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Dietary manganese suppresses α_1 adrenergic receptor-mediated vascular contraction

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Abstract

We examined the effect of dietary manganese (Mn) on the vascular contractile machinery in rat thoracic aortas. Weanling male Sprague–Dawley rats were fed either an Mn-deficient (MnD), Mn-adequate (MnA) or Mn-supplemented (MnS) diet (<1, 10–15 and 45–50 ppm Mn, respectively). After 15 weeks on the diets the rats were sacrificed and 3-mm aortic rings were contracted in six cumulative doses of the α_1 adrenergic receptor agonist L-phenylephrine (L-Phe, 10^{-8} to 3×10^{-6} M) under 1.5-g preload and relaxed with one dose of acetylcholine (3×10^{-6} M) to assess intact endothelium. The maximal force (F_{max}) of contraction and relaxation, as well as the vessel sensitivity (pD_2) were determined. Manganese deficiency, assessed by hepatic Mn content, significantly lowered the rate of animal growth. A two-way analysis of variance revealed that MnS animals developed lower F_{max} when contracted with L-Phe compared with the MnD and MnA animals ($P \leq .001$). Thus, dietary Mn at levels of 45–50 ppm affects the contractile machinery by reducing maximal vessel contraction to an α_1 adrenergic agonist. The observed pD_2 was significantly greater in the MnD group compared with the MnA and MnS animals ($P \leq .001$). Thus, restriction of dietary Mn affects vascular sensitivity to the α_1 adrenergic receptor. Our results demonstrate for the first time that dietary Mn influences the receptor signaling pathways and contractile machinery of vascular smooth muscle cells in response to an α_1 adrenergic receptor.

Keywords: Manganese; Endothelium; Vascular smooth muscle; Vasoconstriction; α_1 Adrenergic agonist

1. Introduction

The crucial role of nutrition on the genesis and progress of cardiovascular disease (CVD) has been studied extensively, since CVD still remains the first cause of death in the U.S. population [1]. Trace minerals, among them manganese (Mn), may be potential risk factors for cardiovascular events that cause and/or promote its development since it seems to participate in cell signal transduction pathways that affect the biomechanical properties of the vessels. Vascular endothelium mediates the relationship between cardiovascular risk factors and development of CVD [2,3]. Endothelial dysfunction is described as a condition in which the endothelial release of relaxing factors is reduced and the secretion of contracting mediators is enhanced [4]. The role of endothelial dysfunction in hypertension, arteriosclerosis and vascular diseases depends on a balance between the above factors [5–8]. These vasoactive mediators are implicated in early inflammation and are known to promote or inhibit vasodilation and vasoconstriction, blood coagulation, thrombogenesis and thrombolysis, as well as endothelial cell growth and remodeling [9–12]. Thus, an alteration in the biomechanical properties of the vascular system might affect not only blood flow, but also platelet aggregation and vessel permeability, processes that participate in the early stages of atherosclerosis and that have been associated with hypertension, atherosclerosis and several cardiovascular disorders [13–17].

Several trace elements such as zinc, copper, selenium, magnesium, manganese, nickel, molybdenum and calcium are reported to affect the process of CVD [18–20] by interacting with ion channels, neurotransmitters, receptors and/or ionic channel–receptor complexes [10]. Previous studies have shown that Mn may affect blood pressure by decreasing the tension of isolated vascular tissue preparations in vitro [21]. However, there have been no animal studies to

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associate the dietary deprivation of trace element Mn with cardiovascular activity in vivo or ex vivo.

Our laboratory was the first to report that Mn plays an important role in maintaining integrity of blood vessels [22–26]. Manganese is involved in arterial glycosaminoglycan metabolism by affecting the total proteoglycan content of the aorta, altering the molecular weight and sulfation pattern of chondroitin sulfate in the same tissue and thus predisposing the vessel to lipid deposition, lipoprotein oxidation and CVD [24,25]. Manganese is essential for preventing surface damage of the aorta and maintaining the density of the extracellular matrix around smooth muscle cells, especially in the medial layer [26]. Transmission electron microscopy of the arterial wall revealed less dense extracellular matrix around smooth muscle cells, especially in the medial layers of the Mn deficient rats, suggesting possible changes in the endothelial and/or vascular smooth muscle cells, which affect the contractile properties of the arteries [24,25].

Vascular ring studies in animals are considered to be a broadly accepted way to experiment on the role of the endothelium in the vasomotor control and on the effect of its dysfunction on the biomechanical properties of the arteries, since in most cases the results match the observations in isolated human blood vessels [4]. Our knowledge on the role of Mn on arterial wall structure and the contractile properties of the arteries is limited and remains to be established. There have been no studies in the past on the effect of different amounts of dietary Mn intake on the vascular contractile properties. In our study we examined the role of dietary Mn on the biomechanical properties and receptor sensitivity of Sprague–Dawley rat aortic rings, as assessed by aortic smooth muscle contraction in response to phenylephrine, an α_1 adrenergic agonist.

2. Methods and materials

2.1. Animal model

2.1.1. Animal care

Thirty weanling male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) were randomly assigned to three groups of 10 rats, each on an Mn-deficient (MnD), Mn-adequate (MnA) and Mn-supplemented (MnS) diet with <1, 10–15 and 45–50 ppm of Mn, respectively. The above Mn levels were chosen because studies indicate that an Mn level of less than 1.0 ppm results in Mn deficiency in about 13 to 15 weeks [22–25]. Dietary Mn levels of 10 ppm have been reported by the American Institute of Nutrition as an adequate level to prevent deficiency in the rat [27]. The animals were individually housed in metal mesh-bottomed cages in an environmentally controlled room maintained at 22°C with a 12:12-h light–dark cycle. All animals were weighed weekly. The Animal Care and Use Committee of the University of Maine approved all animal care and experimental procedures.

2.1.2. Diets

Diets were mixed in our laboratory from purified ingredients, as described before [24,25]. Vitamin (AOAC special vitamin mixture, Harlan Tekland) and mineral mixes (ICN Biochemicals, Cleveland, OH) were commercially prepared. Manganese content of the diets and tap water were determined by atomic absorption spectroscopy at the Maine Forest and Agriculture Experiment Station Analytical Laboratory, Plant and Soil Department of the University of Maine (detection limit, 0.01 ppm). Diet content of Mn was tested every time following preparation. Food consumption was measured daily in all animal groups. Tap water (below the detection limit for Mn) and food was provided ad libitum.

2.1.3. Tissue sampling

At the end of the feeding period, rat food was withheld for 12–14 h. Animals were anesthetized in a chamber with 95% CO_2/5% O_2 for approximately 2 min. Thoracic aortas and livers were removed carefully and washed with physiologic salt solution [PSS, with composition (in mmol/L): NaCl, 118; KCl, 4.7; $NaHCO_3$, 25; KH_2PO_4, 1.18; $MgSO_4$, 1.17; dextrose, 11; $CaCl_2$, 1.25]. Liver tissues were weighed, lyophilized, pulverized and analyzed for Mn content using an atomic absorption spectrophotometer with a graphite furnace atomizer at the Maine Forest and Agriculture Experiment Station Analytical Laboratory, Plant and Soil Department of the University of Maine.

2.2. Vascular ring studies

2.2.1. Aortic preparations

The thoracic aorta was removed and submerged in a petri dish filled with PSS at room temperature. The aortic segment was cleaned of adherent fat and connective tissues and four rings of 3-mm length were prepared from the middle part of the vessel. Two stainless steel wire triangles (0.012 in diameter) were passed carefully through each ring. Each aortic ring was mounted in a 20-ml Radnotti tissue bath, which contained PSS maintained at 37°C by a thermoregulated water circuit and was continuously bubbled with a 95% O_2 and 5% CO_2 mixture in order to keep the pH at 7.4. The aortic ring was attached through one triangle to a fixed glass hook in the tissue bath and through the other triangle to a force transducer, which was connected to a tissue force analyzer (Model 410, MicroMed, Louisville, KY) for the measurement of isometric force, which was continuously displayed and recorded on-line on a computer.

2.2.2. Experimental protocol

A total of 120 intact rings (four rings from each rat from the three diet groups, 10 animals in each diet group) were used. Resting tension (preload) was adjusted to 1.5 g, since this preload provides the optimum concentration–response relationships to a variety of agonists, including the α_1 adrenergic receptor-selective agonist L-Phe [28–32]. Tissues

Table 1
Effects of dietary Mn on body weight, liver weight and hepatic Mn content

Diet groups	Body weight (g)	Liver weight (g)	Liver weight as % of body weight	Hepatic Mn content (ppm)
MnD	452±15.79[a]	12.79±0.88	2.87±0.001	1.516±0.11[a]
MnA	489±7.87	13.68±0.67	2.79±0.001	7.093±0.24
MnS	523±9.41[a]	14.69±0.60	2.81±0.001	7.603±0.20

[a] Statistically significant differences at $P \leq .05$ compared to MnA (control) group.

were allowed to equilibrate for 60 min. During this time, all rings were washed with PSS (37°C, pH 7.4) and were precontracted for 10 min with one dose of L-Phe (10^{-8} M) and one dose of acetylcholine (Ach, 10^{-8} M), to saturate the nonselective receptor binding sites for the agonists. After washing the tissues for four times the preload was corrected to the original baseline levels and remained unchanged throughout the experiment.

Each ring was contracted with cumulative applications of six concentrations of L-Phe (in 3× steps) over the range (10^{-8} to 3×10^{-6} M) as it has been described before [30,31]. A drug–tissue contact time of 6 min was allowed for each L-Phe concentration to achieve the maximum contraction. The presence of viable endothelium was assessed in all preparations by determining the ability of Ach (3×10^{-6} M) to induce more than 70% of relaxation of rings in the presence of L-Phe. After each agonist treatment the rings were washed four times over 25 min with PSS (37°C, pH 7.4) to bring aortic tension down to or slightly below the original preload level. A second L-Phe dose–response curve was obtained, followed by the same dose of Ach, under the same passive tension (preload) in order to duplicate the contraction curve.

2.3. Drugs

Acetylcholine chloride, L-phenylephrine and salts for the stock solutions of the PSS (NaCl, KCl, $NaHCO_3$, KH_2PO_4, $MgSO_4$, dextrose, $CaCl_2$) were purchased in pure forms from Sigma-Aldrich Chemical (St. Louis, MO) and were dissolved in distilled water.

2.4. Statistical analysis

Animal weights and hepatic Mn content were compared using a one-way analysis of variance (ANOVA). The mean daily food intake was measured each week and compared among all groups with Student *t* tests.

The maximal contraction force (F_{max}) that was developed in all intact rings in the three animal groups reveals differences of the contractile machinery among animals with different dietary Mn intake. The pD_2 values for the rings of all animals show differences in the vessel sensitivity to the α_1 adrenergic receptor. Relaxation to the Ach dose lower than 70% detecting possible damage in the endothelium during the experimental procedure of the intact rings was used as a qualitative exclusive criterion. All results are expressed as mean values±S.E.M. The F_{max} and pD_2 values to L-Phe were compared in different two-way ANOVA tests in order to determine the effect of different diets on the contractile machinery and on vessel sensitivity. Student–Newman–Keuls tests were used for statistical analysis and a *P* value level of .05 or less was considered as statistically significant.

3. Results

3.1. Animal growth

All animals fed an MnD, MnA or MnS diet gained weight. However, mean body weights were significantly different among all groups (Table 1). The rate of growth in MnD animals was slower compared with the MnA and MnS rats (Table 1). The difference in growth rate was statistically significant from the fourth week. Liver weights (Table 1) and food intake (data not shown) were not statistically significant among the diet groups. The percentage of liver weight to body weight of the rats was not different among the diet groups (Table 1). Manganese deficiency was confirmed by hepatic Mn content, which was decreased only in the MnD group (Table 1).

3.2. Response to L-Phe-induced vasoconstriction

Six cumulative doses were used to give L-Phe concentrations of 10^{-8} to 3×10^{-6} M in threefold steps in the tissue baths to produce graded increases in concentration force. The maximum contraction force developed in response to L-Phe was observed at higher than 10^{-6} M doses of the drug (fifth and sixth L-Phe doses). Washout of agonist over 25 min reduced contraction force at least to the preload value.

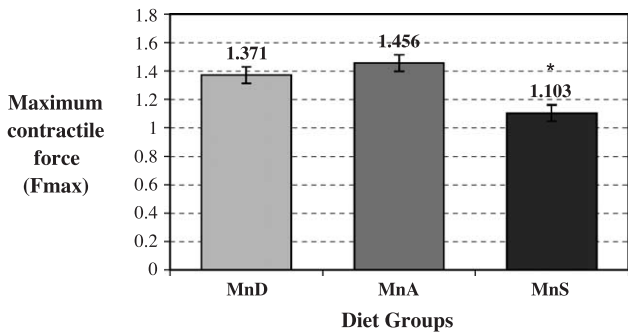

Fig. 1. Effects of dietary Mn on maximal tension (F_{max}, mean value±S.E.M.) generated in response to phenylephrine-induced contractions in isolated rat aortas. MnD, Mn deficient; MnA, Mn adequate; MnS, Mn supplemented. *Statistically significant differences at $P \leq .001$ compared with the MnA (control) group.

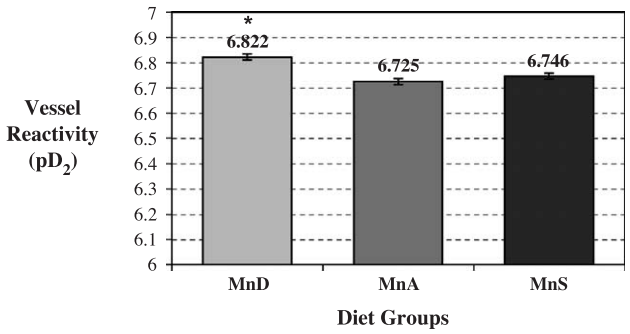

Fig. 2. Effects of dietary Mn on vascular reactivity (pD_2, mean value±S.E.M.) in response to phenylephrine-induced contractions in isolated rat aortas. MnD, Mn deficient; MnA, Mn adequate; MnS, Mn supplemented. *Statistically significant differences at $P \leq .001$ compared with the MnA (control) group.

The mean F_{max} developed in response to L-Phe is presented in Fig. 1. Aortic rings from animals fed an MnD diet did not develop significantly different F_{max} compared with MnA animals. However, aortic rings from animals supplemented with 45–50 ppm of Mn (MnS group) developed lower F_{max} compared with both MnD and MnA animals. Supplementing the diet with 45–50 ppm of Mn did not change the hepatic Mn status (Table 1) but reduced the contractile responses to the α_1 adrenergic agonist (phenylephrine) in the rat aortic rings in comparison with the MnA (10–15 ppm) or the MnD (<1 ppm) diet (Fig. 1).

The decrease in tension to the 3×10^{-6} M Ach dose was divided by the ring tension just prior to the Ach dose (point after the last point of the last L-Phe dose) and was used to calculate a percent relaxation for that ring when the drug was applied. Since all aortas were precontracted to the same extent with the same dose of L-Phe, the relaxations were expressed as percentages of the level of precontraction. Application of the Ach dose at the end of the L-Phe concentration–response curve significantly relaxed the L-Phe contracted aortic rings of all groups (approximately >70%) and that indicated that the endothelium was not damaged during the tissue extraction process and the aortic ring preparation.

The F_{max} for each ring was used to calculate a percent increase of force in each dose in order to determine the EC_{50} value (the effective concentration of L-Phe in which 50% of maximum contraction was obtained). The negative log (base 10) of the EC_{50} value was calculated to give us the pD_2 value for each ring, a measure of vessel sensitivity to the α_1 adrenergic receptor response.

The pD_2 values for aortic ring contractions to L-Phe in MnD animals were significantly greater compared with MnA and MnS animals (Fig. 2). The vascular sensitivity of MnA and MnS animals did not appear to be significantly different. Thus, restriction of dietary Mn below the adequate concentration of 10–15 ppm seems to increase the vascular sensitivity to the α_1 adrenergic receptor.

4. Discussion

Manganese deficiency was confirmed by the suppression of animal growth in the MnD diet group as well as by the lower hepatic Mn content (Table 1). The retardation of growth was independent of the animals' dietary food intake (data not shown). Retardation of rodent growth in Mn deficiency has also been reported by previous studies [22–24,33–35], and it seems to be an effect of reduced efficiency of food conversion with the dietary Mn depletion [24,25]. The decrease in liver weight in MnD rats was proportional to the decrease in body weight in MnD animals.

We document for the first time that the presence of Mn in the diet affects the phenylephrine-induced contractions of the rat aortic vessel. The effect of the trace element includes both the maximal contractile response to phenylephrine and the membrane-related receptor sensitivity. Altering the Mn from control levels in the experimental diet modifies the above responses. When Mn is present at levels lower than 10–15 ppm (MnA, as set by the American Institute of Nutrition) the vessel sensitivity is increased without any significant changes on the development of the maximum contractile force by the artery in response to the α_1 adrenergic agonist L-Phe (Figs. 1 and 2). However, when dietary Mn is present at levels of 45–50 ppm (MnS), there is a significant reduction in the maximal contractile force without any change in the vessel sensitivity in response to the α_1 adrenergic receptor agonist compared with the MnA group (Figs. 1 and 2). These results suggest that there are two separate mechanisms of action of Mn in the Phe-induced vasoconstrictor pathway.

Studies in vitro have shown that when Mn is present in small concentrations (0.3–3 μmol/L), it inhibits the vascular contractions induced by noradrenaline, 5-hydroxytryptamine and potassium in porcine coronary artery, goat and human cerebral arteries and in rat aorta [19–21]. In our study, we observed the effect of dietary intake of Mn on the phenylephrine-induced contractions in the Sprague–Dawley rat aorta and confirmed the suppressor effect of Mn on α_1 adrenergic agonist-induced vasoconstriction ex vivo. Our results showed that dietary Mn shifted the phenylephrine dose–response curves to the right with a significant reduction in the maximum contractile response at Mn levels higher than 10–15 ppm. The exact mechanism involved in such inhibitory action of Mn is still unknown. Interestingly, this shift occurred when dietary Mn was supplemented, but there was no difference in the hepatic Mn concentration between the MnA and MnS groups (Table 1) suggesting that the contractile mechanism is more sensitive than the storage index for Mn.

Previous in vitro observations support several hypotheses that might explain the role of Mn in suppressing agonist-induced vasoconstriction [18–20,36–38]. One of these hypotheses is that Mn can pass through voltage-dependent Ca^{+2} channels and might share a Ca^{+2}-blocking property in smooth muscle cells by antagonizing Ca^{+2} [19,20,37,39,40].

Complete depletion of the intracellular Ca^{+2} pool is known to activate Mn^{+2} nonpermeable Ca^{+2} influx from the extracellular space in portal vein smooth muscle cells in the presence of an adrenergic receptor agonist [41,42]. This observation may explain the reduction in maximal contraction of the rat aorta in the presence of dietary Mn >45 ppm, which affects the contractile machinery.

Manganese is known to affect the synthesis of metalloenzymes that protect the cell membrane structure from oxidative stress, such as Mn superoxide dismutase [35,43,44]. The presence of free radicals represents an important mechanism for endothelial dysfunction by reducing the bioavailability of the endothelium-derived relaxing factor nitric oxide (NO) [9,45,46]. Ensunsa et al. [47] have reported lower levels of liver eNOS in MnD animals and increased production of peroxinitrite products, which in turn may have an effect on the bioavailability of NO in the endothelial cell layer [15]. Decreased bioavailability of endothelial-released NO is associated with decreased vasorelaxation and may affect the biomechanical properties of the contractile machinery.

In addition to a role for Mn in the contractile machinery of the vascular smooth muscle our results show an increase in pD_2 values in the MnD group (Fig. 2). Because these results occurred without a change in F_{max} (Fig. 1), we suggest that there is an increase in α_1 adrenergic receptor sensitivity during dietary Mn deficiency. Since Mn interferes in the composition of the extracellular cell matrix by affecting the synthesis and structure of certain glycosaminoglycan molecules (chondroitin sulfate) [24,25] and affects their sulfation pattern, it might also modulate agonist actions or interfere in the agonist–receptor binding or at the receptor structure itself. It has been reported that glycosaminoglycan structures act as cellular coreceptors in order to facilitate the binding of receptors with ligands such as growth factors (vascular endothelial growth factor, fibroblast growth factor, etc.) and lipoproteins. These cell surface receptor–ligand complexes are involved in the process of cell signal transfer by affecting the responsiveness of the cellular membrane to extracellular ligands, especially in low ligand concentrations [48,49].

Despite the expanding plethora of studies on the biomechanical properties of the vasculature, there are still many gaps on the exact signaling pathways and the second messengers that are implicated and regulate contraction and relaxation within the cell. It has been reported that only approximately one third of all cardiovascular events can be extrapolated on the basis of "accepted" risk factors. Additional determinants may exist, and trace minerals may be potential candidates. Manganese is a multifunctional trace element participating in many fundamental processes in the cell [50]. The effect of Mn on the vascular system, such as the control of blood flow and blood pressure, coagulation, platelet aggregation, vessel permeability, wound healing and angiogenesis still remains to be unraveled.

Our results demonstrate, for the first time, that dietary Mn is implicated in the vascular contractile model, affecting the mechanical properties of blood vessels and regulating vascular tone. This depends on its concentration in the diet. The processes underlying the signaling effect of Mn, the mechanisms of its action on the endothelial and the vascular smooth muscle cell pathways, warrant further study in model systems ex vivo.

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