



Nutritional Bioavailability of Manganese

EDITED BY
Constance Kies



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Nutritional Bioavailability of Manganese

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Foreword

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the Series parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that, in order to save time, the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. Papers are reviewed under the supervision of the Editors with the assistance of the Series Advisory Board and are selected to maintain the integrity of the symposia; however, verbatim reproductions of previously published papers are not accepted. Both reviews and reports of research are acceptable, because symposia may embrace both types of presentation.

Preface

MANGANESE NUTRITION in plants and animals has long been a topic of practical and esoteric research interest. However, only recently has it become a hot topic among investigators whose concerns are centered directly or indirectly around the nutritional and general physiological health of humans. At the symposium on which this book is based, information presented ranged from basic theoretical biochemistry to applied nutrition based on laboratory-controlled or field human studies and on animal research models.

The chapters in this book particularly emphasize the dietary and nondietary factors that apparently influence the absorption and use of manganese and, thus, the bioavailability and bioutilization of manganese. Updated papers that were presented at the symposium are included in this volume; several other chapters that were solicited by the editor give more complete coverage of the topic. Increased knowledge of the involvement of manganese in metabolic functions of the living organism has contributed to the current excitement about manganese research. Also contributing to this excitement is the development of instrumentation that allows for greater accuracy and ease in analysis of manganese and of organic compounds containing manganese or dependent on nutritional adequacy of manganese.

This volume is meant to present current information on the bioavailability of manganese, to share enthusiasm of the participants with other investigators who have a current or possible future interest in manganese, and to alert scientists and practitioners to this field of investigation.

I would like to acknowledge the help and hard work of Donna Hahn in organizing the symposium and this book.

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Chapter 1

Manganese Bioavailability Overview

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Manganese is recognized as an essential nutrient for humans and animals; however, in excessive amounts manganese is also a toxic substance. Manganese has been defined as being a component of several enzymes and an activator of several other enzyme systems although other minerals such as magnesium can substitute for manganese in many but not all of these metabolic processes. Since nutritional adequacy of manganese is necessary for the enzyme manganese superoxide dismutase, research dealing with this enzyme is of current interest. Only one case of frank manganese deficiency in the human has been identified and publicized in the literature. However, animal studies indicate that manganese deficiencies affect bone, brain and reproductive systems. Manganese absorption from the gastrointestinal tract is thought to be poor but its absorption is thought to be at least in part governed by its valence state. In the United States recent research suggests that mean manganese intakes of women are considerably lower than are the NRC Estimated Safe and Adequate Daily Dietary Intakes while those of formula fed infants are greater than the NRC ESADDI listings for this age group. Depending upon manganese source and availability of manganese from these sources, manganese adequacy or toxicity might be a problem for these segments of the American population.

Manganese has been found to be an essential nutrient for the human as well as for many other living organisms; however, in excessive amounts, it is also a toxic material (1-6). Deficiency symptoms for manganese in several species have been created and manganese metabolic roles have, at least in part, been defined (5,7-15). So called "normal" manganese concentrations in blood have been established (1,10,16). Kinetics of manganese uptake and metabolism by

tissues under conditions of manganese toxicity and deficiency have been reviewed by Keen and Lonnerdal in this volume.

Manganese Enzymes Systems

Manganese is a component of pyruvate carboxylase and mitochondrial superoxide dismutase and activates a number of enzymes including phosphatases, kinases, decarboxylases, and glycosyltransferases that are involved in the synthesis of polysaccharides and glycoproteins (12,17,18). It is associated with the synthesis of protein, DNA, and RNA with cartilage mucopolysaccharide synthesis (5,19). Since it has also been shown to be involved in amino acid transport and catabolism, this suggests that increased protein intake might increase the need for manganese in the tissues (5). Recently, investigations of factors affecting activity levels and functions of manganese superoxide dismutase have been particularly active.

Superoxide dismutases, enzymes functioning to protect cell membranes from lipid peroxidation, have been found to exist in two forms, one containing manganese and the other containing copper and zinc (20). A relationship between manganese consumption and superoxide dismutase activity has been found. Hepatic concentrations of manganese and hepatic manganese superoxide dismutase activities were higher but hepatic copper-zinc dismutase levels were lower in ethanol fed monkeys than in control monkeys (21).

When different groups of weanling rats were fed rations containing graded levels of manganese ranging from 0.2 to 29.7 mg/kg of ration, significant correlations between dietary manganese levels with heart and kidney manganese superoxide dismutase enzyme activities, liver arginase and plasma alkaline phosphatase activities and heart, kidney, liver and plasma manganese concentrations were found; however, no changes occurred in the activities of copper-containing superoxide dismutase or glutathione peroxidase in the tissue analyzed (22).

In manganese deficiency in the chicken, manganese is replaced with magnesium so that no loss of pyruvate carboxylase occurs (23). DeRosa et al. (18) verified a decrease in manganese superoxide dismutase activity in manganese deficient rats and mice. Zidenberg-Cherr et al. (17) reported that lipid peroxidation increased to a greater extent in manganese-deficient than in manganese-sufficient rats. Concurrently manganese superoxide dismutase activity increased to a much lesser extent in the deficient animals (17). Hence, mitochondrial membrane damage found in manganese deficient animals might be due to increased free radical production due to depressed manganese superoxide dismutase activity.

Manganese Deficiency Symptoms

Manganese deficiency symptoms in animals affect three systems - bone, reproductive and brain (6,24). Impaired growth, skeletal abnormalities, depressed reproductive function and ataxia in newborn appear to be similar manganese symptoms in all species studied.

The single reported case of frank manganese deficiency in humans arose unintentionally in an adult male participating in a vitamin K deficiency study (25). Inadvertently manganese was omitted from the purified diet mixture. The signs and symptoms of weight loss,

transient dermatitis, nausea, slow growth and reddening of the hair and beard, hypocholesterolemia and depressed vitamin K depending clotting factors did not respond to vitamin K therapy but were corrected by the administration of manganese.

Because of the blood lowering cholesterol effects of a manganese deficiency, involvement of manganese in lipid metabolism has been a topic of research interest as reviewed by Johnson and Kies in this volume.

Manganese Absorption and Excretion

Manganese is only poorly absorbed from the intestinal tract; however, absorption occurs into mucosa cells throughout the small intestines (13,26). Excretion of manganese through bile and pancreatic juice is apparently more important than absorption in maintenance of manganese homeostasis although young animals seem to lack the ability to excrete manganese. Manganese is apparently absorbed in the +2 valence state and competes with iron and cobalt for the same absorption sites (27). Mechanisms of manganese uptake and retention both in experimental animals and humans are discussed in the chapter by Keen et al. Three of the many determinants of manganese absorption and retention are: 1) developmental status; 2) dietary constituents; and 3) membrane translocation of the element. However, much of the information on manganese absorption has been obtained from animal studies with the assumption made that these mechanisms also apply to humans.

Other nutrients have been found to influence the absorption of manganese. Manganese absorption has been found to be associated with high intakes of dietary calcium as discussed by McDermott and Kies in this volume. The possible relationships of calcium, manganese and bone health may be of importance in the occurrence of osteoporosis as discussed by Strauss and Saltman in another chapter. Since iron and manganese compete for binding sites in the intestines it is not surprising that dietary iron apparently inhibits manganese utilization as discussed in the chapter by Gruden.

Dietary Manganese Needs and Intakes of Humans

Because of a lack of information on manganese contents of foods, manganese intakes are not usually included in nutrient intake surveys. However, the several surveys which have been done in the United States and in the United Kingdom have yielded somewhat similar results regarding usual manganese intakes of human adult populations. Schroeder et al. (6) estimated manganese intakes to be between 2.2 and 8.8 mg/day; Wenlock et al. (28) estimated mean intakes to be 4.6 mg/day and Waslien (29) found intakes to range from 0.9 to 7.0 mg/day. Using analyzed, model U.S. diets, Pennington et al. (30) found adult intakes of manganese to range from 3.52 to 3.67 mg/day during the 1977-1982 time period. At the University of Nebraska, manganese intakes of young college women consuming self-selected diets ranged from 0.8 to 5.2 mg/day with a mean of 1.28 mg/day as estimated from one week dietary diaries and from analyses of manganese contents of feces (31).

An interesting recent paper (32) included not only analyzed manganese contents of a large number of foods based on an excellent

sampling procedure but also included estimated mean manganese levels of eight age-sex group diets compared with the NRC Estimated Safe and Adequate Daily Dietary Intakes (ESADDI). The mean intake of 1.10 mg manganese/day for 6-11 month infants slightly exceeded the ESADDI and that for the two-year old child was on the very high end of the scale (a mean intake of 1.47 related to a ESADDI scale of 1.00-1.50). For all of the male group, the mean manganese intakes were within the range limits of the ESADDI's but were toward the lower end of the scale. For all female groups, the mean manganese intakes were considerably below the ESADDI's. Since the ESADDI's for men and women are the same, the low intakes of manganese of women in comparison to the ESADDI's are in part due to the lower food intakes of women due to lower caloric needs. However, these data do suggest that manganese intakes for many Americans may be seriously low.

Manganese Content of Milk and Infant Formulas

Estimation of manganese intakes of infants has been an area of particular research intensity. While estimations of manganese content of human milk vary, there is general agreement that the manganese content of human milk is substantially lower than that of cow's milk (33). Manganese in cow's milk is combined with different and smaller protein molecules than is that of human milk (34-36). Degree of absorption may be different depending upon ligan binding in this milk and may be different than that of free manganese from supplemental manganese salts.

This has created something of a dilemma for producers of infant formulas for bottle feeding which has led to a diversity of levels of manganese content in these products. Since human milk, cow's milk and/or formula are the principal foods consumed by infants, manganese intakes are determined to a large extent by the quantitative manganese contents of these substances. Breast milk-fed infants, therefore, have lower intakes of manganese than those fed cow's milk formulas but whether or not the manganese is equally available is unknown. In this book, Lonnerdal et al. present evidence that manganese retention from milk and from milk formulas is high while that from soy formulas is much lower.

Manganese Contents of Foods

Foods vary in their contents of manganese (32,37,38). Comparisons of manganese contents of different foods are given in Table I. Plant origin foods such as tea, whole grain cereals, some dark green leafy vegetables, and nuts contain high amounts of manganese. However, these products often concurrently contain high amounts of tannins, oxalates, phytates and fiber. These dietary constituents have been found to inhibit the absorption of other minerals; hence, might have a negative effect on manganese absorption.

Animal origin products such as eggs, milk, fish, red meats and poultry contain low amounts of manganese. Absorption of such minerals as iron, copper, phosphorus and calcium is superior from animals products than from plant-origin foods. As reported by Kies et al. (in this book), manganese apparently is better absorbed by humans from meals containing meat and fish than from those containing plant-protein replacement products. Because of the low content

Table I. Comparative Manganese Contents of Foods

Food Item	mg Mn/100 g Food ¹
<u>Milk and milk products</u>	
Cheese, American processed	0.0464
<u>Meat, poultry, fish, eggs</u>	
Beef, ground, cooked	0.019
Beef, chuck, oven-roasted	0.025
Chicken, oven-roasted	0.046
Frankfurters	0.024
Fish fillet	0.058
Egg, soft boiled	0.037
<u>Legumes and nuts</u>	
Pork and beans, canned	0.315
Peanut butter	1.322
<u>Grains and grain products</u>	
Rice, white, enriched, cooked	0.807
White bread, enriched	0.376
Corn bread	0.315
Biscuits	0.244
Whole wheat bread	1.120
<u>Fruits</u>	
Peaches, canned	0.017
Applesauce, canned	0.014
Fruit cocktail, canned	0.122
Pears, canned	trace
Cherries, sweet	0.085
<u>Vegetables</u>	
Coleslaw with dressing	0.093
Cauliflower	0.102
French fries	0.150
Mashed potatoes	0.075
Boiled potatoes	0.083
Spinach, canned or frozen	0.501
<u>Mixed dishes</u>	
Beef-vegetable stew	0.101
Pizza, cheese	0.259
Chili con carne	0.140
Chicken noodle casserole	0.140
Vegetable beef soup	0.181
<u>Desserts</u>	
Yellow cake	0.390
Pumpkin pie	0.620
Gelatin dessert	0.005

¹These values were recalculated from those reported by Tack (50) and are in reasonably good agreement with those reported by Pennington et al. (32) and Gormican et al. (38).

of manganese in meat and fish, this implies manganese absorption and retention from these products is excellent and implies that these animal origin products enhance utilization of manganese supplied by plant-origin products as well.

Methods of Evaluation of Manganese Status

Most studies on factors affecting manganese needs of human subjects have employed the manganese balance technique during short-term feeding periods ranging from five to 14 days. However, measurements of other tissue, blood or urine components might be of value in assessment of nutritional status of humans or animals. For example, children with learning disabilities have been reported to have high hair manganese levels (39), elevated blood serum levels of manganese have been reported in such disease states as congestive heart failure (40), infections (40) and Alzheimer-like diseases (41) and elevated manganese concentrations in whole blood have been found in individuals with excess manganese intake (42,43), rheumatoid arthritis (44) and iron-deficiency anemia (45). Whole blood manganese levels of many but not all adults with convulsive disorders have been found to be lower than in normal controls (46).

Basis for Manganese "Safe Intake Levels"

The Food and Nutrition Board, National Research Council, National Academy of Sciences (47) has listed safe intake levels of manganese although information was, at the time of the 1980 listing, too fragmentary for exact recommendations to be made. These manganese "safe intake level" listings were as follows: 2.5-5.0 mg/day for adults, 0.7-1.0 mg/day for infants and 1.0-5.0 mg/day for toddlers.

In laboratory controlled studies, positive manganese balances (calculated from the formula: manganese balance = dietary manganese - fecal manganese - urine manganese) have been observed when subjects were maintained at 2.5 mg manganese/day or higher but negative balances occurred when subjects were fed 0.7 mg manganese/day (48). An extensive review of the literature relative to human studies on manganese requirements of humans is presented by Freeland-Graves et al. in this volume. A factorial method for estimation of manganese requirements of humans is given by these authors.

In recent studies reported by Rao and Rao (49), Indian men required 3.72 mg manganese/day to maintain manganese balance. In studies conducted at the University of Nebraska, American adult subjects also failed to be in manganese balance when manganese intake was maintained at 2.5 mg/day (31).

Current estimation of dietary manganese adequacy may be too low, particularly if diets contain substantial amounts of fiber or are based largely on plant products. However, for meat containing diets, the current estimated levels of adequacy may be quite adequate.

Conclusion

While manganese nutritional status is not currently recognized as a problem in the United States or in the rest of the world, certain groups may have less than optimal manganese nutritional status

because of lower intakes than previously suspected from self-selected diets. There is a need for establishment of manganese requirements for all age/sex groups consuming diet based on current or recommended food patterns. Furthermore, the feasibility of expressing manganese contents of foods on the basis of biologically available manganese content rather than on chemical laboratory values deserves consideration.

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Chapter 2

Manganese Uptake and Retention

Experimental Animal and Human Studies

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Retention of dietary manganese is very high during the neonatal period. Later in life, retention decreases considerably, due to a combination of decreased uptake and increased excretion of absorbed Mn via bile. Studies on brush border membranes from suckling rat small intestine demonstrate two components involved in the uptake of Mn, one saturable with limited capacity and one non-saturable, indicating passive uptake above a certain level of Mn. Although mucosal factors strongly affect Mn absorption, dietary factors also influence its uptake. In early life, Mn absorption from human milk and cow's milk formula is high compared to soy formula. These differences are also observed at later stages in life, although the differences are less pronounced. Age, Mn intake and dietary factors affect Mn absorption and retention and need to be considered when establishing requirements.

At present our knowledge concerning the uptake and retention of Mn in humans and experimental animals is limited (1). The conventional balance technique has serious limitations for studying the absorption and retention of Mn due to the low retention of the element from any single meal and the slow turnover of the mineral in the body. There have been a few limited studies on the absorption and excretion of Mn using the radioisotope ⁵⁴Mn; yet the mechanisms of Mn absorption are not well understood. It is believed that absorption of Mn occurs throughout the length of the small intestine (2). The efficiency of Mn absorption is relatively low, and it is not thought to be under homeostatic control. For the adult human, it has been reported that approximately 3-4% of dietary Mn is absorbed (3). High levels of dietary calcium, phosphorus, and phytate have been shown to increase the requirements for Mn in several species, possibly by adsorption of Mn in