Beneficial effects of the active principle component of Korean cabbage kimchi via increasing nitric oxide production and suppressing inflammation in the aorta of apoE knockout mice

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Abstract
The present study investigated the effects of 3⁰-(4⁰-hydroxyl-3⁰,5⁰-dimethoxyphenyl)propionic acid (HDMPPA), the active principle compound of kimchi, on vascular damage in the experimental atherosclerotic animal. HDMPPA was administrated by an intraperitoneal injection of 10 mg/kg per d for 8 weeks to apoE knockout (KO) mice with an atherogenic diet containing 1% cholesterol, and its effects were compared with vehicle-treated control mice. HDMPPA increased NO content in the aorta, accompanied by a decrease in reactive oxygen species (ROS) concentration. Furthermore, in the HDMPPA-treated group, aortic endothelial NO synthase (eNOS) expression was up-regulated compared with the control group. These results suggested that HDMPPA could maintain NO bioavailability through an increasing eNOS expression and preventing NO degradation by ROS. Furthermore, HDMPPA treatment in apoE KO mice inhibited eNOS uncoupling through an increase in vascular tetrahydrobiopterin content and a decrease in serum asymmetric dimethylarginine levels. Moreover, HDMPPA ameliorates inflammatory-related protein expression in the aorta of apoE KO mice. Therefore, the present study suggests that HDMPPA, the active compound of kimchi, a Korean functional food, may exert its vascular protective effect through the preservation of NO bioavailability and suppression of the inflammatory response.

Key words: 3⁰-(4⁰-Hydroxyl-3⁰,5⁰-dimethoxyphenyl)propionic acid: ApoE knockout mice: Nitric oxide: Endothelial nitric oxide synthase: Inflammation

The progress of atherosclerosis is implicated with the loss of NO bioavailability and increased reactive oxygen species (ROS). In vascular tissue, NO is derived from L-arginine oxidation by endothelial NO synthase (eNOS), and has a central role in cyclic GMP-mediated vasorelaxation. It has been suggested that NO possesses multiple anti-atherosclerotic properties, which include anti-platelet, anti-proliferative and anti-inflammatory effects(1,2). In atherosclerotic lesions, oxidative stress could be augmented by eNOS uncoupling, which generates superoxide rather than NO. This dysfunction of eNOS activity is caused by an oxidative loss of cofactor, tetrahydrobiopterin (BH₄), and an increased production of inhibitor, asymmetric dimethylarginine (ADMA)(3–5). Because NO has been demonstrated as a critical effector molecule in the maintenance of vascular function(6), it is therefore important to maintain NO bioavailability through prevention of eNOS uncoupling during vascular disease.

Vascular inflammation has been suggested to be an important risk factor in the initiation and development of atherosclerosis(7). Inflammatory response in the endothelium promotes leucocyte adhesion and increases vascular permeability via up-regulation of surface cell adhesion molecules and the release of inflammatory cytokines. Endothelial adhesion molecules such as vascular cellular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are indicative of inflammatory processes. It has been shown that the signal transduction pathways for the expression of adhesion molecules include the activation and translocation of the redox-sensitive transcriptional factor NF-κB(8). Additionally, increased ROS and cytokines have

Abbreviations: AD, atherogenic diet; ADMA, asymmetric dimethylarginine; BH₄, tetrahydrobiopterin; COX-2, cyclo-oxygenase-2; eNOS, endothelial nitric oxide synthase; HDMPAA, 3⁰-(4⁰-hydroxyl-3⁰,5⁰-dimethoxyphenyl)propionic acid; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; KO, knockout; ROS, reactive oxygen species; VCAM-1, vascular cellular adhesion molecule-1.

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been implicated as key mediators of cell signalling pathways that activate and translocate NF-κB to the nucleus, which in turn up-regulates inflammatory gene expression and aggravates further inflammatory response.

Kimchi, a traditional type of Korean fermented vegetable food, was named in the list of top five ‘World Health Foods’ for being abundant in dietary fibre, vitamin C, lactic acid bacteria, minerals and other compounds beneficial to health (15). Several scientific trials to identify the potential health benefits of kimchi have been carried out. In our previous studies, plasma cholesterol-lowering effects of kimchi were demonstrated in human subjects (10–12) and animals (13–15), as well as an anti-atherogenic effect having been demonstrated in rabbits (16). From Korean cabbage kimchi, 3′,4′-dimethoxyphenyl-3′,5′-dimethoxyphenyl) propionic acid (HDMPPA) with a molecular weight of 226 was isolated and identified as an active principle responsible for inhibiting LDL oxidation and 2,2-diphenyl-1-picrylhydrazyl scavenging activity (17). The amount of HDMPPA is approximately 1 mg/100 g kimchi (15). Next, we chemically synthesised HDMPPA which was biologically identical to the HDMPPA isolated from Korean cabbage kimchi (17). The synthesised HDMPPA showed health benefits on atherosclerosis in rabbits (16). Furthermore, HDMPPA retarded atherosclerotic lesions and ameliorated oxidative stress through inhibiting NADPH oxidase activity in the aorta of apoE knockout (KO) mice (18). However, the effect of HDMPPA on NO metabolism and inflammatory response in the aorta of the atherosclerotic animal model was not determined. In the present study, we investigated the protective effect of HDMPPA on experimental atherosclerosis through the preservation of NO bioavailability and inhibition of the inflammatory response.

Materials and methods

Materials and reagents

Chemically synthesised HDMPPA that is biologically identical to the component isolated from cabbage kimchi was used (17). Chemical synthesis was carried out at the Department of Chemistry, Pusan National University, Busan, Republic of Korea. Commercially available kits for plasma TAG and cholesterol analysis were used. The primary antibodies cyclooxygenase-2 (COX-2) (sc-19999), inducible NO synthase (iNOS) (sc-7271), eNOS (sc-654), VCAM-1 (sc-1504), ICAM-1 (sc-1511), Iκ-Bα (sc-371), NF-κB p65 (sc-109), β-actin (sc-47778) and the secondary antibodies of anti-mouse (sc-2005), anti-rabbit (sc-2004) and anti-goat (sc-2020) were purchased from Santa Cruz Biotechnology. Enzymes and other chemicals were purchased from Sigma.

Animals and diets

For the present study, 6-week-old male apoE KO mice were purchased from Central Lab Animal, Inc. and were randomly divided into two dietary groups: atherogenic diet (AD) only (control, n = 15) or AD with HDMPPA treatment (HDMPPA, 10 mg/kg of body weight, n = 15). Each mouse was housed in a room with controlled temperature and lighting and fed an AD for 8 weeks. The AD for apoE KO mice was prepared based on the American Institute of Nutrition (AIN)-76 diet by adding 1% cholesterol and 10% lard to induce atherosclerosis (19). The diet compositions were as follows (w/w): casein, 20%; sucrose, 44%; maize starch, 15%; cellulose, 5%; lard, 10%; AIN-76 mineral mixture, 3.5%; AIN-76 vitamin mixture, 1%; DL-methionine, 0.3%; choline bitartrate, 0.2%; and cholesterol, 1%. HDMPPA dissolved in PBS or PBS (as vehicle) was administered every other day by intraperitoneal injection. The dosage for HDMPPA injected into the mice (10 mg/kg of body weight per d) was calculated based on results from a previous study that demonstrated anti-atherogenic effects of HDMPPA (0.5–5 mg/kg of body weight per d) in rabbits when it was administered via intravenous injection (16). PBS (vehicle) was injected into the control animals. Mice had free access to food and water. After an 8-week experimental period, the mice were anaesthetised with diethyl ether after 12 h of fasting. Blood samples were drawn from the inferior vena cava, and plasma was collected immediately after centrifuging (800 g for 10 min). The heart and descending aorta were removed. Of the fifteen aortas, five of them were used for the measurement of ROS and NO, another five for aortic BH4 determination and the remainder for the protein expression study. All samples were stored at −70 ºC until further analysis. The animal protocol used in this study was reviewed by the Pusan National University Institutional Animal Care and Use Committee on their procedures and scientific care, and the present study was approved (approval no. PNU-2007-00031).

Nitric oxide concentration of the aorta

The production of NO in the aorta was measured using cell-permeable diaminofluorescein-2 diacetate (Calbiochem). The aorta was homogenised on ice with 1 mM-EDTA–50 mM-sodium phosphate buffer (pH 7.4), and then 12.5 µM-diaminofluorescein-2 diacetate were added to the homogenate. During the reaction time for 30 min, changes in fluorescence were determined at an excitation wavelength of 485 nm and emission wavelength of 535 nm (20).

Level of total reactive oxygen species

Total ROS concentration was measured by the method of Ali et al. (21). In brief, the aorta was homogenised on ice with 1 mM-EDTA–50 mM-sodium phosphate buffer (pH 7.4), and then 25 mM-2′,7′-dichlorofluorescein-diacetate were added to the homogenate, and changes in fluorescence for 30 min were determined at an excitation wavelength of 486 nm and emission wavelength of 530 nm.

Western blotting analysis

Aortic tissues were homogenised with ice-cold lysis buffer containing 5 mM-Tris–HCl (pH 7.5), 2 mM-MgCl2, 15 mM-CaCl2 and 150 mM-sucrose, and then 0.1 mM-dithiothreitol and pro tease inhibitor cocktail were added. After centrifugation (10,500 g for 20 min at 4 ºC), the supernatant was used as
Beneficial effects of kimchi on aorta of mice

Detection of asymmetric dimethylarginine in plasma

The proteins in the conditioned medium were removed using 5-sulfosalicylic acid. The levels of ADMA were measured by HPLC with some modifications (25). O-Phthalaldehydadducts of methylated amino acids and internal standard ADMA were monitored using fluorescence detector which was set the excitation wavelengths of 360 nm and emission of 440 nm on a Gemini C18 column (Agilent 1100 Series, Agilent Technologies). Samples were eluted from the column using a linear gradient containing mobile phase A composed of 0·05 m (pH 6·8) sodium acetate–methanol–tetrahydrofuran (81:18:1, by vol.) and mobile phase B composed of 0·05 m sodium acetate–methanol–tetrahydrofuran (22:77:1, by vol.) at a flow-rate of 1 ml/min.

Statistical analysis

All data are presented as means with their standard errors. Student’s t test was performed to determine statistical significance, with \( P<0·05 \) considered statistically significant.

Results

3’-(4’-Hydroxyl-3’,5’-dimethoxyphenyl)propiionic acid prevented the altered nitric oxide bioavailability through inhibition of endothelial nitric oxide synthase uncoupling in the aorta

The induction of eNOS uncoupling generates superoxide rather than NO, consequently enhancing oxidative stress in the atherosclerotic aorta. First, to evaluate the effect of HDMPPA on oxidative stress in the aortas of apoE KO mice, ROS was determined using a fluoro-spectrophotometer (Fig. 1(a)). ROS production was significantly decreased in the aorta treated with HDMPPA (788·7 fluorescence/min per mg protein), compared with control (980·1 fluorescence/min per mg protein). Next, NO concentration in the aorta of apoE KO mice was significantly augmented by HDMPPA treatment (\( P<0·05, \) Fig. 1(b)). Finally, HDMPPA treatment elevated the protein level of eNOS in the aorta of apoE KO mice (Fig. 1(c)).

Detection of tetrahydrobiopterin and total biopterin in the aorta

Freshly isolated whole aortas were homogenised in extraction buffer containing 50 mm-Tris (pH 7·4), 1 mm-dithiotheritol and 1 mm-EDTA at 4°C, and were centrifuged at 12 000 rpm for 15 min at 4°C (22). One whole aorta is needed for n 1 experiment. Samples were oxidised under either acidic conditions (with 0·2 m-HCl containing 50 mm-L-I2) or alkaline conditions (with 0·2 m-NaOH containing 50 mm-L-I2). Biopterin content was assessed using HPLC (Agilent 110 Series, Agilent Technologies). Samples were eluted from the column using a linear gradient containing mobile phase A composed of 0·05 m (pH 6·8) sodium acetate–methanol–tetrahydrofuran (81:18:1, by vol.) and mobile phase B composed of 0·05 m sodium acetate–methanol–tetrahydrofuran (22:77:1, by vol.) at a flow-rate of 1 ml/min.

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(P<0.05, Fig. 1(c)). These results indicate that HDMPPA inhibited eNOS uncoupling through an increase in NO production and a reduction of ROS in the aorta.

3′-(4′-Hydroxyl-3′,5′-dimethoxyphenyl)propionic acid increased endothelial nitric oxide synthase activity through increased cofactor and decreased inhibitor

To see how HDMPPA works on BH4 stabilisation, we measured the biotin content in the aorta of apoE KO mice (Fig. 2(a)). HDMPPA increased BH4 contents in the aorta of apoE-deficient mice by 25.9%, compared to that of the control group (P<0.05) while, as shown in Fig. 2(b), the plasma level of ADMA in the HDMPPA group was significantly decreased (1.04 v. 1.36 μM, P<0.05), compared to that of control mice.

3′-(4′-Hydroxyl-3′,5′-dimethoxyphenyl)propionic acid decreased the adhesion molecules in the aorta

To investigate the anti-inflammatory effect of HDMPPA in the aorta of apoE KO mice, we examined the effect of HDMPPA on protein expression of VCAM-1 and ICAM-1 in the aorta by Western blotting. As shown in Fig. 3, protein levels of VCAM-1 and ICAM-1 in the aorta of the HDMPPA group was significantly reduced compared to the control group (P<0.05).

3′-(4′-Hydroxyl-3′,5′-dimethoxyphenyl)propionic acid reduced the pro-inflammatory enzymes in the aorta

The inhibitory effect of HDMPPA on inflammatory response was examined in terms of determining the protein expressions of COX-2 and iNOS by Western blotting. A marked decrease in COX-2 protein expression was observed in the aorta of apoE KO mice treated with HDMPPA (P<0.01, Fig. 4). Also, the HDMPPA-treated group showed lower protein level of iNOS than the control group in the aorta of apoE KO mice (P<0.05, Fig. 4).

Fig. 3. Effect of 3′-(4′-hydroxyl-3′,5′-dimethoxyphenyl)propionic acid (HDMPPA) on protein expression of adhesion molecules in the aorta of apoE knockout (KO) mice. Control (\(\bullet\)), PBS (vehicle)-treated apoE KO mice; HDMPPA (■), HDMPPA 10 mg/kg of body weight-treated apoE KO mice. Values are means, with their standard errors represented by vertical bars (n=5). * Mean values were significantly different from those of the control group: *P<0.05, **P<0.01.

Fig. 4. Effect of 3′-(4′-hydroxyl-3′,5′-dimethoxyphenyl)propionic acid (HDMPPA) on protein expression of inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) in the aorta of apoE knockout (KO) mice. Control (การ), PBS (vehicle)-treated apoE KO mice; HDMPPA (■), HDMPPA 10 mg/kg of body weight-treated apoE KO mice. Values are means, with their standard errors represented by vertical bars (n=5). Mean values were significantly different from those of the control group: *P<0.05, **P<0.01.

Discussion

The alterations of NO pathway, such as increased NO decomposition by the superoxide anion (formation of peroxynitrite) or altered NO-generating enzyme (mostly eNOS) expression, play a central role in endothelial dysfunction induced by hypercholesterolaemia(23). Under physiological conditions, endothelial stimulation induces the production and release of NO, which diffuses to surrounding tissue and cells and exerts its cardiovascular protective effect by relaxing media-smooth muscle cells, preventing leukocyte adhesion and migration into the arterial wall, muscle cell proliferation, platelet adhesion and aggregation, and adhesion molecule expression(24). Several reports have determined that eNOS deficiency accelerates plaque formation, confirming the important role of endothelial NO production for atheroprotection(25,26). Therefore, preventing NO breakdown by ROS and/or decreased production by eNOS could be a therapeutic target against the process of vascular disease. Moreover, several studies have shown that some agents used to increase NO production and/or to inhibit the loss of NO bioavailability were helpful to retard the process of vascular disease(27). In this study, HDMPPA treatment significantly augmented NO concentration in the aorta of apoE KO mice, accompanied by a reduction of ROS levels. In our previous study, we demonstrated that HDMPPA effectively reduced vascular ROS level through inhibiting NADPH oxidase activity in apoE KO mice(18). Furthermore, the protein expression of eNOS was up-regulated in the aorta of the HDMPPA-treated group. These results suggested that HDMPPA could prevent the loss of NO bioavailability via reduction of ROS level and up-regulation of eNOS.

Another important factor related to the preservation of NO bioactivity is the prevention of eNOS uncoupling, which generates superoxide rather than NO. BH₄ is an essential cofactor required for the activity of eNOS. Recent research demonstrated...
that eNOS activity (to generate NO) can be modestly augmented by increasing BH$_4$ levels even under the normal physiological conditions (28). BH$_4$ deficiency is believed to lead to eNOS uncoupling, resulting in impaired endothelium-dependent vasodilation and the production of superoxide radicals from the uncoupled enzymatic form. Additionally, an increased oxidation of BH$_4$ is often considered as a mechanism explaining BH$_4$ deficiency in several vascular conditions (29). Laursen et al. (30) demonstrated that peroxynitrite was the principal ROS which oxidises BH$_4$. In this study, HDMPPA showed scavenging activity of peroxynitrite in vitro (data not shown) and inhibited ROS generation in the aorta, suggesting that HDMPPA might further prevent the formation of peroxynitrite. Moreover, the HDMPPA-treated group showed higher BH$_4$ concentration than that of the control group, suggesting that HDMPPA could prevent the oxidation of BH$_4$. Therefore, HDMPPA elevated protein expression of eNOS, at least in part, through increased BH$_4$ levels.

In addition, eNOS activity is determined by an endogenous inhibitor, ADMA, which inhibits cellular l-arginine uptake by endothelial cells, leading to the reduction of NO generation from l-arginine. It is postulated that altered NO bioavailability may result from an increase in ADMA, which may be a critical factor for vascular disease (31–35). Circulating ADMA levels have been assessed in a variety of systemic CVD, and are increased in conditions associated with hypercholesterolaemia, atherosclerosis, hypertension, chronic renal failure and chronic heart failure (34). Animal studies using the rabbit, rat and mouse have shown that the concentration of ADMA in the plasma was increased under a variety of hypercholesterolaemic conditions (35–37). Administration of exogenous ADMA for 4 weeks aggravated atherosclerotic lesions both in apoE KO mice and in C57BL/6J mice (38). Other studies have documented that lysophosphatidylcholine or oxidised-LDL elevated the production of ADMA while certain antioxidants such as vitamin E, probucol and xanthines markedly prevented the elevation of ADMA in the plasma (39,40). Therefore, plasma ADMA may be involved in the progression of atherosclerosis, and therefore, the reduction of ADMA beneficiably influences the process of vascular disease. In the present study, HDMPPA significantly decreased plasma ADMA levels in apoE KO mice. These data suggest that HDMPPA improves reduced NO bioactivity and eNOS expression in the aorta of atherosclerotic mice via decreased plasma ADMA.

Atherosclerosis is a chronic inflammatory process which is involved and interacted with various factors such as immunomodulatory compounds, immune cells and blood lipid profile (41). Elevated LDL oxidation by ROS as well as a loss of vascular protective effect of NO are strongly associated with the inflammatory process of atherosclerosis (42). As an initial event in the pathogenesis of atherosclerosis, expression of adhesion molecules, especially both of ICAM-1 and VCAM-1, plays a central role in the recruitment of circulating monocytes and invasion into the intima. Up-regulation of VCAM-1 and ICAM-1 at the endothelial cell surface initiates pathological leukocyte–endothelial cell interaction, which ultimately exposes the vascular wall and surrounding tissues to the damaging action of activated leukocytes and causes the subsequent development of endothelial dysfunction/atherosclerosis (43). The elevated expression of iNOS has been observed in atherosclerotic lesions where high amounts of NO are produced and combine with superoxide, which might enhance the progression of atherosclerosis (44,45). COX-2 induces the pathogenesis of inflammatory disorders in response to the production of a variety of inflammatory cytokines, many of which are known to be produced during the progression of atherosclerosis (46). The expression of COX-2, cyclo-oxygenase-2; iNOS, inducible NO synthase. (A colour version of this figure can be found online at www.journals.cambridge.org/bjn)
NF-κB has been implicated as a key mediator of inflammatory response in atherosclerosis\(^{(51)}\). This transcription factor is a DNA binding protein complex that is usually present in the cytosol in an inactive complex. IkB, an associated protein, renders this complex inactive by shielding the nuclear localization signal. Upon IkB phosphorylation and its subsequent degradation, the heterodimeric NF-κB complex translocates from the cytosol to the nucleus, where it binds to specific DNA sequences in the promoter region of several genes and up-regulates their transcription. Most inflammatory genes expressed in endothelial cells during the initial phase of lesion formation and in response to inflammatory mediators are dependent on NF-κB activation\(^{(32)}\). Genes encoding a variety of inflammatory effectors including cytokines, chemokines, growth factors, leukocyte adhesion molecules and inducible enzymes such as iNOS are NF-κB responsive\(^{(53–55)}\). From the results of another report, H\(_2\)O\(_2\) or oxygen radicals produced during the inflammatory processes act as a second messenger to activate NF-κB directly or indirectly\(^{(56)}\). However, numerous studies suggest that ROS inhibitors such as flavonoids, α-tocopherol, ascorbate, troglitazone, aspirin, gallate, etc. decrease NF-κB activation induced by IL-1 or TNF-α and suppress the activation of adhesion molecules and chemoattractant which are indispensable molecules for atherogenesis\(^{(57–61)}\). The present data showed that aortic protein expression of IkB-α was increased but that of NF-κB p65 was reduced in the HDMPPA-treated group, compared with the control group. Although we did not examine the nuclear activation of NF-κB, our experimental results could demonstrate that HDMPPA regulate inflammatory response by the inhibition of NF-κB expression, which results may be due to the antioxidant activity of HDMPPA.

Several studies to identify the potential health benefits of kimchi have demonstrated that kimchi exerts its lipid-lowering activity as in experimental animal\(^{(10,13–15)}\) and human studies\(^{(11,12)}\), and that its active compound, HDMPPA, showed anti-atherosclerotic effect by decreasing the aortic intima thickness and fatty streak size of aortic sinus in hypercholesterolemic rabbits\(^{(16)}\) and mice\(^{(20)}\), respectively. On the basis of average kimchi consumption (150 g/d) by Korean adults, the physiological amount of HDMPPA is about 1.5 mg/d. Unfortunately, the dose of HDMPPA used in this study is not physiologically relevant to human consumption levels. However, the pharmacological dose of HDMPPA (for example, pill-format) may be more beneficial for therapeutic applications in human atherosclerosis. In Fig. 6, the anti-atherosclerotic effect of HDMPPA in the aorta of apoE KO mice was depicted. HDMPPA increased NO content in the aorta, while reducing ROS concentration. Furthermore, in the HDMPPA-treated group, aortic eNOS expression was up-regulated compared with the control group. These results suggest that HDMPPA could maintain NO bioavailability through increasing eNOS expression and preventing NO degradation by ROS. HDMPPA treatment in apoE KO mice inhibited eNOS uncoupling through an increase in vascular BH\(_4\) content and a decrease in serum ADMA levels. Moreover, HDMPPA ameliorated inflammatory response in the aorta of apoE KO mice probably through inhibiting NF-κB expression. Therefore, the present study suggests that HDMPPA, the active compound of kimchi, a Korean functional food, may exert its vascular protective potential through the preservation of NO bioavailability and suppression of the inflammatory response.

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