Ginsenoside Rg3 Attenuates Microglia Activation Following Systemic Lipopolysaccharide Treatment in Mice

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Neuroinflammation, characterized by activation of microglia and expression of major inflammatory mediators, contributes to neuronal damage in addition to acute and chronic central nervous system (CNS) disease progression. The present study investigated the immune modulatory effects of ginsenoside Rg3, a principle active ingredient in Panax ginseng, on pro-inflammatory cytokines and microglia activation in brain tissue induced by systemic lipopolysaccharide (LPS) treatment in C57BL/6 mice. Systemic LPS treatment induces immediate microglia activation in the brain. Based on this information, ginsenoside Rg3 was treated orally with 10, 20, and 30 mg/kg 1 h prior to the LPS (3 mg/kg, intraperitoneally (i.p.)) injection. Ginsenoside Rg3 at 20 and 30 mg/kg oral doses significantly attenuated up-regulation of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and IL-6 mRNA in brain tissue at 4 h after LPS injection. Morphological activation of microglia and Iba1 protein expression by systemic LPS injection were reduced with ginsenoside Rg3 (30 mg/kg) treatment. In addition, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression in brain tissue were also attenuated with oral treatment of ginsenoside Rg3 at 30 mg/kg. These results indicate that ginsenoside Rg3 plays a modulatory role in neuroinflammation. This study shows that ginsenoside Rg3 attenuates microglia activation using an in vivo animal model.

Key words ginsenoside Rg3; neuroinflammation; microglia; cytokine; lipopolysaccharide

Neuroinflammation which involves inflammation of the central nervous system (CNS) is now recognized to be a feature of all neurological disorders. In a wide variety of acute and chronic CNS disorders, inflammatory processes contribute to the damage of neurons and progression of disease.1) Neuroinflammation is considered a mediator for secondary damage and is characterized by activation of microglia, resident macrophages in the brain, and expression of major inflammatory mediators.2)

Cerebral ischemia leads to the activation of microglia and astrocytes and subsequent production of inflammatory mediators.3) Once activated, inflammatory cells release a variety of cytokoty agents including cytokines, matrix metalloproteinases (MMPs), nitric oxide (NO) and reactive oxygen species (ROS). These substances may induce more cell damage as well as cause disruption of the blood–brain barrier (BBB) and extracellular matrix.3,4) Furthermore, neurodegenerative conditions are characterized by chronic neuroinflammatory processes. The progressive deposition of amyloid beta-peptide (Aβ) in Alzheimer's disease might provide a chronic stimulus to microglial cells.5) Parkinson's disease is also characterized by chronic inflammation induced dopaminergic neuron degeneration within the substantia nigra.6) Hence, determining the modulatory effects of various drugs on neuroinflammation is critical for developing therapeutic approaches for CNS disorders.

Ginseng (the root of Panax ginseng C.A. Meyer, Araliaceae) has been used for the treatment of neurological disorders and other diseases in traditional medicine. Ginsenosides, or ginseng saponins, are the principle active constituents in ginseng.7) Ginsenoside Rg3 demonstrated neuroprotective effects against cerebral ischemia in rats through inhibition of mitochondrial permeability transition pore and intracellular Ca2+ elevation by L-type Ca2+ channels or N-methyl-d-aspartate (NMDA) receptors.8–11) Recently, ginsenoside Rg3 has also been known to play a role in the modulation of inflammatory processes.12) In BV-2 microglial cell culture studies, ginsenoside Rg3 reduced cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokine expressions, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, induced by lipopolysaccharide (LPS) or Aβ42 stimulation.13,14) These reports indicated that ginsenoside Rg3 might play a modulatory role on microglia in the brain.

However, little information is available about the effects of orally administered ginsenoside Rg3 on neuroinflammation using an in vivo animal study. Therefore, to better understanding the neuroprotective and anti-inflammatory effects of ginsenoside Rg3, the present study investigated its effects on the early stage of neuroinflammation induced by systemic LPS treatment in mice.

MATERIALS AND METHODS

Animals Male C57BL/6 mice (25–28 g, Nara Biotechnology, Korea) were used for this study. All animal protocols were approved by the Ethics Committee for the Care and Use of Laboratory Animals at Kyung Hee University. The animals were housed in plastic cages at a constant temperature (22±2°C) and humidity (55±10%) with 12 h–12 h light–dark conditions. The animals were allowed free access to food and water before the experiment.

Reagents 20(S)-Ginsenoside Rg3 (C36H52O13; formula weight, 785.01) was purchased from LKT Laboratories (Saint Paul, MN, U.S.A.). Lipopolysaccharide (LPS; from Escherichia coli O55:B5) and 3,3-diaminobenzidine (DAB) were purchased from Sigma-Aldrich (St. Louis, MO, U.S.A.). Rabbit anti-ionized calcium binding adaptor molecule 1 (Iba1) antibodies (#016-20001, #019-19741) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Mouse anti-actin antibody was purchased from Chemicon International

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Mouse anti-iNOS antibody was purchased from BD Biosciences (Laguna Hills, CA, U.S.A.). Rabbit anti-COX-2 antibody was purchased from Cayman Chemical (Ann Arbor, MI, U.S.A.). Goat anti-rabbit and goat anti-mouse immunoglobulin G (IgG) hors eradish peroxidase (HRP) conjugated secondary antibody were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, U.S.A.). Cy2-conjugated donkey anti-mouse or donkey anti-rabbit IgG, and Cy3-conjugated donkey anti-mouse IgG were purchased from Jackson ImmunoResearch Laboratories (West Grove, PA, U.S.A.). The other chemicals and reagents used were of high quality and obtained from various commercial sources.

**Experimental Groups** Mice were randomly divided into five groups. The normal group (Normal) was allowed free access to food and water without any treatment. The control group (LPS) was intraperitoneally (i.p.) injected with a single dose of LPS (3 mg/kg) and received vehicle (normal saline) orally 1 h before the LPS injection. The ginsenoside Rg3 treatment groups [LPS+Rg3(10), LPS+Rg3(20), LPS+Rg3(30)] were administered 3 oral doses of ginsenoside Rg3 (10, 20, or 30 mg/kg, dissolved in normal saline) once 1 h prior to LPS injection. A total of 48 mice were used in this study.

**Real-Time Polymerase Chain Reaction (PCR) Measurement** Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) mRNA expression in the brain tissue was measured by the quantitative real-time PCR method. At 4 h after the LPS injection, mice were sacrificed by decapitation and brain tissue was rapidly dissected. Total RNA was extracted from the samples with Trizol (Qiagen, Germany) according to the manufacturer’s protocol. One microgram of total RNA was transcribed into DNA by using iScript cDNA synthesis Kit (Bio-Rad, U.S.A.). After reverse transcription, quantitative real-time PCR was performed using preoptimized primer/probe mixture with iQ SYBR Green Supermix kit (Bio-Rad, U.S.A.). The sections were incubated overnight at 4°C with primary antibodies against Iba1 (1:500, #019-19741, Wako, Japan), as a microglia marker. The sections were then incubated with biotinylated anti-mouse secondary antibody (1:200, Vector Laboratories, U.S.A.) for 1 h at room temperature, after which the avidin–biotin complex (Vector Laboratories, U.S.A.) method was carried out with peroxidase coupling in a mixture containing 0.05% DAB (Sigma-Aldrich, U.S.A.) and 0.03% H2O2 for 2–5 min. For observation of iNOS and COX-2 expression in the brain tissue, immunofluorescent labeling was performed using primary antibodies against iNOS (1:200, #610329, BD, U.S.A.) and COX-2 (1:200, #160106, Cayman, U.S.A.). The brain sections were stained by a floating DAB reaction. The sections were rinsed with 0.05 M PBS and then incubated for 15 min in 1% hydrogen peroxide PBS at room temperature. The sections were incubated overnight at 4°C with primary antibodies against β-actin (1:1000, #019-19741, Wako, Japan), as a microglia marker.

**Western Blotting** The brain tissue was homogenized and sonicated on ice in lysis buffer (50 mM Tris–HCl, pH 8.0, 150 mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate (SDS), 1 mM ethylenediaminetetraacetic acid (EDTA), 1% protease inhibitor cocktail; Sigma). After centrifugation, the supernatant was collected and assayed for protein concentration by using the Bradford method. The lysates containing 50 μg proteins were fractionated by SDS–10% polyacrylamide gel electrophoresis, and then subjected to Western blot analysis. The primary antibodies used in this study were rabbit anti-Iba1 antibody (#016-20001, Wako, Japan) and mouse anti-β-actin antibody (Chemicon, U.S.A.).

**Immunohistochemistry** Microglia activation in the brain tissue was observed with immunohistochemistry. At 4 h after the LPS injection, the mice were deeply anesthetized and perfused transcardially with 0.05 M phosphate-buffered saline (PBS) containing 4% paraformaldehyde. The brain was removed and was postfixed in the same perfusing solution overnight at 4°C. Coronal sections of 30 μm thickness were made using a freezing microtome (Leica, 2800N, Germany). The brain sections were stained by a free-floating DAB reaction. The sections were rinsed with 0.05 M PBS and then incubated for 15 min in 1% hydrogen peroxide PBS at room temperature. The sections were incubated overnight at 4°C with primary antibodies against Iba1 (1:500, #019-19741, Wako, Japan), as a microglia marker. The sections were then incubated with biotinylated anti-mouse secondary antibody (1:200, Vector Laboratories, U.S.A.) for 1 h at room temperature, after which the avidin–biotin complex (Vector Laboratories, U.S.A.) method was carried out with peroxidase coupling in a mixture containing 0.05% DAB (Sigma-Aldrich, U.S.A.) and 0.03% H2O2 for 2–5 min. For observation of iNOS and COX-2 expression in the brain tissue, immunofluorescent labeling was performed using primary antibodies against iNOS (1:200, #610329, BD, U.S.A.) and COX-2 (1:200, #160106, Cayman, U.S.A.). The sections were then incubated with biotinylated anti-mouse secondary antibody (1:200, Vector Laboratories, U.S.A.) for 1 h at room temperature, after which the avidin–biotin complex (Vector Laboratories, U.S.A.) method was carried out with peroxidase coupling in a mixture containing 0.05% DAB (Sigma-Aldrich, U.S.A.) and 0.03% H2O2 for 2–5 min. For observation of iNOS and COX-2 expression in the brain tissue, immunofluorescent labeling was performed using primary antibodies against iNOS (1:200, #610329, BD, U.S.A.) and COX-2 (1:200, #160106, Cayman, U.S.A.). The anti-rabbit or anti-mouse Cy2 (Jackson ImmunoResearch, U.S.A.) was used as a secondary antibody. Images of the DAB-colorized brain sections were captured using a light microscope (BX51, Olympus, Japan) equipped CCD camera (DP70, Olympus, Japan) and the fluorescence-labeled images were captured using confocal laser-scanning microscopy (Carl Zeiss, LSM 510 META, Germany).

**Count of Iba1 Immuno-positive Cells** Immunohistochemistry stained sections were used for analysis of the number of the immuno-positive cells. The count of Iba1 immuno-positive microglia was analyzed by using ImageJ software (Ver. 1.44p, NIH, U.S.A.). Four sections and four fields per section were chosen for analysis in each rat. Data were normalized with the same area (105 μm2) and the mean values for the four sections in each rat were used for statistical analysis.

**Area Percentage Measurement of iNOS and COX-2 Expression** The images captured using confocal laser-scanning microscopy and ImageJ software were used for analysis of the area % of iNOS and COX-2 expression. In brief, image contrast was adjusted adequately (step-1), then the image inverted to black–white binary image (step-2). Threshold gray value was determined and pixels which gray value was greater than

<table>
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<th>Primer Sequences</th>
<th>TNF-α Forward</th>
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<th>IL-6 Forward</th>
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<td>5′-TTT CCA GCC TTC CTT GGG TAT G-3′</td>
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Table 1. Primer Sequences
the threshold were defined, refer to original image (step-3). All pixels in the same area (52714 µm²) were measured and calculated to area percentage (step-4). Four sections and four fields per section were chosen for analysis in each rat. The mean values for the four sections in each rat were used for statistical analysis.

**Statistical Analysis** All data in this study are presented as means±standard errors. Differences between groups were evaluated using Student’s t-test and one way analysis of variance (ANOVA). A probability value of less than 0.05 was used to indicate a significant difference.

**RESULTS**

**Ginsenoside Rg3 Attenuates Pro-inflammatory Cytokines mRNA Expression in the Brain Tissue of LPS-Treated Mice** To determine the effect of ginsenoside Rg3 on TNF-α, IL-1β, and IL-6 mRNA expression in the brain tissue following systemic LPS treatment, LPS (3 mg/kg) was treated with i.p. injection and 3 doses of ginsenoside Rg3 (10, 20, or 30 mg/kg) were treated orally 1 h before the LPS injection into male C57BL/6 mice. Quantitative real-time PCR measurement of brain TNF-α, IL-1β, and IL-6 mRNA was performed at 4 h after the LPS injection. LPS increased the brain TNF-α mRNA ∼80-fold (80.3±6.2 fold), while ginsenoside Rg3 treatment attenuated TNF-α mRNA of the brain tissue significantly at both 20 and 30 mg/kg (59.8±6.4 fold, p<0.05; 51.1±6.6 fold, p<0.01) compared to the LPS group. Inhibitory effect of ginsenoside Rg3 on brain TNF-α mRNA expression showed a dose dependent pattern (Fig. 2A). LPS also increased brain IL-1β mRNA ∼110-fold (109.4±14.1 fold), while ginsenoside Rg3 treatment attenuated IL-1β mRNA in brain tissue significantly at doses of 20 and 30 mg/kg (71.1±8.1 fold, 73.2±6.2 fold, p<0.05, respectively), as compared to the LPS group (Fig. 2B). Similarly, brain IL-6 mRNA increased ca. 210-fold (207.9±31.1 fold) by the LPS injection and ginsenoside Rg3 treatment attenuated IL-1β mRNA in brain tissue significantly at both 20 and 30 mg/kg (127.6±12.5 fold, 133.4±11.2 fold, p<0.05, respectively) compared to the LPS group (Fig. 2C). These results support that ginsenoside Rg3 attenuated the over-expression of cytokines in the brain induced by systemic LPS injection.

**Fig. 1. Chemical Structure of 20(S)-Ginsenoside Rg3**

**Fig. 2. Effects of Ginsenoside Rg3 on TNF-α, IL-1β, and IL-6 mRNA in Brain Tissue** LPS increases brain inflammatory cytokines mRNA, while ginsenoside Rg3 treatment attenuates brain TNF-α (A), IL-1β (B), and IL-6 (C) mRNA at 20 and 30 mg/kg administration. Data are represented by mean±S.E.M. (n=6 in each group). Statistical significances are based on comparison to the LPS group (*p<0.05; **p<0.01).

**Fig. 3. Effect of Ginsenoside Rg3 on Iba1 Expression in the Brain** Representative Western blots illustrate differences in the bands of Iba1 (A). LPS up-regulates Iba1 expression in brain tissue, while ginsenoside Rg3 treatment attenuates up-regulation of Iba1 expression at doses of 20 and 30 mg/kg administration (B). Data are represented by mean±S.E.M. (n=6 in each group). Statistical significances are based on comparison to the LPS group (*p<0.05; ***p<0.001).
Ginsenoside Rg3 Attenuates Microglia Activation in the Brain Tissue of LPS-Treated Mice  
Studies indicated that systemic LPS treatment induced activation of microglia in the brain immediately.15) Iba1 protein is specifically expressed in microglia and is upregulated during the activation of these cells.16) The effects of ginsenoside Rg3 on microglia activation following systemic LPS injection were tested by quantification of Iba1 protein with Western blotting and immunohistochemistry against Iba1 antibody in the brain tissue 4h after LPS injection (Fig. 3A). LPS increased the % increase of Iba1 expression in brain tissue (188.7±5.5%). Ginsenoside Rg3 treatment attenuated, significantly and dose dependently, the % increase of Iba1 expression in the brain tissue at doses of 20 and 30 mg/kg (159.7±7.9%, p<0.05; 142.9±7.2%, p<0.001; respectively) as compared to the LPS group (Fig. 3-B).

Immunohistochemistry against Iba1 antibody was processed with 30 mg/kg dose of ginsenoside Rg3 administration because ginsenoside Rg3 plays an important role in modulating the inflammatory responses in the brain, immunofluorescent labeling on iNOS and COX-2 expression in the brain tissue was performed with 30 mg/kg dose of ginsenoside Rg3 administration. Effect of ginsenoside Rg3 was evaluated by the area % of iNOS or COX-2 expression in the brain tissue was performed. LPS treatment reduced numbers of Iba1-expressed microglia in the DG was not counted due to the heterogeneous tissue properties. These results indicate that ginsenoside Rg3 attenuated microglia activation in the brain induced by systemic LPS injection.

Ginsenoside Rg3 Attenuates iNOS and COX-2 Expression in the Brain Tissue of LPS-Treated Mice  
In order to better understand the effect of ginsenoside Rg3 on inflammatory responses in the brain, immunofluorescent labeling on iNOS and COX-2 expression in the brain tissue was performed with 30 mg/kg dose of ginsenoside Rg3 administration. Effect of ginsenoside Rg3 was evaluated by the area % of iNOS or COX-2 expression in the brain tissue. Ginsenoside Rg3 treatment significantly reduced the area % of iNOS expression (1.72±0.11% vs. 1.31±0.14%, p<0.05) with respect to the LPS group (Figs. 5A,B). The area % of COX-2 expression in the cerebral cortex was also reduced significantly (4.94±0.59% vs. 2.66±0.60%, p<0.05) with respect to the LPS group (Figs. 5C,D). This result also indicates that ginsenoside Rg3 attenuated the inflammatory response in the brain induced by systemic LPS injection.

DISCUSSION

Ginsenoside Rg3 is an effective neuroprotective ingredient in Panax ginseng.8–11) Recently, it has been reported that ginsenoside Rg3 plays an important role in modulating the inflammatory processes with in vitro studies.13,14) Modulatory effect of ginsenoside Rg3 on microglia activation could be presupposed depending on its neuroprotective and anti-inflammatory effects reported previously through in vivo and
in vitro studies. Ginsenosides (protopanaxadiols; Rb1, Rb2, Rd, Rh2, etc.) which has a similar chemical structure to Rg3 may also affect microglia activation and neuroinflammation. Ginsenoside Rb1 depressed the activation of microglia in the penumbra around a cerebral ischemic insult in rats. Ginsenoside Rh2 showed anti-inflammatory effect against LPS and interferon-gamma-stimulated BV-2 microglial cells. The present study further extends these observations by showing that ginsenoside Rg3 exhibits suppressive effects against neuroinflammation induced by systemic LPS treatment in vivo. As a result, ginsenoside Rg3 significantly attenuated microglia activation, pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), iNOS and COX-2 expressions in the brain tissue induced by systemic LPS injection.

Systemic LPS injection (intraperitoneal) activates the inflammatory response in the brain through the toll-like receptors (TLRs) located on glia. This in turn promotes inflammation through activation of microglia and overproduction of inflammatory cytokines. Moreover, concerning with neurodegenerative disease’s study models, it was reported that systemic LPS treatment increased expression of amyloid precursor protein (APP) and the Aβ generation and also induced delayed and progressive loss of dopaminergic neurons in the substantia nigra. In an acute systemic LPS treatment study, in vivo BV-2 microglial cell cultures. In the present study, there were robust increases of TNF-α, IL-1β, IL-6, and IL-6 mRNA, microglia activation, iNOS and COX-2 expression in the brain tissue at 4h after the single LPS (3 mg/kg) i.p. injection. These parameters show the features of acute inflammation in the brain by LPS treatment.

There is abundant evidence suggesting that pro-inflammatory cytokine production and signaling results in neuronal cell death and is closely related to neurodegeneration. In previous studies, ginsenoside Rg3 effectively suppressed pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, in LPS-stimulated BV-2 microglial cells, in Aβ-treated BV-2 microglial cells, and in oxazolone applied anaphylactic mice. These suppressive effects against pro-inflammatory cytokines suggested that ginsenoside Rg3 might be associated with intracellular NF-κB which is a major transcription factor that regulates genes responsible for both the innate and adaptive immune response. This study shows that ginsenoside Rg3 significantly reduced TNF-α, IL-1β, and IL-6 mRNA in the brain tissue following systemic LPS treatment. This result may expand our understandings of the immune modulatory effects of ginsenoside Rg3 on neuroinflammation from in vitro to in vivo.

Microglia, the resident immune cells in the CNS, are key cellular elements of the acute neuroinflammatory response and is the primary source for pro-inflammatory cytokines detected in the brain. Microglia are activated in response to brain injuries and immunological stimuli to undergo dramatic alterations in morphology, changing from resting, ramified microglia into activated, amoeboid microglia, which is believed to favor phagocytosis and mobility. Microglia are readily activated by an extensive list of pro-inflammatory stimuli, such as LPS and Aβ. Despite major roles of microglia on inflammatory responses in the brain, there were no reports to demonstrate effects of ginsenoside Rg3 on microglia activation in vivo. This effect of ginsenoside Rg3 was investigated only with in vitro BV-2 microglial cell cultures. In the present study, ginsenoside Rg3 lessened the microglia morphological changes to an activated-form which can manifest as increased
cell size, irregular shape, thickened and shortened processes in all brain regions. Moreover, ginsenoside Rg3 significantly reduced Iba1 protein expression in the brain compared to that of LPS group. Iba1, which is highly and specifically expressed in microglia and macrophage, and is involved in RacGTPase-dependent membrane ruffling and phagocytosis. By immunohistochemical analyses, anti-Iba1 antibody was found to specifically recognize ramified microglia in normal rat brain, and Iba1 protein was strongly upregulated in activated microglia. Therefore, Iba1 may play significant roles in the regulation of some immunological and pathophysiological functions of microglia, and serve as a novel marker for detecting the activation of microglia. However, this study is the first to show that ginsenoside Rg3 plays a modulatory role in microglia activation using an in vivo animal study.

Activated microglia are responsible for the induction of iNOS and COX-2 in the brain by pro-inflammatory cytokines or LPS stimulation. Nitric oxide (NO) and prostaglandins are major pleiotropic mediators produced by iNOS, COX-1 and COX-2. Microglia can generate superoxide, by using the constitutively expressed NADPH oxidase, which reacts with NO to form the powerful oxidant peroxynitrite. Cyclooxygenase plays a central role in the inflammatory cascade by converting arachidonic acid into bioactive prostanooids. Therefore, induction of iNOS and COX-2 leads microglia-mediated neurotoxicity. On the other hand, genetic deletion of microglial iNOS, pharmacological suppression of COX-2 activity, or the addition of exogenous superoxide dismutase (SOD) reduces microglia-mediated neurotoxicity. In previous reports, ginsenoside Rg3 attenuated iNOS and COX-2 expressions in the liver and kidney of the LPS-treated rats and in LPS/interferon-gamma-stimulated BV-2 microglial cells. Based on our study findings, ginsenoside Rg3 significantly attenuated both iNOS and COX-2 over-expressions in the brain induced by systemic LPS treatment. These results suggest that ginsenoside Rg3 may play a role in the microglia-mediated neurotoxicity as well as in the modulation of inflammation. The findings from this study indicate that ginsenoside Rg3 can effectively attenuate pro-inflammatory cytokines and microglia activation in the brain induced by systemic LPS treatment and may potentially protect against microglia-mediated neurodegenerative diseases. Further in-depth and long-term in vivo research is required to confirm these findings.

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REFERENCES


