Anti-inflammatory effects of schisandrin isolated from the fruit of Schisandra chinensis Baill

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A B S T R A C T

Schisandrin is the main active ingredient isolated from the fruit of Schisandra chinensis Baill. Recent studies have demonstrated that schisandrin exhibits anti-oxidative effects in vivo. In the present study, the effect of schisandrin on plasma nitrite concentration in lipopolysaccharide (LPS)-treated mice was evaluated. It also significantly inhibited carrageenan-induced paw edema and acute acid-induced vascular permeability in mice. Furthermore, schisandrin had a protective effect on lipopolysaccharide (LPS)-induced sepsis. In vitro, our results are the first that show that the anti-inflammatory properties of schisandrin result from the inhibition of nitric oxide (NO) production, prostaglandin E2 (PGE2) release, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, which in turn results from the inhibition of nuclear factor-kappaB (NF-κB), c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) activities in a RAW 264.7 macrophage cell line.

1. Introduction

Inflammation, classified either as acute or chronic, has been described as the basis of many human diseases. Acute inflammation occurs from minutes to hours and days following tissue damage caused by physical force or an immune response. Chronic inflammation occurs over longer time, and is characterized by the infiltration of mononuclear immune cells (monocytes, macrophages, lymphocytes, and plasma cells), tissue destruction, and attempts at healing, which include angiogenesis and fibrosis, such as the diseases of pulmonary emphysema, chronic cor pulmonale and rheumatoid arthritis.

There are many inflammatory mediators that participate in the regulation of inflammatory response. They include vascular amines, metabolites of arachidonic acid (prostaglandin, leukotriene and lipoxin), cytokines (interleukin-1β, interleukin-6β and tumor necrosis factor-α), platelet activating factor, neuropeptides and nitric oxide, all of which are released from cells. Also, generating inflammatory mediators are complementary systems including the kinin system, the clotting system and the fibrinolytic system (Wei et al., 2004).

In these mediators, nitric oxide (NO) is generated enzymatically by synthases (NOS) and is formed by inducible NOS (iNOS) in macrophages and in other cells that plays a role in the inflammatory response. Large amounts of NO can stimulate many proteins and enzymes crucial to inflammatory reactions, such as the NF-κB and MAPKs pathways (Nijkamp and Parnham, 2005). Many studies have reported that MAPKs mediate the activation of transcriptional factor NF-κB (DeFranco et al., 1995; Aga et al., 2004) and, subsequently, regulate COX-2 expression (Mestre et al., 2001) as well as iNOS–NO expression (Chan and Riches, 2001). Furthermore, iNOS expression and NO production, both stimulated by LPS, have been proved to contribute to septic shock (Jacobs et al., 2001). Prostaglandin E2, one of the prostaglandins, is produced by the cyclooxygenase pathway. Prostaglandins regulate vascular permeability, platelet aggregation and thrombus formation in the development of inflammation. Inhibition of COX-2 activity can reduce the deleterious consequences of sepsis (Knoferl et al., 2001). All of these cytokines can be the targets in the treatment of inflammatory diseases, and a proper understanding of the inflammatory basis is helpful to atherosclerosis, cancer, ischemic heart disease, and other maladies.
Schisandrin is one of the lignan components of *Schisandra chinensis* Baill, which is clinically prescribed to treat hepatitis. Schisandraceae Fructus has been reported to protect against CCl₄-induced hepatic damage (Ko et al., 1995). Its components can induce liver cytochrome P-450 and promote certain anabolic metabolisms such as serum protein biosynthesis and repairing injured liver cells (Liu, 1989), and they are thought to be mediated through anti-inflammatory activity. However, the mechanism of this compound has as yet gone unreported. In the present paper, we focused mainly on the anti-inflammatory activities of schisandrin in the acute and sepsis animal models as well as on the cytokines in macrophages.

2. Materials and methods

2.1. Materials

Schisandrin (purity >96.0%) was isolated according to a previous report (Peng et al., 2005). The chemical structure of schisandrin is shown in Fig. 1. RAW 264.7 cells, murine macrophages, were obtained from the American Type Culture Collection (Rockville, MD, U.S.A.). Dulbecco’s modified Eagle’s medium (DMEM), Dulbecco’s phosphate buffer saline (D-PBS), N-tosyl-l-phenylalanyl-chloromethyl ketone (TPCK), lipopolysaccharide (*E. coli*, serotype O127:B8; LPS), λ-carrageen, acetic acid, 4-methylumbelliferone phosphate (4-MUP), and dimethyl sulfoxide were acquired from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Genetin (antibiotic G-418) was purchased from Gibco BRL (Grand Island, NY, U.S.A.). A Cell-Counting Kit-8 (CCK-8) was purchased from Dojindo Laboratories (Tokyo, Japan). Other chemicals and solvents were obtained from Aldrich Chemical Co. (Milwaukee, WI, U.S.A.). All of the samples, solutions and buffers were prepared from deionized water.

Primary antibodies for COX-2, iNOS, h-80, pb-80, pp38, p38, pJNK, JNK and secondary antibodies were acquired from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Nitrocellulose membrane (NC membrane) was obtained from Whatman GmbH (Germany). An enhanced chemiluminescence (ECL) detection kit was purchased from LabFrontier (Seoul, Korea).

ICR mice (male, 4 weeks of age) were supplied from Samtaco (Osan, Korea). The animals were fed with a standard laboratory diet and water *ad libitum* for one week (12 h light/dark cycle; temperature, 22 ± 2 °C). The study as conducted was approved by the Animal Ethics Committee of Seoul National University, the guidelines of which are in accordance with the *Guide for the Care and Use of Laboratory Animals* as adopted and promulgated by the National Institutes of Health.

2.2. Cell culture and cell viability assay

The macrophage RAW264.7 cell line was incubated in Dulbecco’s modified Eagle’s medium (DMEM) at 37 °C under 5% CO₂ humidified air. The cells were seeded into 96-well plates at the density of 1 × 10⁴ cells/well and allowed to adhere for 24 h, also at 37 °C under 5% CO₂. After 24 h treatment with schisandrin (10, 50 and 100 µM), 10 µl of the CCK-8 solution was added to each well, followed by incubation for 2 h at 37 °C. The resulting color was assayed at 450 nm using an Emax microplate reader (Molecular Devices, Sunnyvale, CA, U.S.A.).

2.3. Nitrite assay

The cells (1 × 10⁵ cells/well) were pretreated with schisandrin (10, 50 and 100 µM) for 2 h and then incubated for 24 h with LPS (1 µg/ml). After incubation, the nitrite concentrations of supernatants (100 µl/well) were measured by adding 100 µl of Griess reagent (1% sulfanilamide in 5% phosphoric acid and 0.1% naphthylethyleneediamine dihydrochloride in water). The optical density at 540 nm was measured using an Emax microplate reader (Molecular Devices, Sunnyvale, CA, U.S.A.). The nitrite concentration was calculated by comparison with the absorbance at 540 nm of standard solutions of sodium nitrite prepared in culture medium.

2.4. PGE₂ enzyme-linked immunosorbent assay (ELISA)

PGE₂ levels were analysed by using the prostaglandin E₂ Biotrak ELISA system (Amersham Biosciences, Piscataway, NJ) according to the manufacturer’s instructions. RAW264.7 cells (1 × 10⁵ cells/well) were pretreated with schisandrin (25, 50 and 100 µM) for 2 h and then incubated with LPS (1 µg/ml) for 24 h. PGE₂ concentrations of supernatants were measured with a PGE₂ ELISA assay kit (Alexis, USA).

2.5. Western blot analysis

The cells (1 × 10⁶ cells/well) were pretreated with schisandrin (12.5, 25, 50 and 100 µM) for 2 h and then incubated with LPS (1 µg/ml) for 5 min (pb-80), 20 min (h-80), 30 min (pp38, p38, pJNK, JNK) and 18 h (iNOS, COX-2). After incubation, total cytoplasmic extracts were lysed as described previously (Zhou et al., 2007). Then, an SDS-PAGE was performed, and proteins were transferred onto NC membranes. After being blocked by 5% skim milk, the membrane was incubated with primary and secondary antibodies in turn. Finally, the blot was developed for visualization using the ECL Plus detection kit. The intensity of each band was quantitatively determined using UN-SCAN-IT™ software (Silk Scientific, UT, USA), and the density ratio showed the relative intensity of each band against those of the controls in each experiment.

2.6. Reverse transcriptase polymerase chain reaction (RT-PCR)

RAW264.7 cells were pretreated with schisandrin (12.5, 25, 50 and 100 µM) for 2 h, and then incubated with LPS (1 µg/ml) for 4 h. Briefly, total RNA was extracted using the Easy-BLUE™ Total RNA Extraction Kit (Intron Biotechnology, Korea). The RT-PCR was performed using the ONE-STEP RT-PCR PreMix kit™ (Intron Biotechnology, Korea). The primers (iNOS, COX-2 and β-actin) were the same as described previously (Zhou et al., 2007). The products of the RT-PCR were separated by electrophoresis using 1.5% agarose gel stained with ethidium bromide, and the gels were viewed under UV transillumination.

2.7. Reporter gene assay

The reporter enzyme activity was measured using a cell-based assay system for monitoring NF-κB activity. Transfected RAW264.7 cells (1.5 × 10⁵ cells/well) were pretreated with the compounds for 2 h, and then treated with LPS (1 µg/ml) alone or with LPS plus each indicated compound for 18 h. The fluorescence from the product of the SEAP/MUP (secretory alkaline phosphates/methylumbelliferyl phosphate) reaction, according to the excitation at 360 nm and the
emission at 449 nm, was measured using a 96-well plate Gemini XS fluorometer (Molecular Devices, Sunnyvale, CA, USA) (Moon et al., 2001).

2.8. Plasma nitrite concentration

The plasma nitrite concentration was measured using a fluorometric method (Gilliam et al., 1993). Twenty-five mice were randomly divided into 5 groups. Thirty minutes after intraperitoneal injection of the vehicle (olive oil), dexamethasone (50 mg/kg) and schisandrin (100, 200 mg/kg), LPS (10 mg/kg) was injected. Four hours later, blood was collected from the eye sockets of the mice. To obtain plasma, the blood was centrifuged (574 ×g for 10 min); then, the plasma was removed and filtered through a 10,000 Mr filter (10,770 ×g for 20 min) to remove the hemoglobin. The filtrate was stored in a refrigerator (−80 °C) before being used. Samples (100 μl) were 1:20 diluted and incubated with 10 μl of nitrate reductase (1.38 U/ml) and 10 μl of b-nicotinamide adenine dinucleotide 2′-phosphate-reduced tetradsodium salt (NADPH; 0.833 mg/ml) for 1 h at room temperature, and then added 10 μl/well of 2,3-diaminonaphthalene (DAN) in the dark room. After incubation for 10 min at room temperature, the reaction was stopped with 5 μl of 2.8 N NaOH. The nitrite concentration was measured on a fluorescence plate reader with excitation at 365 nm and emission at 450 nm. The nitrite concentration was calculated using a nitrate standard curve.

2.9. Acetic acid-induced vascular permeability in mice

Twenty mice were randomly divided into 4 groups. Thirty minutes after intraperitoneal injection of the vehicle (olive oil), dexamethasone (50 mg/kg) and schisandrin (100, 200 mg/kg), 1% Evans blue solution (0.1 ml/10 g) was injected. One hour later, the mice were treated with 0.6% acetic acid in saline by intraperitoneal injection. Fifty minutes later, the mice were sacrificed by cervical dislocation. The peritoneal cavity was washed with saline (8 ml). The wash solution was collected, and mixed with 1 N NaOH to a ratio of 0.1 ml/10 ml. The absorbance of Evans blue was measured using a UV/VIS spectrophotometer at 610 nm (Whittle, 1964).

Fig. 2. Effect of schisandrin on NO production in macrophages (A) and plasma nitrite in LPS-treated mice (B). Effect of schisandrin on iNOS protein expression (C). In parallel experiments, the mRNA expression of iNOS (D) was measured by RT-PCR analysis. A: Cells were pretreated with schisandrin (10, 50 and 100 μM) for 2 h and then incubated for 24 h with LPS (1 μg/ml). B: Twenty-five mice were randomly divided into 5 groups. Thirty minutes after intraperitoneal injection of the vehicle (olive oil), dexamethasone (50 mg/kg) and schisandrin (100, 200 mg/kg), LPS (10 mg/kg) was injected. Four hours later, blood was collected from the eye sockets of the mice. C, D: Cells were pretreated with schisandrin (12.5, 25, 50 and 100 μM) for 2 h and then incubated with LPS (1 μg/ml) for 18 h.
2.10. Carrageenan-induced paw edema in mice

Thirty-six mice were randomly divided into 4 groups. Thirty minutes after schisandrin (100, 200 mg/kg) was administered, the mice were treated with 0.05 ml of \(\lambda\)-carrageenan (1%) by intraperitoneal injection into the right hind paw. The control group received the vehicle (olive oil), and the positive control group received dexamethasone (50 mg/kg). After the \(\lambda\)-carrageenan injection, the paw volumes were measured at 1, 2, 3, 4 and 5 h by dial thickness gage (Mitutoyo, Japan).

2.11. Endotoxin-induced shock model in mice

Forty-five mice were randomly divided into 4 groups. LPS (80 mg/kg) was administered by intraperitoneal injection 1 h after schisandrin (100, 200 mg/kg) injection. The control group was treated with the vehicle (olive oil), and the positive control group received dexamethasone (50 mg/kg). The number of surviving mice was observed for 72 h.

Fig. 3. Effect of schisandrin on PGE_2 production (A) COX-2 protein expression (B). In parallel experiments, the mRNA expression of COX-2 (C) was measured by RT-PCR analysis. A: Cells were pretreated with schisandrin (25, 50 and 100 \(\mu\)M) for 2 h and then incubated for 24 h with LPS (1 \(\mu\)g/ml). B, C: Cells were pretreated with schisandrin (12.5, 25, 50 and 100 \(\mu\)M) for 2 h and then incubated with LPS (1 \(\mu\)g/ml) for 18 h.

Fig. 4. Effect of schisandrin on NF-\(\kappa\)B activity. Macrophages were treated with schisandrin for 2 h before LPS stimulation for 18 h.

Fig. 5. Effect of schisandrin on I\(\kappa\)B\(\alpha\) protein expression. Macrophages were treated with schisandrin for 2 h before LPS stimulation for 18 h.
2.12. Statistical analysis

The results were expressed as means±S.E.M. Differences in mean values between groups were analyzed by a one-way analysis of variance (ANOVA) and Student’s t-test. For the septic shock assay, we used the log-rank test. Statistical significance was assessed as \( p < 0.05 \) \( \ast \), \( p < 0.01 \) \( \ast \ast \), \( p < 0.001 \) \( \ast \ast \ast \).

3. Results

3.1. Inhibition of NO production, iNOS protein and mRNA expression in LPS-stimulated RAW 264.7 macrophages and inhibition of plasma nitrite concentration in LPS-treated mice

Pretreatment of RAW 264.7 cells with schisandrin inhibited LPS-stimulated NO production in a dose-dependent manner (Fig. 2A). This inhibitory effect was achieved with nontoxic concentrations of schisandrin. The effect of schisandrin on iNOS protein expression in the macrophages was detected by western blotting. As shown in Fig. 2C, the iNOS protein expression was markedly decreased in a dose-dependent manner. To determine if the expression of iNOS protein was decreased at the mRNA level, we analyzed the iNOS mRNA expression by RT-PCR. We observed that 100 \( \mu \)M of schisandrin inhibited the LPS-stimulated mRNA expression of iNOS (Fig. 2D). In an in vivo study, we detected the inhibitory effects of schisandrin on plasma nitrite levels. Time-course experiments showed that after treatment with LPS for 4 h, the level of nitrite in the plasma of the mice was significantly increased (data not shown). Then, we compared the dexamethasone group and the schisandrin group after LPS treatment for 4 h. The levels of nitrite in the plasma from the dexamethasone and schisandrin groups were significantly lower than that in the plasma of the LPS group (Fig. 2B).

3.2. Inhibition of prostaglandin E2 production, COX-2 protein and mRNA expression in LPS-stimulated RAW 264.7 macrophages

We studied the effect of schisandrin on PGE2 release, the expression of COX-2 protein and mRNA expression by LPS-stimulated macrophages. Our results suggest that schisandrin significantly inhibits PGE2 release (Fig. 3A) and COX-2 protein expression (Fig. 3B) in a dose-dependent manner. Furthermore, LPS-induced COX-2 mRNA expression was inhibited by 50 \( \mu \)M of schisandrin (Fig. 3C).

We studied the effect of schisandrin on carrageenan-induced vascular permeability in mice. Twenty mice were randomly divided into 4 groups. Thirty minutes after intraperitoneal injection of the vehicle (olive oil), dexamethasone (50 mg/kg) and schisandrin (100, 200 mg/kg), 1% Evans blue solution (0.1 ml/10 g) was injected. One hour later, the mice were treated with 0.6% acetic acid in saline by intraperitoneal injection. Fifty minutes later, the mice were sacrificed by cervical dislocation. The peritoneal cavity was washed with saline (8 ml). The wash solution was collected and measured.

Fig. 7. Effect of schisandrin on acetic acid-induced vascular permeability in mice. Twenty mice were randomly divided into 4 groups. Thirty minutes after intraperitoneal injection of the vehicle (olive oil), dexamethasone (50 mg/kg) and schisandrin (100, 200 mg/kg), 1% Evans blue solution (0.1 ml/10 g) was injected. One hour later, the mice were treated with 0.6% acetic acid in saline by intraperitoneal injection. Fifty minutes later, the mice were sacrificed by cervical dislocation. The peritoneal cavity was washed with saline (8 ml). The wash solution was collected and measured.

3.2. Inhibition of prostaglandin E2 production, COX-2 protein and mRNA expression in LPS-stimulated RAW 264.7 macrophages

We studied the effect of schisandrin on PGEl release, the expression of COX-2 protein and mRNA expression by LPS-stimulated macrophages. Our results suggest that schisandrin significantly inhibits PGEl release (Fig. 3A) and COX-2 protein expression (Fig. 3B) in a dose-dependent manner. Furthermore, LPS-induced COX-2 mRNA expression was inhibited by 50 \( \mu \)M of schisandrin (Fig. 3C).

Fig. 8. Effect of schisandrin on carrageenan-induced mice paw edema. Thirty-six mice were randomly divided into 4 groups. Thirty minutes after schisandrin (100, 200 mg/kg) was administered, the mice were treated with 0.05 ml of \( \lambda \)-carrageenan (1%) by intraperitoneal injection into the right hind paw. After the \( \lambda \)-carrageenan injection, the paw volumes were measured at 1, 2, 3, 4 and 5 h by dial thickness gage (Mitutoyo, Japan).
3.3. Inhibition of the activation of NF-κB in LPS-stimulated transfected-RAW 264.7 macrophages

To further elucidate the effect of schisandrin at the transcriptional level, the activation of NF-κB, one of the important transcription factors involved in the process of inflammation, was examined. An analysis of reporter gene expression in the transfected-RAW 264.7 cells demonstrated that schisandrin inhibited the activation of NF-κB in a dose-dependent manner (Fig. 4).

3.4. Effects of schisandrin on phosphorylation and degradation of IκBα

The activation of NF-κB is preceded by the phosphorylation of IκBα at serine residues and the subsequent proteasome-mediated degradation of IκBα (Tsao et al., 2005). The expression of IκBα was examined by Western blot. IκBα was completely degraded 30 min and phosphorylated 5 min after stimulation with LPS (data not shown). We demonstrated that schisandrin weakly inhibited LPS-induced degradation of IκBα (Fig. 5). And there was no effects on IκBα phosphorylation (data not shown).

3.5. Effects of schisandrin on activation of JNK and p38 MAPKs

To investigate whether the JNK and p38 MAPKs signaling pathways are involved in the suppression of iNOS and COX-2 expression by schisandrin, the activation of these two MAPKs was examined by Western blot. Time-course experiments (data not shown) showed that treatment with LPS for 30 min achieved a significant increase in the phosphorylation of JNK and p38 MAPKs. We demonstrated that schisandrin significantly inhibited the phosphorylation of JNK (Fig. 6A) and p38 MAPKs (Fig. 6B) in a dose-dependent manner. This data suggests that the anti-inflammatory activity of schisandrin was due to the inhibition of the LPS-induced phosphorylation of JNK and p38 MAPKs.

3.6. Anti-inflammatory effects of schisandrin in vivo

As shown in Fig. 7, schisandrin (200 mg/kg) markedly inhibited acetic acid-induced peritoneal vascular permeability. In the paw edema assay, the rate of increase is 33.41% in the control group at 3 h. Treatment of mice with dexamethasone (50 mg/kg) and schisandrin (100 mg/kg; 200 mg/kg) showed a significant reduction in carrageenan-induced paw edema (Fig. 8). The inhibitory effects of dexamethasone and schisandrin started at 1 h and sustained themselves for 4 h. At 3 h, the inhibitory rates of schisandrin are 33.43% (100 mg/kg) and 57.38% (200 mg/kg) against the rate of control group.

We performed an experiment to assess whether schisandrin inhibited endotoxic shock or not. Survival was monitored for 72 h. After 72 h, the survival rate of the LPS group (n = 15) was 20%. A lower dose...
of schisandrin (n = 10) had little effect on the endotoxic shock. The mice given a higher dose of schisandrin (n = 10) showed a 70% survival, a rate significantly different from that of the LPS group. The mice of the dexamethasone group (n = 10) all survived (Fig. 9).

4. Discussion

Schisandrin significantly inhibited NO and PGE2 production. Therefore, we conducted a further, protein-level study, and found that schisandrin also decreased the protein expression of COX-2 and of iNOS in a dose-dependent manner. However, it inhibited the mRNA expression of COX-2 and iNOS only weakly, which suggests post-translational regulation. To further elucidate the anti-inflammatory mechanism, we examined the phosphorylation and degradation of iNOS protein. Schisandrin weakly inhibited the degradation of iNOS. Interestingly, there was no effect on iNOS phosphorylation. In stimulated cells, iNOS undergoes rapid phosphorylation, which occurs at Ser-32 and Ser-36. This phosphorylation targets them for rapid polyubiquitination followed by degradation through the 26S proteasome pathway (Chen et al., 1995). According to the results, it is likely that schisandrin interrupts the ubiquitin–proteasome system, thereby preventing iNOS degradation and inhibiting NF-κB activation. With regard to the JNK and p38 MAP kinase pathways, the studies showed that the phosphorylation of JNK and p38 was inhibited by schisandrin in a dose-dependent manner. In vitro studies indicated that schisandrin reduced NO and PGE2 production as well as iNOS and COX-2 expression through inhibition of NF-κB activation and blocking of the p38, JNK MAPK pathways (Fig. 10).

These inflammatory mediators are all associated with many acute and chronic inflammatory diseases, including septic shock and rheumatoid arthritis. Carrageenan-induced paw edema in mice has been attributed to the expression of COX-2 and the release of prostaglandin (Seibert et al., 1994) and NO production (Salvenmini et al., 1996). Furthermore, subcutaneous injection of carrageenan to the paw can rapidly induce local edema by increasing vascular permeability (Ando et al., 1991). Therefore, schisandrin’s inhibition of carrageenan-induced swelling from 1 to 4 h was attributed to the diminished release of PGE2, the suppression of the LPS-induced levels of nitrite in the plasma, and the attenuation of the acetic acid-induced vascular permeability.

Schisandrin exerts a therapeutic effect on LPS-induced septic shock in mice. The fructus of S. chinensis has been reported to have hepatoprotective effects (Ko et al., 1995). Inhibiting hepatocellular apoptosis can protect mice against septic liver damage (Klintman et al., 2005). Therefore, schisandrin’s inhibition of carrageenan-induced swelling from 1 to 4 h was attributed to the diminished release of PGE2, the suppression of the LPS-induced levels of nitrite in the plasma, and the attenuation of the acetic acid-induced vascular permeability.

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References


Further reading
