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Beneficial effects of magnolol in a rodent model of endotoxin shock

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ABSTRACT

Magnolol is a compound extracted from the Chinese medicinal herb *Magnolia officinalis*. It has multiple pharmacological effects, notably as an anti-oxidant. The aim of this study was to evaluate the effects of magnolol on sepsis induced by intravenous (i.v.) administration of lipopolysaccharide (LPS; 10 mg/kg) in anaesthetized Wistar rats. Magnolol (4 μg/kg, i.v.) was administered at 30 min after LPS injection. Post-treatment with magnolol significantly attenuated the deleterious haemodynamic changes (e.g., hypotension and bradycardia) caused by LPS. Meanwhile, magnolol significantly inhibited the elevation of plasma levels of tumor necrosis factor alpha, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase and blood urine nitrogen caused by LPS. The induction of inducible nitrous oxide (NO) synthase and the overproduction of NO and superoxide anions by LPS were also significantly reduced by post-treatment with magnolol. Moreover, the plasma level of the thrombin–antithrombin complex following administration of LPS was also reduced by post-treatment with magnolol. Thus, the beneficial effects of magnolol on LPS-induced sepsis result from its anti-inflammatory, anti-coagulatory, and anti-oxidant effects.

1. Introduction

Sepsis is a generalized systemic inflammatory condition that can be defined as a progressive failure of the circulation, clinically characterized by systemic hypotension, hyporeactiveness to vasoconstrictors and subsequent organ perfusion, and function abnormalities followed by multiple organ failure (Bone et al., 1997). Sepsis results from the generalized activation of inflammatory cascades following invasion of the blood stream by bacteria, viruses or parasites, with the systemic release of various toxic products (Parrillo, 1993). These products include bacterial cell wall components, such as endotoxin and the lipopolysaccharide (LPS) membrane component of Gram-negative bacteria (Glauser et al., 1994). Many of the pathological consequences of Gram-negative shock are attributable to LPS. This induces experimental endotoxaemia and has become a valuable experimental model for septicaemia that has been studied extensively in laboratory animals (Höcherl et al., 2008). The first phagocytic cells that come into contact with LPS are macrophages and neutrophils. In response, macrophages secrete pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), the interleukins IL-6, IL-1β, and IL-12 (Ato et al., 2002; Li et al., 2002), free radicals, and reactive oxygen species (ROS) such as superoxide anion (Minuz et al., 2006; Victor and De La Fuente, 2003). An excess of ROS can cause cell death by oxidizing proteins, DNA damage, or lipid peroxidation of cellular membranes (Laskin and Pendino, 1995). It is well documented that pro-inflammatory cytokines and ROS contribute to the development of septic shock, multiple organ failure, and death. Septic shock causes a dramatic decrease in blood pressure and the onset of disseminated intravascular coagulation (DIC). Hypotension is caused by an excessive increase in vascular permeability, vasodilation, and decreased peripheral resistance (Wheeler and Bernard, 1999). DIC ensues from the activation of the coagulation cascade and subsequent multiple organ failure (Tslotou et al., 2005).

The bark of *Magnolia officinalis* is widely used as a folk remedy for gastrointestinal disorders, cough, anxiety, and allergic diseases (Maruyama et al., 1998). Magnolol (Fig. 1), a principal constituent isolated from this Chinese medicinal plant (Wang et al., 2004), has been shown to be a potent anti-oxidant (Wang et al., 1999). A number of other pharmacological effects of magnolol have also been found, including the induction of apoptosis (Yang et al., 2003), enhancement of differentiation (Fong et al., 2005), calcium mobilization (Zhai et al., 2003), and inhibition of platelet aggregation (Pyo et al., 2002).

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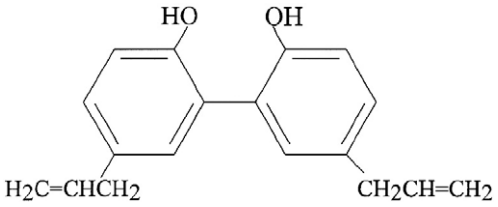

Fig. 1. The chemical structure of magnolol.

Magnolol has a broad spectrum of anti-inflammatory effects. It suppresses the expression of inducible nitric oxide synthase (iNOS) in macrophages (Matsuda et al., 2001), the production of inflammatory cytokines IL-8 and TNF-α in THP-1 cells (Park et al., 2004; Lee et al., 2005), and the formation of prostaglandin E2 in cortical cells (Lee et al., 2000). Although a previous study showed that magnolol could attenuate peroxidative damage and improve the survival of rats after surgically induced sepsis (Kong et al., 2000) or sepsis-induced haemorrhagic shock (Shih et al., 2003, 2004), the effects of magnolol on systemic inflammation remain unclear. Therefore, the aim of this study was to evaluate the therapeutic effects of magnolol on LPS-induced sepsis *in vivo*.

2. Materials and methods

2.1. Materials

Male Wistar–Kyoto rats (250–300 g) were purchased from the National Laboratory Animal Breeding and Research Center of the National Science Council, Taiwan. Reagents including LPS (*Escherichia coli*, serotype 0127:B8) and anti-β-actin antibody were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise specified.

2.2. Experimental groups

Animals were randomly divided into four groups ($n=6$ each) for treatment as follows: (I) Control group treated with the vehicle dimethyl sulfoxide (DMSO; 0.1%, i.v., 0.25–0.30 ml); (II) magnolol treatment group (4 μg/kg, i.v.); (III) LPS treatment group (10 mg/kg, i.v.) (Wang et al., 2003), and (IV) magnolol post-treatment group (LPS + magnolol) treated with magnolol (2–8 μg/kg, i.v.) at 30 min after LPS administration (10 mg/kg, i.v.). Magnolol, a gift from Dr. Huang of the Department of Pharmacy, National Defense Medical Center, Taipei, Taiwan, was dissolved in 0.1% DMSO. All animals were housed at an ambient temperature of 23 ± 1 °C and 55 ± 5% humidity. All experimental protocols were evaluated and approved by the Institutional Animal Care and Use Committee of the National Defense Medical Center.

2.3. Haemodynamic measurements

The rats were anaesthetized by an intraperitoneal injection of urethane (1.2 g/kg) and pentobarbital (5 mg/kg, i.v.). The trachea was cannulated to facilitate respiration. The left femoral artery was cannulated with polyethylene-50 (PE-50) and connected to a pressure transducer (P231D, Statham, Oxnard, CA, USA) for measuring the mean arterial pressure and heart rate, displayed on a Gould model TA5000 polygraph recorder (Gould, Valley View, OH, USA). The left femoral vein was cannulated for administering drugs. After the surgical procedure was complete, all cardiovascular parameters were allowed to stabilize for 30 min.

After recording the baseline haemodynamic parameters, animals were injected with vehicle or LPS and then monitored for 6 h. Immediately before (at time 0) and every hour after vehicle or LPS administration, 0.5 ml of blood was withdrawn to measure the level of TNF-α and nitrate. Any blood withdrawn was immediately replaced by an injection of an equal volume of saline (i.v.) to maintain the blood volume. Blood samples were centrifuged for 5 min at 12,000 *g* and plasma samples were stored at −80 °C until analysis.

2.4. Quantification of organ function and injury

Plasma samples for the measurement of glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), and blood urine nitrogen (BUN), were obtained at 0 and 6 h after the injection of saline or LPS as described above. These parameters were measured using an automatic analyzer (Fuji DRI-CHEM FDC 3000; Fuji Photo Film, Tokyo, Japan). Ten microliters of the plasma sample was used in each assay, as described (Cheng et al., 2007).

2.5. Measurement of plasma TNF-α concentration

Blood samples (0.5 ml) were collected at 0, 1, 2, and 4 h after the injection of LPS for measuring the TNF-α concentration in plasma using an enzyme-linked immunosorbent assay (mouse TNF-α ELISA Kit, Genzyme Co., Cambridge, MA, USA), as described (Cheng et al., 2007).

2.6. Pulmonary superoxide anion detection by chemiluminescence

Detection of superoxide anions was performed as described (Cheng et al., 2007). Lung tissues were cut into 5 × 5 mm fragments and incubated in 95% O_2/5% CO_2 oxygenated modified Kreb's/HEPES solution for 30 min at 37 °C. Then the tissue fragments were dispensed into a 96-well plate, with each well filled with 100 μl modified Kreb's/HEPES solution and placed in a luminescence measurement system (Hidex Microplate Luminometer, Finland). This was used to perform auto-injection of 1.25 mM lucigenin (final volume of 250 μl) into the tissue fragments for interacting with superoxide. Counts were obtained at 60 s intervals at room temperature. After recording was complete, the tissue was dried in a 70 °C oven for 48 h. The results were expressed as count per second (cps) per milligram dry weight.

2.7. Plasma nitrite/nitrate determination

Aliquots of 30 μl thawed plasma were deproteinized with 100 μl 95% ethanol for 30 min at 4 °C then centrifuged for 6 min at 12,000 *g*. The supernatant (6 μl) was injected into a collection chamber containing 5% VCL_3. In this strong reducing environment, both nitrate and nitrite are converted to NO. A constant stream of helium gas carries the NO into a NO analyzer (Sievers 280NOA; Sievers Instruments Inc., Boulder, CO, USA), where the NO reacts with ozone (O_3), resulting in the emission of light. Light emission is proportional to the NO formed. Standard amounts of sodium nitrate were used for calibration (Sigma-Aldrich).

2.8. Thrombin–antithrombin complex (TAT) immunoassay

Blood was drawn from the abdominal aorta into plastic syringes at 3 and 6 h after the injection of vehicle or LPS. All samples were diluted (1:9, v/v) with 0.13 mol/l sodium citrate. A commercial ELISA system (Enzygnost TAT; Behringwerke, Marburg, Germany) was used to determine plasma levels of TAT.

2.9. Western blot analysis of iNOS protein expression in lungs

At 6 h after the injection of vehicle or LPS, the experimental animals were euthanized. Lung tissues were taken and frozen at −80 °C before assay. Frozen samples were ground in a mortar containing liquid nitrogen. The powdered tissue was suspended in 1 ml of lysis buffer containing protease inhibitors, as described (Cheng

et al., 2007). Lung proteins were electrophoresed in 10% sodium dodecyl sulphate-polyacrylamide gels and transferred to a nitrocellulose membrane (Millipore, Bedford, USA). The membranes were incubated with antibodies against iNOS (1:1000 dilution, Stressgen Biotechnologies Co., Victoria, BC, Canada) or β-actin (1:2000 dilution, Sigma-Aldrich). Immunodetection was performed using an enhanced chemiluminescence kit (Pierce, Rockford, IL, USA). Protein quantities were measured by densitometric scanning of the blots using Image-Pro software (Media CyberMetrics, Inc., Phoenix, AZ, USA).

2.10. Survival rate

Male Wistar–Kyoto rats (250–300 g) were divided into four groups ($n=20$ each), LPS was administrated i.p. at a lethal dose of 20 mg/kg. Magnolol (4 μg/kg, i.p.) was administrated at 30 min and 24 h after LPS administration. The double injection was to increase bioavailability and efficacy. Survival of rats was monitored for 72 h.

2.11. Statistical analysis

Data are expressed as the mean ± S.E.M. Statistical evaluation was performed with one-factor analysis of variance (ANOVA) followed by the Newman–Keuls method. $P<0.05$ was assumed statistically significant. Mortality rates were compared between groups using the Kaplan–Meier test.

3. Results

3.1. Effect of magnolol on mean arterial pressure and heart rate in rats with endotoxaemia

To determine a suitable dose of magnolol, a dose–response study was carried out and the results are shown in Fig. 2A. In the control group, the mean arterial pressure was 106 ± 3.8 mm Hg. At 6 h after administration of LPS, the mean arterial pressure reduced to 68.46 ± 3.8 mm Hg. When we used a series of doses of magnolol (2–8 μg/kg) 30 min after the injection of LPS, the mean arterial pressure was maintained at significantly higher levels at 6 h than in the LPS-treated controls. Magnolol at 4 μg/kg was the optimum dose for a cardiovascular protective effect.

The baseline mean arterial pressure of four groups was about 104 ± 3 to 113 ± 5 mm Hg and did not show significant differences between groups. The mean arterial pressure of the control group was not changed significantly during the period of the experiment. The injection of LPS resulted in a rapid decrease in mean arterial pressure within 15 min. The mean arterial pressure then slowly returned to 95 ± 3 mm Hg at 1 h and gradually decreased to 68 ± 4 mm Hg at the end of the experiment (6 h). However, the mean arterial pressure after treatment with magnolol decreased within 15 min, then returned to 103.3 ± 3 mm Hg at 3 h and maintained at significantly higher levels at 6 h than in the LPS-treated controls (98.7 ± 2 mm Hg vs. 68 ± 4 mm Hg; $P<0.05$; Fig. 2B). Magnolol treatment alone did not have any significant effect on the mean arterial pressure.

The mean baseline heart rate in the four groups ranged from 432 ± 7 to 470 ± 10 bpm and there were no significant differences between groups. In the LPS group, heart rate increased progressively, peaked at 4 h, and then decreased until the end of the experiment. However, post-treatment with magnolol partially prevented LPS-induced bradycardia at 4–6 h ($P<0.05$) (Fig. 2C). In addition, magnolol alone did not have any significant effect on the heart rate.

3.2. Effect of magnolol on liver function

Baseline values of GOT and GPT were not significantly different between groups (Fig. 3A and B). LPS caused a significant increase in the plasma levels of GOT (from 83.83 ± 6.8 to 222.3 ± 17.28 U/l; $P<0.05$) and GPT (from 33.3 ± 1.3 to 146 ± 21.1 U/l; $P<0.05$) at the latest stage (6 h). The elevated plasma levels of GOT and GPT caused by LPS were reduced significantly by post-treatment of rats with magnolol ($P<0.05$).

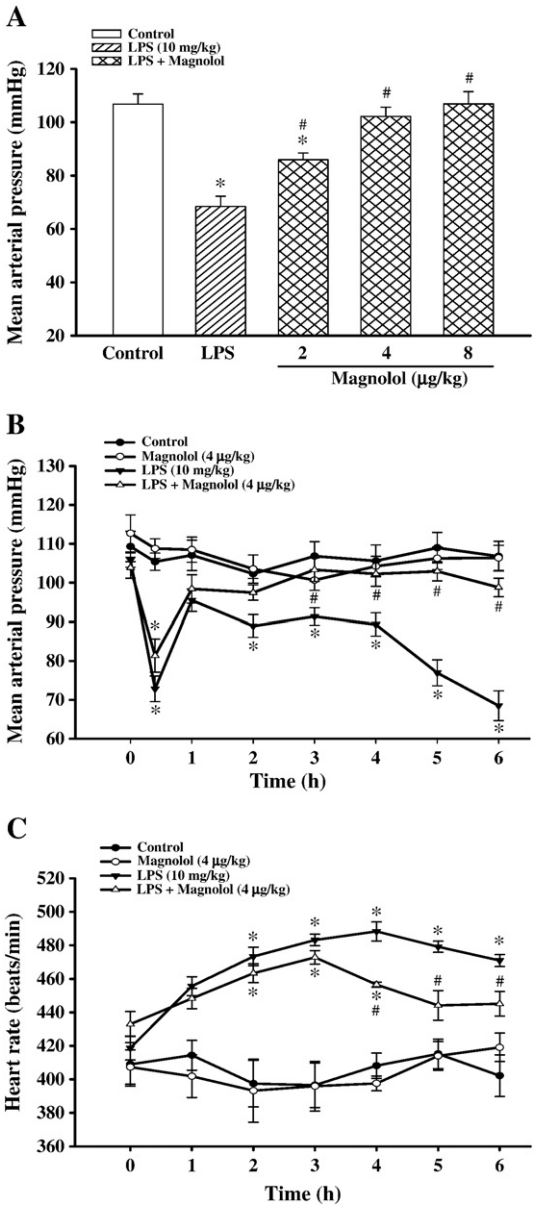

Fig. 2. Effect of treatment with magnolol (2–8 μg/kg, i.v.) on the mean arterial pressure (A) of rats treated with LPS (10 mg/kg, i.v.) for 6 h. The effects of magnolol (4 μg/kg) are shown on the time course of mean arterial pressure (B) and heart rate (C) changes after LPS administration for 6 h. Data are shown as the mean ± S.E.M. ($n=6$). * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

3.3. Effect of magnolol on renal function

Baseline values of BUN were not significantly different between groups (Fig. 3C). LPS caused a significant increase in the BUN level from 22.3 ± 1.29 to 60.1 ± 2.1 mg/dl ($P<0.05$) at the late stage (6 h). The elevated plasma levels of BUN caused by LPS were partially reduced by the post-treatment of rats with magnolol ($P<0.05$).

3.4. Effect of magnolol on plasma TNF-α level

The basal plasma levels of TNF-α were not significantly different between groups. LPS caused a significant increase in the plasma TNF-

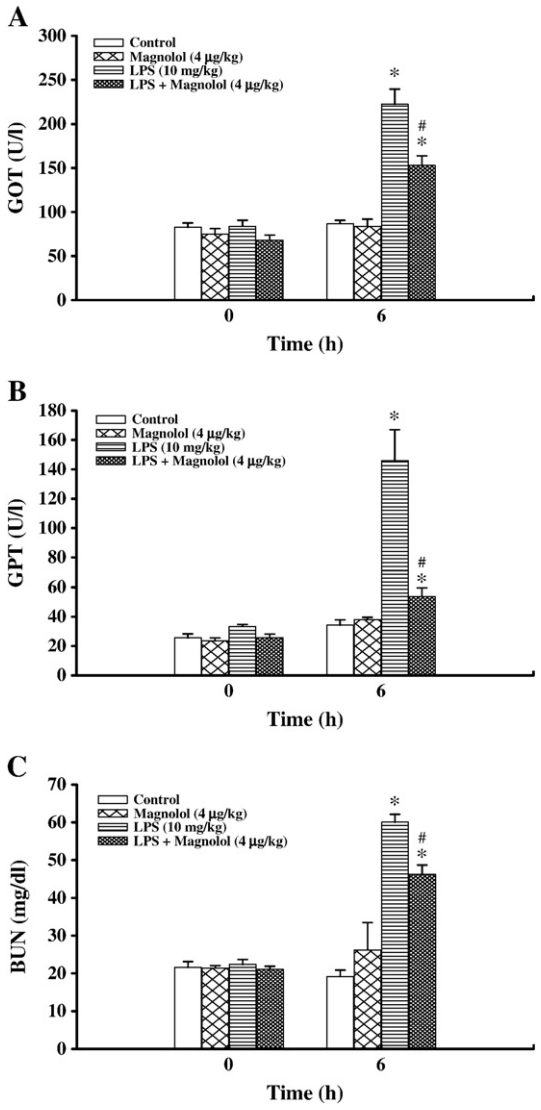

Fig. 3. Effect of magnolol (4 μg/kg) post-treatment on plasma levels of glutamate-oxaloacetate transaminase (GOT) (A), glutamate-pyruvate transaminase (GPT) (B), and blood urine nitrogen (BUN) (C) in rats treated with LPS. Data are shown as the mean ± S.E.M. ($n = 6$). * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

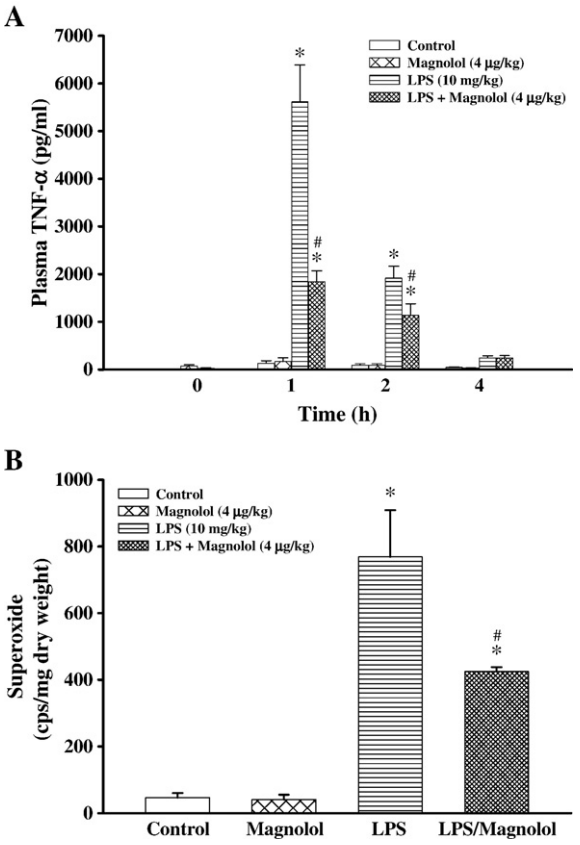

Fig. 4. Effect of post-treatment with magnolol (4 μg/kg) on plasma TNF-α levels (A) and superoxide anion formation in pulmonary tissues (B) from rats treated with LPS for 6 h. Data are shown as the mean ± S.E.M. ($n = 6$). * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

α level, which reached a peak at 1 h after LPS injection and subsequently decreased slowly. Magnolol alone did not cause an increase in the plasma TNF-α level. However, post-treatment with magnolol significantly decreased the LPS-induced increase of plasma TNF-α level at 1–2 h compared with the LPS group ($P<0.05$; Fig. 4A).

3.5. Effect of magnolol on pulmonary superoxide anion formation

The content of superoxide anions in lung tissues at 6 h after LPS injection was significantly higher than in the control group (769 ± 140 vs. 47 ± 14 cps/mg dry weight; $P<0.05$). However, post-treatment with magnolol significantly reduced superoxide anion formation compared with the LPS group (425 ± 14 vs. 769 ± 140 cps/mg dry weight; $P<0.05$; Fig. 4B).

3.6. Effect of magnolol on plasma TAT levels

To evaluate the extent of coagulation in magnolol-treated rats during systemic infection, we measured plasma TAT complex levels in magnolol-treated rats after LPS injection. There was no significant difference in the basal plasma TAT complex concentration between groups. LPS caused a significant increase from 6.45 ± 3.15 ng/ml to 275.1 ± 15.39 ng/ml at 3 h after LPS injection and to 662.63 ± 65.31 ng/ml at 6 h after LPS injection. However, after post-treatment with magnolol, the TAT complex level was significantly attenuated to 94.64 ± 11.23 ng/ml at 3 h, and 120.3 ± 17.88 ng/ml at 6 h after LPS injection ($P<0.05$; Fig. 5). Magnolol alone did not have any significant effect on the TAT complex level.

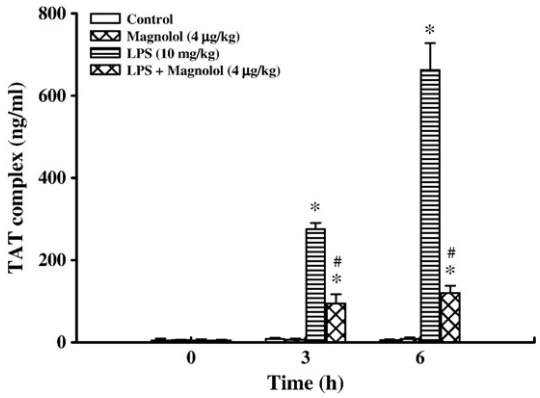

Fig. 5. Effect of post-treatment with magnolol (4 μg/kg) on the plasma thrombin–antithrombin complex (TAT) levels from rats treated with LPS. Data are shown as the mean ± S.E.M. ($n = 6$). * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

3.7. Effect of magnolol on plasma nitrite/nitrate content

In the control and magnolol alone groups, the level of plasma nitrite/nitrate did not significantly change throughout the experimental period. LPS injection significantly induced the elevation of plasma nitrite/nitrate content at 4–6 h compared with the control group ($P<0.05$). However, post-treatment with magnolol significantly suppressed this LPS-induced increase in plasma nitrite/nitrate levels ($P<0.05$; Fig. 6A).

3.8. Effect of magnolol on expression of iNOS protein in lungs

As shown in Fig. 6B, iNOS protein expression was low in lung homogenates obtained from the control rats, whereas a significant induction of iNOS protein was observed in rats treated with LPS for 6 h ($P<0.05$). Post-treatment of rats with magnolol significantly reduced the induction of iNOS in rats challenged with LPS ($P<0.05$).

3.9. Effect of magnolol on the survival rate of rat treated with LPS

As shown in Fig. 7, only 31.6% rats survived at 72 h after the administration of LPS. However, in the magnolol post-treatment group, the survival rate increased to 65%.

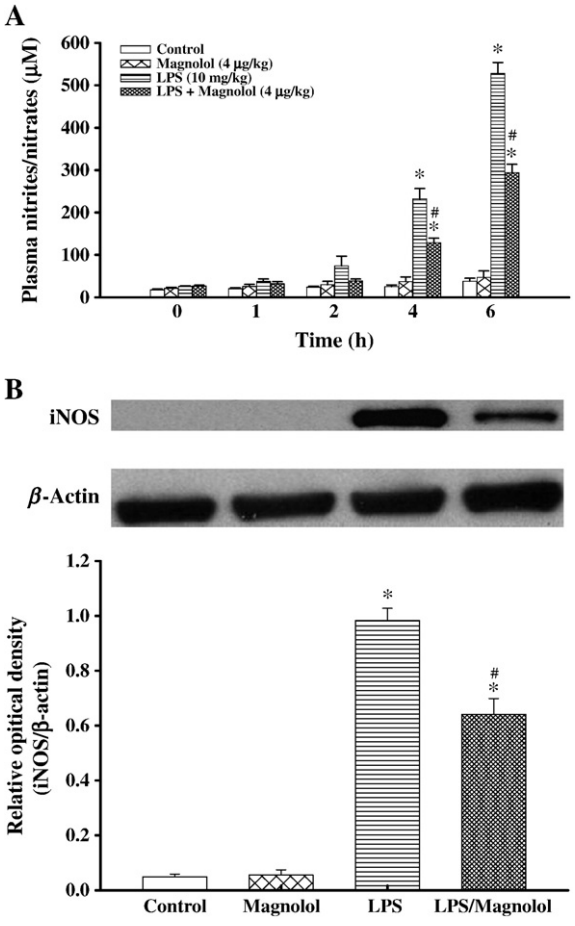

Fig. 6. Effect of post-treatment with magnolol (4 μg/kg) on plasma nitrite/nitrate ratio (A) and inducible nitrous oxide synthase (iNOS) protein expression in the lung (B) from rats treated with LPS for 6 h. Depicted is a typical display of iNOS protein expression (upper panel) and a statistical analysis of the changes in iNOS protein (lower panel). Data are shown as the mean ± S.E.M. ($n=6$). * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

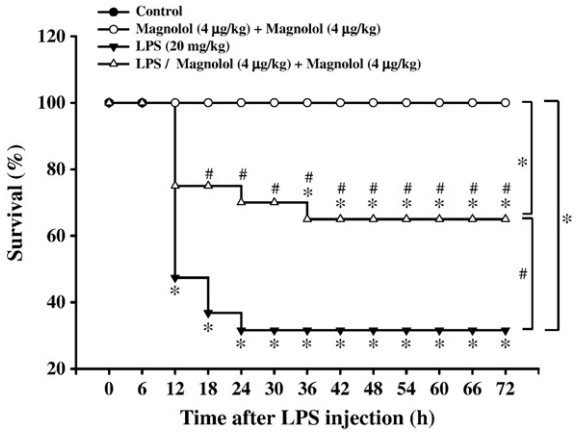

Fig. 7. Effect of magnolol on the survival rate of LPS-treated rats. Each group consisted of 20 animals. Vehicle (saline) was injected in control animals. LPS (20 mg/kg) was injected (i.p.) in LPS-treated group. Magnolol (4 μg/kg) was injected at 30 min and 24 h after LPS injection in the LPS + magnolol group. * $P<0.05$, LPS or LPS + magnolol vs. control; # $P<0.05$, LPS + magnolol vs. LPS alone.

4. Discussion

Here we demonstrated that post-treatment with magnolol was effective therapeutically against LPS-induced septic shock in rats. Magnolol significantly improved circulatory function, preventing hypotension as well as bradycardia in a late stage. It also prevented organs against dysfunction, leading to decreased mortality in the endotoxaemic rats. Possible mechanisms contributing to these beneficial effects of magnolol include (a) reducing the plasma TNF-α and nitrate/nitrite concentrations, (b) suppressing the organ superoxide anion level, and (c) suppressing the blood coagulation cascade and expression of inflammatory genes.

Severe hypotension, development of vascular hypoactivity, and progressive multiple organ dysfunction characterize the pathophysiology of Gram-negative bacterial septic shock (Titheradge, 1999). Previous studies suggested that an overproduction of NO by iNOS might contribute to hypotension and vascular hyporeactivity during septic shock (Piepot et al., 2003). LPS is known to induce the expression of iNOS, followed by the production of large amounts of NO in various cells, especially macrophages and endothelial cells. This contributes to several key features of septic shock syndrome, such as hypotension. In the present study, magnolol significantly ameliorated the hypotension and bradycardia induced by LPS, implying that it could suppress iNOS production. This point was further supported by the results in which magnolol reduced plasma nitrate/nitrite concentration and iNOS protein expression in the lung tissue of rats challenged with LPS (Fig. 6). The production of NO by iNOS is beneficial in fighting bacteria, but its overproduction can be harmful, as shown during endotoxic shock (Titheradge, 1999). There is increasing evidence that the overproduction of TNF-α during infection also leads to severe systemic toxicity and even death (Langrehr et al., 1993). Evidence supporting this hypothesis comes from reports indicating that mediators produced by endotoxin challenge, such as TNF-α, can induce iNOS expression leading to the production of large amounts of NO (Thiemermann et al., 1993). Consistent with those reports, in the current study LPS induced increases in the plasma TNF-α level, NO production, and the expression of iNOS (Figs. 4A and 6). The survival of rats was significantly reduced after LPS injection (Fig. 7). However, the elevated plasma TNF-α levels and mortality induced by LPS were reversed by magnolol treatment (Fig. 4A), indicating that this anti-inflammatory activity of magnolol might contribute to improve circulatory function (Fig. 2) and increased survival rate (Fig. 7) in rats subjected to endotoxaemia.

DIC is a severe complication of sepsis, which arises by activation of the coagulation cascade via the Hageman factor (factor XII), leading to thrombosis, tissue ischemia, and eventual multiple organ failure (Parrillo, 1993; Yamaguchi et al., 2000). LPS induces monocytes and endothelial cells to release cytokines, such as TNF-α, IL-1, and IL-6, which in turn activate coagulation (Levi and Ten Cate, 1999). As a result, large amounts of thrombin are generated. Thrombin transforms fibrinogen into fibrin and stimulates platelet aggregation, leading to the formation of stable microthrombi. Exhaustion of antithrombin III, the main inhibitor of coagulation, might help perpetuate fibrin generation (Fenton, 1986), thus enabling microvascular thrombi to develop in various organs with subsequent multiple organ failure (Levi and Ten Cate, 1999; Robboy et al., 1972). The TAT complex is one of the most sensitive markers of activation of the coagulation cascade and reflects the amount of thrombin generated in the circulating blood (Pelzer et al., 1988). Based on our finding that magnolol treatment led to a significant reduction in the LPS-induced plasma TAT complex elevation, it appears that magnolol suppressed haemostatic activation in this model of LPS-induced sepsis (Fig. 5).

During sepsis, abundant ROS are produced and several sources of oxygen-derived free radical species have been proposed as being the cause of tissue damage (Martins et al., 2003). Following transmigration and activation, infiltrating neutrophils produce abundant ROS via oxidative bursts. Other sources of ROS include activated macrophages and various extracellular molecular processes such as arachidonic acid metabolism and xanthine dehydrogenase oxidation (Crimi et al., 2006). Both $ONOO^-$ and $^{\bullet}OH$ are responsible for cellular lipid peroxidation, protein oxidation, and mitochondrial damage, which cause further injuries to tissues and can induce cell death (Kukreja and Hess, 1992). Our results here demonstrated that post-treatment with magnolol significantly suppressed the superoxide anion production in lungs induced by LPS (Fig. 4B). Moreover, LPS-induced multiple organ injuries/dysfunctions, which were further evidenced by alterations in biochemical parameters (Fig. 3). Treatment with magnolol not only ameliorated the deterioration of haemodynamic changes (hypotension and bradycardia) but also attenuated the liver and lung abnormalities caused by LPS treatment (Fig. 3). These results indicate that some of the beneficial effects of magnolol might be associated with its anti-oxidant properties (as shown in Fig. 4B). In this study, we did not show the cellular mechanisms of action responsible for the inhibitory effects of magnolol on TNF-α release, NO synthesis and superoxide anion generation. However, magnolol has been shown to inhibit the induction of iNOS expression and the activation of nuclear factor-kappa B (NF-κB) induced by LPS in macrophages (Matsuda et al., 2001; Oh et al., 2009). Moreover, magnolol inhibited TNF-α-stimulated phosphorylation and the degradation of cytosolic NF-κB (Tse et al., 2007). Although our *in vivo* data corroborated these earlier reports *in vitro*, the molecular mechanisms of how magnolol alleviates the symptoms of sepsis remain to be clarified.

In conclusion, magnolol is capable of reducing circulatory failure and improves survival in animals with LPS-induced endotoxic shock. These findings provide insights into the potential novel effect of magnolol as a therapeutic agent against septic shock.

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