621-628.

7. Sarban S, Isikan UE, Kocabey Y et al. Relationship between synovial fluid and plasma manganese, arginase, and nitric oxide in patients with rheumatoid arthritis. Biol Trace Elem Res. 2007;115:97-106.

8. UK Expert Group on Vitamins and Minerals. Risk assessment – manganese. Food Standards Agency 2003. http://www.food.gov.uk/multimedia/pdfs/evm_manganese.pdf

9. Drinking Water Inspectorate, 2011. 55 Whitehall, London SW1A 2EY http://www.dwi.gov.uk

10. Pfeiffer C. Mental and elemental nutrients, a physician's guide to nutrition and health care. Pub Keats, Lincolnwood, Illinois, USA 1976. ISBN-10: 0879831146 pp 1-519.

11. Donaldson J. The physiopathologic significance of manganese in brain: its relation to schizophrenia and neurodegenerative disorders. Neurotoxicology 1987;8:451–462.

12. McMillan DE. A brief history of the neurobehavioral toxicity of manganese: some unanswered questions. Neurotoxicology 199;20:499–507.

13. Cowan DM, Zheng W, Zou Y et al. Manganese exposure among smelting workers. Neurotoxicology 2009;30:1214-1222.

14. Willis AW, Evanoff BA, Lian M et al. Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. Am J Epidemiol 2010;172:1357-1363.

15. Hayes WJ, Laws ER (eds). Handbook of pesticide toxicology, vol 3. Academic Press NY, 1991 pp 1451.

16. Riojas-Rodríguez H, Solís-Vivanco R, Schilmann A, et al. Intellectual function in Mexican children environmentally exposed to manganese living in a mining area. Environ Health Perspect 2010 118:1465–1470.

17. Zoni S, Albini E, Lucchini R. Neuropsychological testing for the assessment of manganese neurotoxicity: a review and a proposal. Am J Ind Med 2007;50:812–830.

18. Woolf A, Wright R, Amarasiriwardena C et al. A child with chronic manganese exposure from drinking water. Environ Health Perspect 2002;110:613-616.

19. Rodushkin I, Axelsson M. Application of double focusing sector field ICP-MS for multielemental characterization of human hair and nails. Part II. A study of the inhabitants of northern Sweden. Sci Total Environ 2000;262:21-36.

20. Lyden A, Larsson BS, Lindquist NG. Melanin affinity of manganese. Acta Pharmacol Toxicol (Copenh) 1984;55:133–138.