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Soluble silica and coral sand suppress high blood pressure and improve the related aortic gene expressions in spontaneously hypertensive rats

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Abstract

Silicon is rich in the normal human aorta but decreases with age and the development of atherosclerosis. We hypothesized that soluble silica (Si) and coral sand (CS), as a natural Si-containing material, would suppress high blood pressure (BP) in spontaneously hypertensive rats (SHRs), and clarify the observed antihypertensive mechanism by cell cultures by quantifying messenger RNA expressions in the aorta. In SHR fed diets containing 1% Ca supplemented with $CaCO_3$ as the control (CT) and CS in a Ca-deficient diet and containing 50 mg/kg Si in the CT diet for 8 weeks, systolic BP was significantly ($P < .05$) lowered by 18 mm Hg for the Si group and 16 mm Hg for the CS group compared with the control CT group with 207 mm Hg. Magnesium (Mg) uptake by rat aortic smooth muscle cells significantly increased (177%, $P < .005$) in cells cultured with a physiologic Mg level plus Si compared with those with no Si addition. Furthermore, the increase of systolic BP by the CT diet was significantly suppressed by 17 mm Hg ($P < .001$) in SHR fed the diet containing Mg along with Si, but not by the Mg-deficient diet with or without Si. Soluble silica and CS treatments suppressed the aortic gene expressions of angiotensinogen and growth factors related to vascular remodeling, whereas, Si stimulated the expression of peroxisome proliferator–activated receptor-γ, the activation of which has anti-inflammatory and antihypertensive effects on vascular cells. These findings suggest that Si reduces hypertension in SHR by stimulating the intracellular Mg uptake and related gene expression in the aorta.

Keywords: Antihypertension; Soluble silica; Intracellular magnesium; Aortic gene expressions; Spontaneously hypertensive rats

Abbreviations: ACE, angiotensin-converting enzyme; AGN, angiotensinogen; Ang II, angiotensin II; ASMC, aortic smooth muscle cells; AT1A, angiotensin II type 1A receptor; bFGF, basic fibroblast growth factor; BP, blood pressure; CS, coral sand; DMEM, dulbecco's modified eagle's medium; eNOS, endothelial nitric oxide synthetase; Mg, magnesium; PDGF-A, platelet-derived growth factor A chain; PPAR, peroxisome proliferator–activated receptor; PCR, polymerase chain reaction; RAS, renin-angiotensin system; SHR, spontaneously hypertensive rats; Si, soluble silica; TGF-β1, transforming growth factor β1.

1. Introduction

Next to oxygen, silicon is the most abundant (29.5%) element of the Earth's crust. The most commonly occurring mineral is quartz, SiO_2, which is a major constituent of igneous and sedimentary rocks. The biologically important form is silicic acid, $Si(OH)_4$, which is referred to as "a soluble silica (Si)" and freely diffusible across cell walls and membranes. Silicic acid is not found naturally in large quantities; at concentrations above 2 mmol/L (56 mg/L),

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silicic acid molecules undergo polymerization to form insoluble polysilicic acid [1]. Bioavailable soluble silicate (monosilicic acid) reacts with molybdate reagent to give a yellow color, whereas, polysilicic acid does not react with this reagent [1,2]. Silicon levels in human serum have been estimated at an average of about 0.5 mg/L in the soluble form [1,3], and this range is similar to those found for most of the other well-recognized trace elements in human nutrition. Connective tissues such as the aorta, trachea, tendon, bone, skin, and appendages are unusually rich in Si, containing 4 to 5 times more Si than the liver, heart, and muscles in the rat [3]. The Si content of the normal human aorta decreases considerably with age; furthermore, the level of silicon in the arterial wall decreases with the development of atherosclerosis [4]. The potential involvement of Si in atherosclerosis has been suggested by others [5,6], but so far, to our knowledge, no attention has been paid to the possible effects of Si intake on blood pressure (BP).

Elevated BP is a major contributor in cardiovascular and renal diseases and stroke worldwide [7]. Although the multigenic nature of essential hypertension is widely accepted, the importance of dietary factors including minerals in the primary prevention and control of high BP has been emphasized for normotensive and hypertensive individuals [8]. An inverse relationship between dietary magnesium (Mg) intakes and BP has been reported [9,10]. A large volume of evidence [11] has accumulated showing that Mg, a natural Ca antagonist [12,13], modulates vasomotor tone, BP, and peripheral blood flow through the regulation of intracellular Ca ions. Low serum Mg levels have been involved in various events of atherosclerosis in basic [14] and clinical studies [15].

Because the key role of genetic factors in regulating the multiple pathways in neural, endocrinal, and vascular systems is proposed to be related to the pathogenesis of essential hypertension [16], alterations of gene expression can affect hypertension. In this study, we hypothesized that Si may improve high BP in spontaneously hypertensive rat (SHR), a model used to study multiple factors in the etiology of essential hypertension, and test in vivo the mechanism of the suppressive effect of Si on the elevation of BP by culturing rat aortic smooth muscle cells (ASMCs). This will be done by quantifying messenger RNA (mRNA) expressions related to hypertension in the SHR aorta. We also examined the antihypertensive effects of coral sand (CS) as a natural Si-containing material, together with strontium (Sr), which is a constituent of CS, to demonstrate similar antidiabetic effects for Si and CS, including genetic expressions in our previous study [17].

2. Methods and materials

2.1. Animal experiments

The experimental protocols of this study were approved by the Animal Experiment Ethics Committee of the University of the Ryukyus. Male SHR, aged 4 weeks, were purchased from Japan SLC, Inc (Shizuoka, Japan). The rats were divided into 4 groups of 8 each and housed 2 per cage at 24°C with a 12-hour light-dark cycle. Before the start of the experiment, the rats were given free access to a commercial diet (MF; Oriental Yeast Co, Tokyo, Japan) and tap water. They were also acclimated to the measurement of systolic BP by the tail-cuff method using an automatic BP analyzer (model BP-98A; Softron Co, Tokyo, Japan) for 3 weeks according to the manufacturer's instructions. The rats at 7 weeks of age were maintained for 8 weeks on an ad libitum semisolid experimental diet of 34% tap water and 66% the experimental powder diet (or powder diet), containing 1% Ca supplemented with $CaCO_3$ as the control (CT) and CS in Ca-deficient purified diet (Oriental Yeast Co) and diet with 50 mg/kg Si or 750 mg/kg Sr added to the CT diet (Tables 1 and 2); these doses have been used in previous studies without toxic effects [3,5,17,18]. Systolic BP was measured twice a week, and the mean of 3 repeated measurements was used for each datum. Available soluble silicon compound, sodium metasilicate $Na_2SiO_3 \cdot 9H_2O$, and strontium chloride $SrCl_2 \cdot 6H_2O$ were used in the animal studies. The CS used was defined in detail previously [18]. In brief, CS smaller than approximately 1 cm is collected from the sea floor at 55- to 60-m depth in the designated sea region by using a sand pump with a mesh filter, and larger CS is returned to the sea. Crude CS smaller than approximately 2 mm is disinfected at 120 to 200°C and ground into a fine powder less than 22 μm.

At the end of the 8-week-experiment, rats from each group were euthanized by ether anesthesia at regular intervals after 6-hour fasting, and heparinized blood was obtained from each rat by heart puncture. Blood samples were centrifuged, and plasma was divided into aliquots and stored at −80°C until analysis. The immediately excised thoracic-to-abdominal aorta (from which other tissues were removed) was homogenized for RNA isolation. The results

Table 1
Ingredient composition of the experimental diet [a]

Ingredient (g/kg diet)	Basal diet
Cornstarch	380
Casein	250
α-Cornstarch	100
Cellulose	80
Soybean oil	60
Oriental mineral mix [b]	60
Oriental vitamin mix [c]	20
Sucrose	50

[a] Purified basal diet was prepared by Oriental Yeast Co.

[b] Oriental mineral mix composition (g/kg): $CaHPO_4$??$2H_2O$, 145.6; Ca lactate, 350.9; KH_2PO_4, 257.2; $NaHPO_4$ 93.5; NaC1, 46.6; Fe citrate, 31.8; $MgSO_4$, 71.7; $ZnCO_3$, 1.1; $MnSO_4$•4–$5H_2O$, 1.2; $CuSO_4$•$5H_2O$, 0.3; KI, 0.1.

[c] Oriental vitamin mix composition (g/kg): thiamin HC1, 1.2; riboflavin, 1.2; pyridoxine HC1, 0.8; nicotinic acid, 6.0; inositol, 6.0; Ca pantothenate, 5.0; *p*-aminobenzoic acid, 5.0; folic acid, 0.2; D-biotin, 0.02; vitamin B_{12}, 0.0005; vitamin C, 30; vitamin A acetate, 500 000 IU; vitamin D_3, 100 000 IU; vitamin E acetate, 5.0; vitamin K_3, 5.2.