Editorial

Role of Zn in blood pressure and renal function

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Abstract

Zn-excess ingestion elevated blood pressure (BP) and reduced renal blood flow (RBF) and inulin clearance. The fall in inulin clearance may be the result of a decline in RBF. Intravenous injection of the nitric oxide (NO) synthase inhibitor, L-NAME potentiated an increase in BP and a decrease in RBF in the Zn-excess setting. However, intravenous administration of the exogenous superoxide radical scavenger, tempol significantly reduced BP and substantially augmented RBF in the Zn-excess setting. Resultantly, tempol treatment restored BP and RBF levels observed in the Zn-excess setting to levels comparable to those seen in the control setting. These findings suggest that both an increment in BP and a decrement in RBF observed in the Zn-excess setting result from a decrement in the action of the vasodilator, NO through peroxynitrite formation derived from the non-enzymatic reaction of NO with increased superoxide radical. In fact, the activity of the endogenous superoxide radical scavenger, Cu/Zn-superoxide dismutase (SOD) was significantly diminished in the vessel wall of the Zn-excess vs. the control setting. The reduction in the activity of Cu/Zn-SOD in the Zn-excess setting was the effect of Cu deficiency secondary to Zn-excess ingestion. With regard to BP, RBF, inulin clearance, L-NAME and tempol treatment and the activity of Cu/Zn-SOD, similar results were seen in the Zn-deficient setting. Therefore, inadequate intake of Zn causes the aggravation of BP and renal function via superoxide radical-induced oxidative stress.

KEY WORDS　Zinc, Blood pressure, Renal function, Oxidative stress, Cu/Zn-superoxide dismutase

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Introduction

Zinc (Zn), is an essential trace element in humans and animals[1-3]. Zn deficiency causes a variety of physical disorders derived from the skin epithelium, the gastrointestinal system, the reproductive system, the neural system, the endocrine system, the ocular system and the immune system[1-3]. Zn tablets and Zn-supplemented food have been recently circulating in Japan, the USA and Europe in order to obtain good health and health promotion[2,3]. Moreover, oral Zn therapy has been more recently done to treat hypogeusia and decubitus ulcers in adults [2,3] and hypogonadism and growth retardation from infants to adolescents[4,5]. However, Zn toxicity has not been fully understood. Here, we therefore describe the novel aspects, the deterioration of blood pressure (BP) and renal function observed in Zn-deficient and Zn-excess rats.

1. Role of Zn-excess ingestion in blood pressure and renal function

Rats fed on 22 g/day of 0.05% Zn-excess diet (11 mgZn/day) and 0.2% Zn-excess diet (44 mgZn/day) for 4 weeks showed a dose-dependent increase in basal systolic blood pressure (BP), diastolic BP and mean BP levels[3,6,7] and a dose-dependent decrease in basal renal blood flow (RBF) and inulin clearance levels[3,7] relative to rats fed on a control diet containing 0.005% Zn (1.1 mgZn/day) for 4 weeks (Fig.1). These findings indicate an increase in basal systemic BP levels

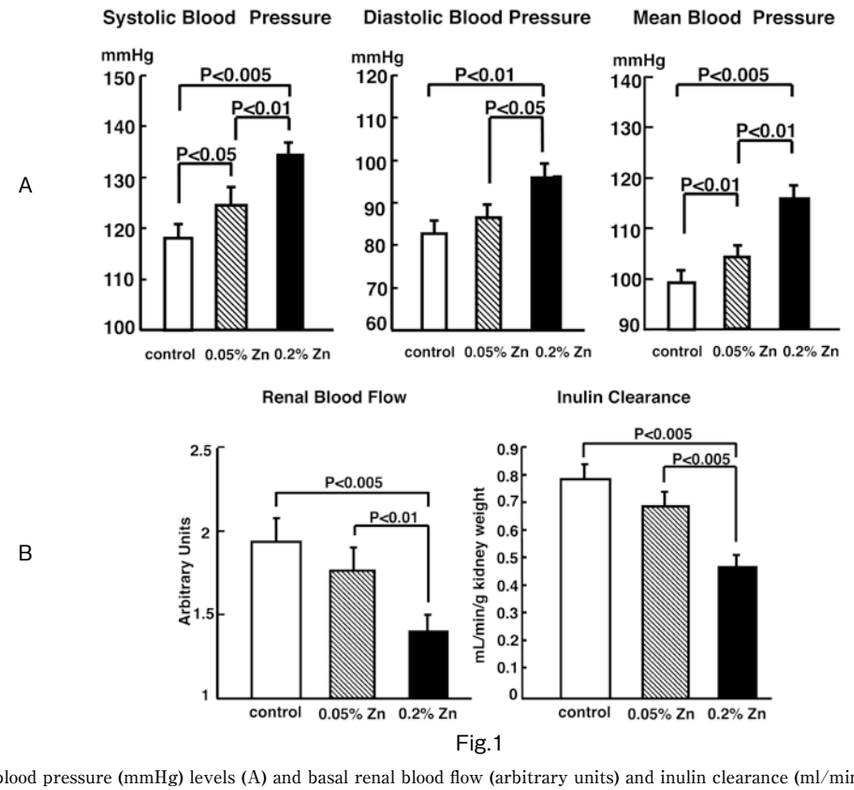

Fig.1

Basal blood pressure (mmHg) levels (A) and basal renal blood flow (arbitrary units) and inulin clearance (ml/min/g kidney weight) levels (B) obtained from rats fed on a control diet containing 0.005% Zn or two Zn-excess diets containing 0.05% Zn or 0.2% Zn for 4 weeks. Blood pressure, renal blood flow and inulin clearance were measured at 4 weeks after the start of dietary treatment. Data reported represent means ± SD of the values obtained from seven rats in each group. Statistical analysis was based upon one-way analysis of variance. References[3,7]

and a fall in basal renal function derived from Zn-excess intake[3,7]. The fall in inulin clearance in rats fed on two Zn-excess diets may be due to a decrease in RBF because hematoxylin-eosin (H-E) staining exhibited no significant morphologic changes in the kidneys from rats fed a 0.2% Zn-excess diet[3,7].

Intravenous administration of the NOS inhibitor, N$^{\omega}$-nitro-L-arginine methyl ester (L-NAME) elevated mean BP levels[3,7,8] and reduced RBF levels[7,8] in rats fed on a control diet and two Zn-excess diets (Fig.2). The mean BP levels elevated[6-8] and the RBF levels[3,7] reduced were comparable among the three groups of rats. These observations suggest the involvement of NO in the regulation of systemic BP and RBF in the three groups of rats[3,7,8]. Thus, the vasodilator, NO may play a central role in suppressing an elevation in systemic BP and a fall in renal function in the Zn-excess setting[3,7,8].

Intravenous injection of the membrane-permeable SOD mimetic compound, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (tempol) caused a decrease in mean BP levels[3,7,8] and an elevation in RBF levels[7,8] in rats fed on a control diet and two Zn-excess diets (Fig.3). These observations indicate that superoxide radical may be a modifier of systemic BP and renal function through a reduction in the action of the vasodilator, NO based on the formation of peroxynitrite in rats fed on two Zn-excess diets[3,7,8] (Fig.4). Thus, the mechanisms underlying an elevation in systemic BP and the deterioration of renal function in rats fed on two Zn-excess diets may be due to an increase in the action of superoxide radical in the vessel wall[3,7,8]. Actually, a dose-dependent increment in 8-hydroxy-2'-deoxyguanosine formation caused by enhanced superoxide radical production was observed in rats fed on two Zn-excess diets relative to rats fed on a control diet[3,7]. Additionally, the activity of the intrinsic superoxide radical scavenger, Cu/Zn-SOD in the thoracic aorta was significantly reduced in rats fed on two Zn-excess diets relative to rats fed on a control diet in a dose-dependent manner[3,7,8]. This fall in the activity of Cu/Zn-SOD may be the

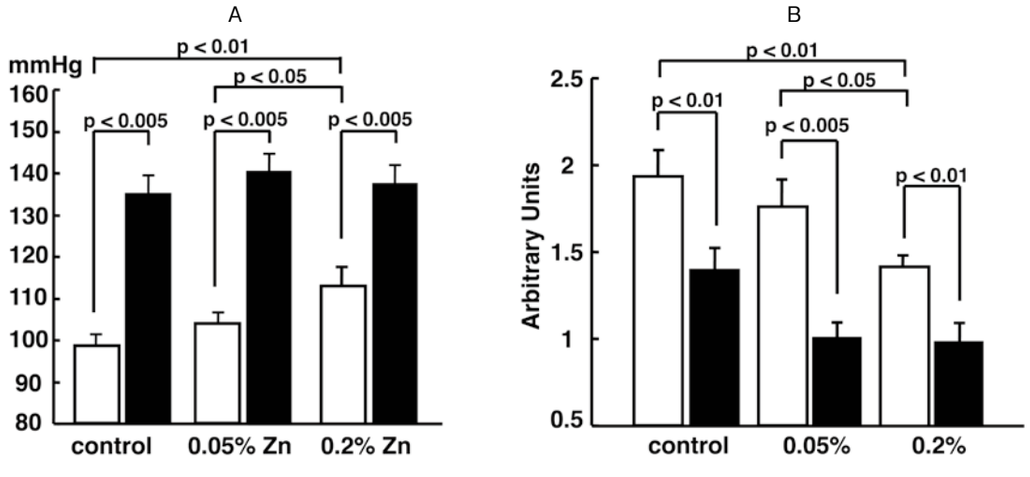

Fig.2

Effects of L-NAME treatment on mean blood pressure (mmHg) levels (A) and renal blood flow (arbitrary units) levels (B) seen in rats fed a control diet containing 0.005% Zn or two Zn-excess diets containing 0.05% Zn or 0.2% Zn for 4 weeks. Data reported represent means ± SD of the values obtained from seven rats in each group. Statistical analysis was based upon two-way analysis of variance. White bars; basal condition groups. Black bars; L-NAME treatment groups. Reference[3,7]

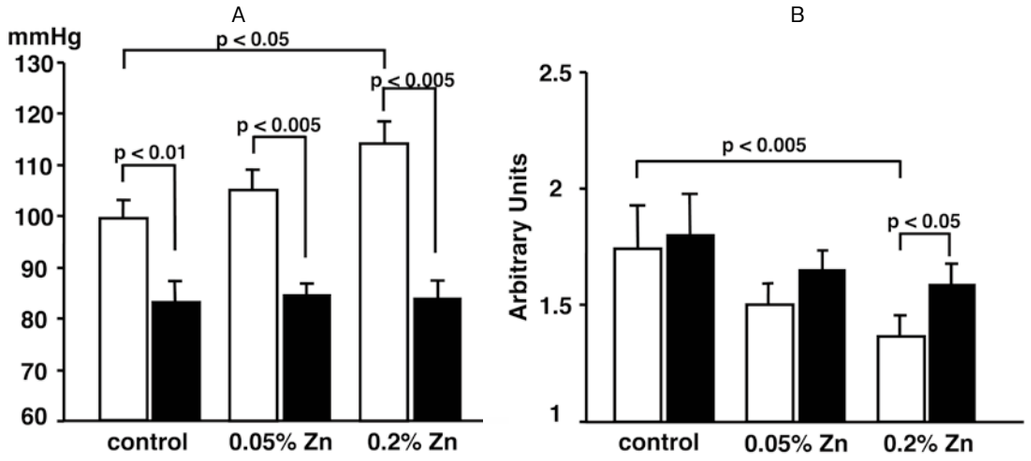

Fig.3

Effects of tempol treatment on mean blood pressure (mmHg) levels (A) and renal blood flow (arbitrary units) levels (B) seen in rats fed a control diet containing 0.005% Zn or two Zn-excess diets containing 0.05% Zn or 0.2% Zn for 4 weeks. Data reported represent means ± SD of the values obtained from eight rats in each group. Statistical analysis was based upon two-way analysis of variance. White bars; basal condition groups. Black bars; tempol treatment groups. Reference[3,7]

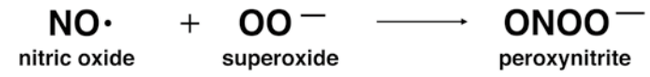

Fig.4

Peroxynitrite formation as a result of non-enzymatic reaction of nitric oxide with superoxide radical. Reference[3]

result of Cu deficiency secondary to Zn-excess ingestion, contributing to an increment in the action of superoxide radical in the vessel wall of rats fed on two Zn-excess diets[3,7,8].

There were no significant differences in mean BP and RBF levels after L-NAME or tempol treatment among rats fed on a control diet and two Zn-excess diets[3,7,8] (Figs.3, 4). Mean BP levels obtained from rats fed on two Zn-excess diets were essentially comparable to those obtained from rats fed a control diet[3,7,8]. However, RBF levels obtained from rats fed on two Zn-excess diets were somewhat different from those obtained from rats fed on a control diet[3,7]. This observation suggests that in addition to both NO and superoxide radical, some vasoconstrictive factor takes part in the modulation of RBF levels in the Zn-excess settings[3,7]. We have recently found a significant and dose-dependent increase in the potent vasoconstrictor, angiotensin Ⅱ in the kidneys of rats fed on two Zn-excess diets relative to those of rats fed on a control diet[3,8]. This increased angiotensin Ⅱ may contribute in part to an alteration in RBF levels seen in Zn-excess intake[3,8].

2. Effects of zinc-deficient intake on blood pressure and renal function

Spontaneously hypertensive rats (SHR) fed on a Zn-deficient diet for 4 weeks exhibited a significant elevation in systolic BP levels at 2 and 4 weeks following the initiation of dietary treatment relative to SHR fed on a control diet for 4 weeks[3,9]. Intravenous L-NAME treatment significantly increased mean BP levels in SHR

fed on a control or a Zn-deficient diet for 4 weeks[3,9]. Mean BP levels after L-NAME administration were comparable in the two groups of rats[3,9], demonstrating the involvement of the vasodilator, NO in the regulation of BP. Inversely, intravenous tempol administration significantly decreased mean BP levels in SHR fed on a control or a Zn-deficient diet for 4 weeks[3,9]. As a consequence, intravenous tempol administration completely restored mean BP levels observed in SHR fed on a Zn-deficient diet for 4 weeks to levels comparable to those seen in SHR fed on a control diet for 4 weeks[3,9], indicating the participation of superoxide radical in the regulation of BP. Similar to the Zn-excess setting for 4 weeks[3,6-8], these findings demonstrate that an increase in BP levels observed in SHR fed on a Zn-deficient diet for 4 weeks may be the result of a decrease in the action of the vasodilator, NO based upon the formation of peroxynitrite derived from the non-enzymatic reaction of NO with increased levels of superoxide radical[3,9]. In fact, the activity of Cu/Zn-SOD scavenging superoxide radical was significantly diminished in rats fed on a Zn-deficient diet for 4weeks than in rats fed on a control diet for 4 weeks[3,9].

Normotenvive rats (NMR) fed on a Zn-deficient diet for 4 weeks had no significant increases in mean BP levels during the dietary manipulation relative to NMR fed on a normal diet for 4 weeks[3,10,11]. However, NMR fed on a Zn-deficient vs. a normal diet for 4 weeks showed a significant reduction in RBF levels and a significant elevation in renal vascular resistance (RVR) levels, resulting in a fall in inulin clearance[3,10,11]. Intravenous L-NAME treatment significantly augmented mean BP and RVR levels and significantly reduced RBF levels in rats fed on a control or a Zn-deficient diet for 4 weeks[3,10,11]. However, intravenous tempol administration significantly decreased mean BP and RVR levels in rats fed on a control or a Zn-deficient diet for 4 weeks, while there are no significant differences in RBF levels between the two groups of rats[3,11]. These observations are similar to those observed in the Zn-excess setting[3,6-8]. Therefore, the mechanisms underlying the aggravation of renal function observed in rats fed a Zn-deficient diet for 4 weeks may be due to a fall in the action of the vasodilator, NO based upon an elevation in the action of superoxide radical[3,11]. Indeed, the activity of the intrinsic superoxide radical scavenger, Cu/Zn-SOD was significantly reduced in the kidneys of rats fed a Zn-deficient diet for 4 weeks relative to rats fed a control diet for 4 weeks[3,11].

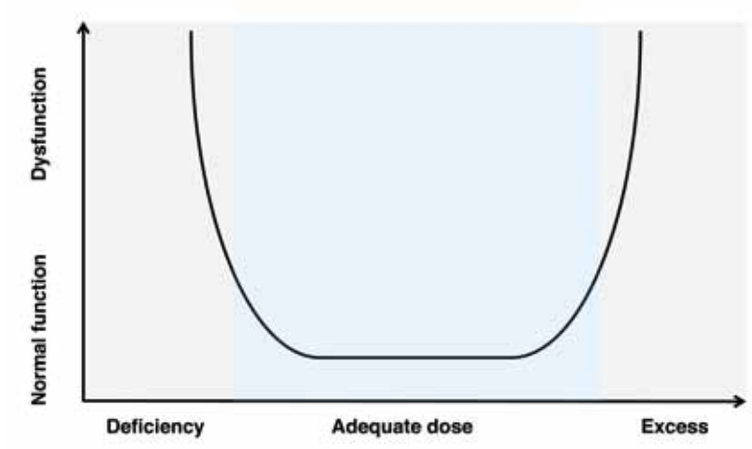

Fig.5
U-shaped relationship between Zn ingestion and function. Reference[9]

3. Summary and conclusions

Zn contributes to the regulation of BP and renal function. Both the Zn-deficient and Zn-excess settings alter BP levels and renal function via superoxide radical-induced oxidative stress. The mechanisms may be a reduction in the action of the vasodilator, NO derived from the formation of peroxynitrite generated by the non-enzymatic reaction of NO with superoxide radical. Thus, adequate intake of Zn is essential to maintain BP and renal function (Fig.5).

As shown in Fig.1, values for both systemic BP and RBF seen in rats fed a 0.05% Zn-excess diet (11 mgZn/day) were at the borderline in statistical significance relative to those obtained from rats fed a control diet (1.1 mgZn/day). This suggests that the lowest observed adverse effect level of Zn is approximately 11 mg/day in rats[3,7].

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