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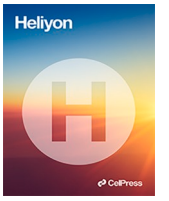

Research article

Luteolin improves vasoconstriction function and survival of septic mice via AMPK/NF-κB pathway

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ABSTRACT

Septic shock, the leading cause of death in sepsis, is related to vasoconstriction dysfunction. To investigate the effects of Luteolin (LTL), a flavonoid polyphenol compound, on vasoconstriction dysfunction in septic mice and the underlying mechanism, cecal ligation and puncture (CLP) surgery was performed on wild-type C57BL/6 mice to induce septic shock. Mice were intraperitoneally injected with 0.2 mg/kg LTL within 10 min after CLP surgery with or without 20 mg/kg Compound C (AMPK inhibitor) (CC) 1 h before CLP surgery, and re-administrated every 12 h. The survival rate, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) were explored. After the mice were sacrificed, the vasoconstriction function, inflammatory indicators, and possible regulatory signaling pathways were examined. Our data showed that CLP decreased the survival rate, SAP, DAP, MAP, vasoconstriction function, and expression of ADRA1A and *p*-AMPK/AMPK, as well as increased the mRNA expression of inflammatory cytokines and iNOS, the serum levels of inflammatory cytokines, and the levels of iNOS, p-p65/p65, and *p*-IκBα/IκBα in aortas ($P < 0.05$), which could be reversed by LTL treatment ($P < 0.05$). However, inhibition of AMPK could abolish the protective effects of LTL ($P < 0.05$). In conclusion, our study manifested that LTL could prevent vasoconstriction dysfunction and increase survival of septic mice via activating AMPK, which suggested that LTL could be a novel therapeutic option for patients with sepsis.

1. Introduction

Sepsis is a severe and life-threatening infectious disease with multiple organ dysfunction in its advanced stages [1]. Studies have shown that one-third of patients in intensive care units have sepsis, whose mortality rate is significantly higher than that of other patients [2,3]. In addition, sepsis has placed a heavy burden on global health because of the high cost of treating it [4]. Therefore, it is of great significance to explore the mechanism and new possible treatment strategies for sepsis.

Shock is one of the most common complications of sepsis and can directly cause death in patients [5]. Vascular hyporeactivity, characterized by vasoconstriction dysfunction, is the leading cause of shock in sepsis [6]. Arteries damaged by sepsis are less responsive to vasoconstrictors, such as epinephrine and norepinephrine, resulting in a decline in vasoconstriction function, persistent hypotension, and poor tissue perfusion [7].

The leading causes of vasoconstriction dysfunction in sepsis include excessive nitric oxide (NO) production induced by the up-regulation induced nitric oxide synthase (iNOS) [8,9] and decreased adrenergic receptor expression and function [10]. In a healthy

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body, iNOS barely expresses in cells. However, under some pathological conditions, such as inflammation, iNOS would be induced to express, which could induce a large amount of NO production [11,12]. NO is an important vasodilator and could resist vasoconstriction [13]. Adrenergic receptors could be divided into α and β types. α1 receptor distributes in the presynaptic membrane and vascular smooth muscle and mainly causes vasoconstriction when activated [14]. A study has shown that the increased inflammatory cytokines in sepsis reduce the expression of α1 adrenergic receptors, impairing vasoconstriction function and promoting circulatory failure [15]. In conclusion, reducing the transcription and expression of iNOS and protecting the expression and function of α1-adrenergic receptors are critical to treating septic vascular hyporeactivity.

LTL is a bioactive flavonoid polyphenol compound that exists in many vegetables, fruits, and herbs [16]. The biological and pharmacological effects of LTL, such as anticancer, antioxidant, and anti-inflammatory, have been reported in many studies [17,18]. LTL therapy has been verified to alleviate sepsis-induced acute lung injury by reducing the transcription of inflammatory cytokines and iNOS mediated by NF-κB [19]. In addition, it is reported that LTL could enhance autophagy by activating AMPK, thereby preventing septic myocardial injury [20]. However, the effect of LTL on vascular function in sepsis remains unknown. Evidences have shown that activation of AMPK could suppress inflammatory response by inhibiting NF-κB [21,22]. Therefore, we designed this experiment to investigate the effect of LTL treatment on vascular hyporeactivity and survival in septic mice and the role of AMPK/NF-κB pathway in it.

2. Materials and methods

2.1. Materials

Primary antibodies against iNOS (13120), Phospho-AMPKα (Thr172) (*p*-AMPK) (50081), and Phospho-IκBα (Ser32) (*p*-IκBα) (2859) were purchased from Cell Signaling Technology (Danvers, MA, US). Primary antibody against Phospho-NF-κB p65 (Ser536) (p-p65) (sc-136548) was purchased from Santa Cruz (Dallas, TX, USA). Primary antibody against AMPK (WL02254) was purchased from Wanleibio (Shenyang, Liaoning, China). Primary antibodies against IκBα (10268-1-AP), adrenergic receptor α1A (ADRA1A) (19777-1-AP), β-actin (66009-1-Ig), and NF-κB p65 (p65) (66535-1-Ig), and secondary antibodies (Goat anti-Mouse, SA00001-1; Goat anti-Rabbit, SA00001-2) were obtained from Proteintech (Rosemont, IL, USA). LTL (HY–N0162) and Compound C (CC) (HY-13418A) were purchased from MedChemExpress (Monmouth Junction, NJ, USA). Mouse TNF-α ELISA Kit (PT512), Mouse IL-1β ELISA Kit (PI301), and Mouse IL-6 ELISA Kit (PI326) were purchased from Beyotime (Shanghai, China).

2.2. Animals

8-week-old male wild-type C57BL/6 mice were obtained from the experimental animal center of Chongqing medical university. The mice were housed in a controlled facility under a 12-h light/dark cycle with free access to sterile water and standard rodent food. The temperature in the facility is kept constant at 22 °C. All study protocols were approved by the ethical committee of Chongqing Medical University.

2.3. Cecal ligation and puncture (CLP)

CLP was performed to induce sepsis in mice as previously described [23,24]. In brief, The mice were anesthetized with 2% isoflurane and fixed on a 37 °C operating platform. An incision of about 0.5 cm was made in the left lower abdomen. The cecum was exteriorized and ligated by 4-0 silk thread at half of it. Next, the distal end of the ligation was punctured by a 20-g needle and squeezed. Then, the cecum was return to the abdomen. After the incisions were sutured layer by layer, warm saline was injected subcutaneously at a dose of 5 mL/100 g for resuscitation. The sham operation group (Sham) received a similar procedure, except for ligation or puncture of the cecum. Mice were sacrificed 24 h after CLP, and their aortas were harvested for subsequent experiments. 0.2 mg/kg LTL was intraperitoneally injected into mice 10 min after surgery, and 20 mg/kg CC was intraperitoneally injected into mice 1 h before the surgery. LTL with or without CC was re-administrated every 12 h. The administration dosages were based on previous research [19,25].

2.4. Survival observation

There were 10 mice in each group. The mice were observed every 12 h for 4 days after surgery. No other operation was performed except injection of LTL and CC.

2.5. Blood pressure

The SAP, DAP, and MAP were measured by a noninvasive mice tail sphygmomanometer (Softron BP-2010, Japan). The awake mice were immobilized in a small warm cage (37 °C), and their SAP, DAP, and MAP were measured when they calmed down. Each mouse was measured 3 times, and the mean value was calculated and recorded.

2.6. Vascular reactivity

After the mice were sacrificed, their thoracic aortas were isolated for vascular reactivity measurement using the DMT620 system (Denmark). Thoracic aortas were cut into 3 mm in length, and their connective tissue and endothelium were cleaned up. Afterward, the aortas were placed and mounted in a chamber filled with 37 °C aerated (5% CO_2 and 95% O_2) physiological saline solution (PSS) (KCl 4.7 mM, NaCl 119 mM, $CaCl_2$ 2.5 mM, $NaHCO_3$ 25 mM, KH_2PO_4 1.2 mM, Glucose 5.5 mM, and $MgSO_4$ 1.2 mM). The aortas were equilibrated under 0.3g resting tension for 1 h. Next, the KCl(60 mM)-PSS was used to confirm the viability of the aortas 2 times. The cumulative dose-response curve for norepinephrine (NE) was then conducted.

2.7. Western blot

The aortas were lysed by RIPA containing 1% protease inhibitor and 1% phosphatase inhibitor at a temperature of 4 °C for 1 h. After adding the loading buffer, the samples were heated in a 100 °C water bath for 10 min. Afterward, the samples were separated by 10% SDS-PAGE gels and transferred to PVDF membranes. After being blocked with 5% skim milk in TBS with 0.1% Tween-20, the membranes were incubated with appropriate primary antibodies at 4 °C for 12 h. Next, the membranes were incubated with secondary antibodies conjugated with horseradish peroxidase at 25 °C for 1 h. ECL Western Blotting System (Bio-Rad, CA, USA) was used to visualize the image.

2.8. Quantitative real-time PCR

Total RNA was extracted with RNAiso plus (Takara, Japan), and 1 μg of the extracted RNA was taken for reverse transcription using the PrimeScript RT reagent kit (Takara, Japan). The total cDNA was amplified and analyzed by SYBR Green PCR Master Mix (Takara, Japan) in a CFX96 Real-time System (Bio-Rad, USA). The sequences of mouse-specific primers are shown in Table 1.

2.9. ELISA

The level of TNFα, IL-1β, and IL-6 in serum was measured using commercially available mouse TNFα, IL-1β, and IL-6 ELISA kit (Beyotime, Shanghai, China) follow the manufacturer's instructions.

2.10. Statistical analysis

All data were expressed as mean ± SD. Statistical analyses were performed using one-way ANOVA followed by the Bonferroni post hoc test. Survival curves were performed using Kaplan-Meier survival curves and analyzed using log-rank tests. $P < 0.05$ were considered to be statistically significant. All statistical analyses were performed using GraphPad Prism 8.0 software.

3. Results

3.1. LTL increased the survival rate in septic mice

The experimental schedule is shown in Fig. 1A and the chemical structural formula of LTL is shown in Fig. 1B. The mice were observed for 4 days after CLP, and the survival was recorded every 12 h. Data showed that in the CLP group, 60% of the mice survived 12 h after surgery, only 30% survived 24 h, and none survived 60 h. In contrast, LTL treatment significantly improved the survival of mice with sepsis (Fig. 1C) ($P < 0.05$). The death of mice mainly occurred 1 day after surgery, so we chose this time point for the subsequent experiment.

Table 1
The sequences of mouse-specific primers.

iNOS	Forward	5'-CGAAACGCTTCACTTCCAA-3'
	Reverse	5'-TGAGCCTATATTGCTGTGGCT-3'
MCP-1	Forward	5'-CAGCCAGATGCAGTTAACGC-3'
	Reverse	5'-GCCTACTCATTGGGATCATCTTG-3'
TNFα	Forward	5'-GAGTGACAAGCCTGTAGCC-3'
	Reverse	5'-CTCCTGGTATGAGATAGCAAA-3'
IL-1β	Forward	5'-CCAGCTTCAAATCTCACAGCAG-3'
	Reverse	5'-GGCGTATCAGTGGGGGTCAG-3'
IL-6	Forward	5'-GGAGCCCACCAAGAACGATAGTCAA-3'
	Reverse	5'-TGTCACCAGCATCAGTCCCAAGAAGG-3'
β-actin	Forward	5'-CCACCATGTACCCAGGCATT-3'
	Reverse	5'-CAGCTCAGTAACAGTCCGCC-3'

A

Sham	Vehicle	1 h	Sham Operation	10 min	Vehicle	12 h	Vehicle	12 h	Blood pressure test	Euthanasia & harvesting
Sham+LTL					0.2 mg/kg LTL		0.2 mg/kg LTL			
CLP			CLP		Vehicle		Vehicle			
CLP+LTL					0.2 mg/kg LTL		0.2 mg/kg LTL			
CLP+LTL+CC	20 mg/kg CC						0.2 mg/kg LTL+20 mg/kg CC			

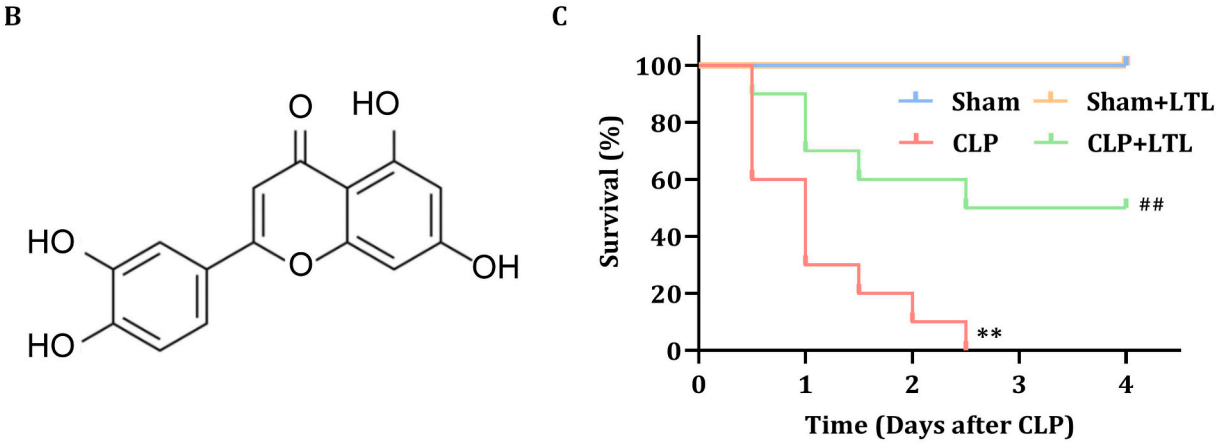

Fig. 1. LTL increased the survival rate in septic mice. (A) Experimental schedule of current study. (B) The chemical structural formula of LTL. After CLP surgery, the mice were observed for 4 days without any other operation except LTL administration, and the results were shown in (C). n = 10, $^{**}P < 0.01$ compared with Sham group, $\#\#P < 0.01$ compared with CLP group.

3.2. LTL prevented a decrease in blood pressure and vasoconstriction function in septic mice

Septic shock, one of the most common causes of death in sepsis, is associated with reduced blood pressure and vasoconstriction dysfunction. Our results manifested that a decline in SAP (Fig. 2A), DAP (Fig. 2B), MAP (Fig. 2C) and vasoconstriction function (Fig. 2D) was found in mice of the CLP group. However, LTL treatment could partly reverse it ($P < 0.05$). It has been reported that the excessive NO produced by iNOS and the inhibition of α1-adrenergic receptor expression and function are the leading causes of septic vasoconstriction dysfunction [3,26]. The iNOS and ADRA1A expression in aortas were measured. As shown in Fig. 2E–G, Data displayed that CLP induced a significant increase in iNOS expression and an evident decrease in ADRA1A expression ($P < 0.05$). However, LTL could inhibit the up-regulation of iNOS and prevent the decline in ADRA1A ($P < 0.05$). These data indicate LTL could prevent the vasoconstriction dysfunction in sepsis and increase the blood pressure by suppressing the iNOS and up-regulating the ADRA1A.

3.3. LTL activates AMPK to inhibit the NF-κB-induced transcription of inflammatory cytokines and iNOS in septic mice

It has been widely confirmed that AMPK/NF-κB pathway regulates inflammatory response and induces iNOS transcription in sepsis [21,27]. Inflammatory cytokines could down-regulate the expression of α1-adrenergic receptors. Our data showed that CLP could inhibit the level of *p*-AMPK/AMPK (Fig. 3A and B) ($P < 0.05$) as well as up-regulate the levels of p-p65/p65 (Fig. 3A and C) and *p*-IκBα/IκBα (Fig. 3A and D) ($P < 0.05$), mRNA expression of iNOS (Fig. 3E), MCP-1 (Fig. 3F), TNF-α (Fig. 3G), IL-1β (Fig. 3H), and IL-6 (Fig. 3I) ($P < 0.05$), and levels of TNF-α (Fig. 3J), IL-1β (Fig. 3K), and IL-6 (Fig. 3L) in serum ($P < 0.05$). However, these effects induced by CLP could be partly reversed by LTL treatment ($P < 0.05$). LTL could elevated the level of *p*-AMPK/AMPK in aortas of mice in Sham + LTL group compared to these in Sham group ($P < 0.05$), but have no effects on the other indexes ($P > 0.05$). These results suggested that LTL may activate AMPK to suppress the NF-κB-induced transcription of inflammatory cytokines and iNOS in the aortas of septic mice.

3.4. AMPK plays a crucial role in the protective effects of LTL against septic vascular hyporeactivity

To determine the role of AMPK in LTL against septic shock, CC was used to inhibit AMPK. The data manifested that LTL could reverse the CLP-induced decline in *p*-AMPK/AMPK (Fig. 4A and B) and ADRA1A (Fig. 4K and M) expression levels, SAP (Fig. 4N), DAP (Fig. 4O), MAP (Fig. 4P), and vasoconstriction function (Fig. 4Q) ($P < 0.05$), as well as the increase of p-p65/p65 (Fig. 4A and B), *p*-

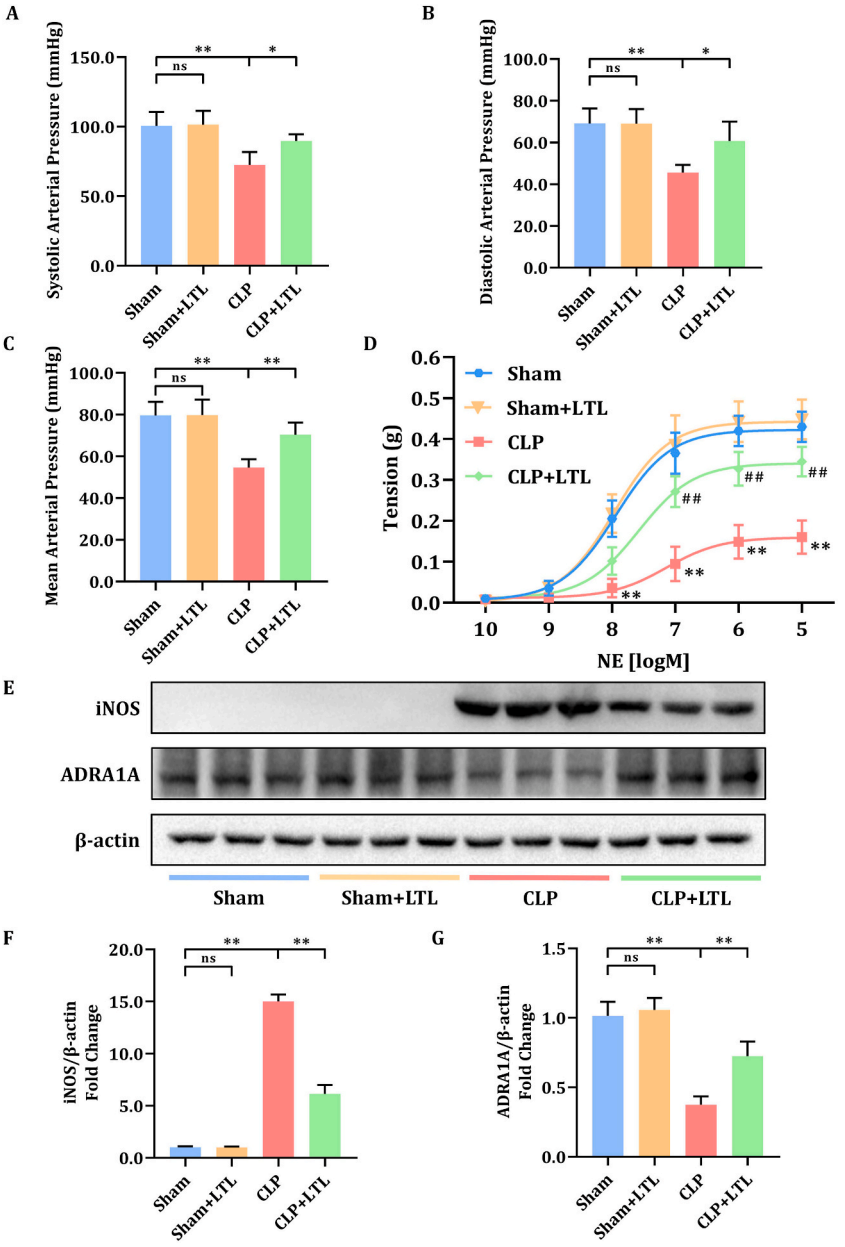

Fig. 2. LTL prevented a decrease in blood pressure and vasoconstriction function in septic mice. SAP (A), DAP (B), and MAP (C) of mice were measured by noninvasive mice tail sphygmomanometer. n = 5, $^{*}P < 0.05$, $^{**}P < 0.01$. (D) NE-induced vasoconstriction of aortas in all groups. n = 5, $^{**}P < 0.01$ compared with Sham group, $\#\#P < 0.01$ compared with CLP group. (E) Expression of iNOS and ADRA1A in aortas were determined by Western blot. The original blots are presented in supplementary material. Quantification of iNOS (F) and ADRA1A (G). n = 5, $^{**}P < 0.01$.

IκBα/IκBα (Fig. 4A and B) and iNOS (Fig. 4K and L) expression levels, iNOS (Fig. 4C), MCP-1 (Fig. 4D), TNF-α (Fig. 4E), IL-1β (Fig. 4F) and IL-6 (Fig. 4G) mRNA expression ($P < 0.05$), and serum levels of TNF-α (Fig. 4H), IL-1β (Fig. 4I) and IL-6 (Fig. 4J) ($P < 0.05$). However, inhibition of AMPK could abolish the protective effects of LTL ($P < 0.05$). These findings suggest that AMPK plays a critical role in the protective effects of LTL against septic vascular hyporeactivity.

3.5. AMPK plays a vital role in LTL-induced increase in survival rates in septic mice

To determine the role of AMPK in LTL-induced increase in survival rates in septic mice, a 4-day observation of mice in sepsis was then carried out. As shown in Fig. 5, data showed that in the CLP group, 70% of the mice survived 12 h after surgery, only 40% survived 24 h, and none survived 60 h. In contrast, LTL treatment significantly improved the survival of mice with sepsis ($P < 0.05$). However,

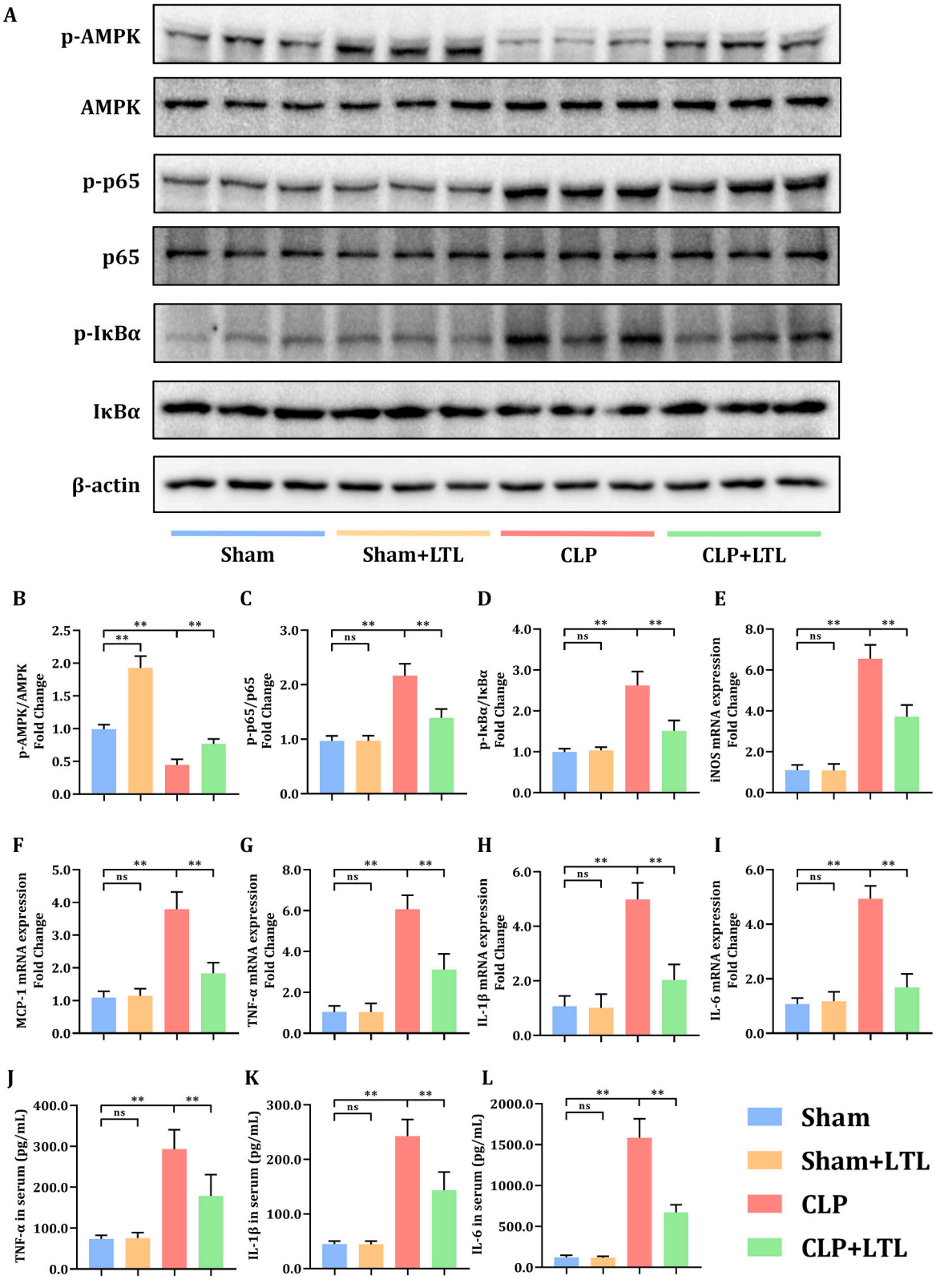

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Fig. 3. LTL activates AMPK to inhibit the NF-κB-induced transcription of inflammatory cytokines and iNOS in septic mice. (A) Western blot was used to measure the expression level of *p*-AMPK, AMPK, p-p65, p65, *p*-IκBα, IκBα, and β-actin. The original blots are presented in supplementary material. Quantification of *p*-AMPK/AMPK (B), p-p65/p65 (C), and *p*-IκBα/IκBα (D). n = 5, $^{**}P < 0.01$. PCR was used to detect the mRNA expression of iNOS (E), MCP-1 (F), TNF-α (G), IL-1β (H), and IL-6 (I). n = 5, $^{**}P < 0.01$. ELISA kit was used to measure the levels of TNF-α (J), IL-1β (K), and IL-6 (L) in serum. n = 5, $^{**}P < 0.01$.

AMPK inhibition could abolish the protective effects of LTL in survival rate ($P < 0.05$). The data indicate that AMPK plays a vital role in LTL-induced increase in survival rates in septic mice.

4. Discussion

In this study, the role of LTL in improving vascular hyporeactivity induced by sepsis and the possible mechanisms were examined. We found that LTL treatment could prevent vasoconstriction dysfunction, improve blood pressure, and reduce mortality of septic mice, in which AMPK/NF-κB pathway plays a vital role.

Sepsis is a severe disease with a poor prognosis and a high mortality rate [28]. In this disease, the decreased response of blood vessels to vasoconstrictors, such as norepinephrine and epinephrine, leads to vasoconstriction dysfunction, which often results in hemodynamic disorders and blood pressure decline, and even septic shock [29]. When septic shock occurs, due to the excessive vasodilation of the vascular bed, the circulating blood volume is seriously reduced, and the local tissue perfusion is very poor, which puts the patient's life at risk [30–32]. Therefore, preventing vascular hyporeactivity is essential for the treatment of sepsis.

The leading causes of vascular hyporeactivity in sepsis include inhibition of function and expression of the α1-adrenergic receptor, which is responsible for a poor vascular response to epinephrine and norepinephrine [10], and activation of iNOS, which leads to excessive production of NO [33]. Therefore, improving the α1-adrenergic receptor and inhibiting iNOS are of great significance for preventing vascular hyporeactivity in sepsis. Our results show that LTL treatment improves blood pressure and vascular reactivity to norepinephrine in mice, which is associated with the effects of LTL in up-regulating the expression of ADRA1A and inhibiting the expression of iNOS.

Evidence has shown that excessive inflammation caused by NF-κB activation could damage α1-adrenergic receptors and down-regulate their expression [34]. In addition, the activation of NF-κB is also closely related to the transcription and synthesis of iNOS in inflammatory diseases [35]. NF-κB is a critical component of the inflammatory response pathway, and p65 is the most important subunit of NF-κB [36]. Under normal conditions, IκBα binds to NF-κB and stays in the cytoplasm. When inflammatory response is activated, the phosphorylation of p65 and IκBα increases, and IκBα and NF-κB are separated. NF-κB enters the nucleus and initiates the transcription of inflammatory cytokines and iNOS [37,38]. Our study showed that LTL reduced CLP-induced increase in phosphorylation levels of NF-κB and IκBα and transcription of inflammatory cytokines and iNOS.

Recent studies have shown that LTL could improve the autophagy function of the myocardium by activating AMPK, thereby reducing septic cardiac function injury [20]. AMPK is a key molecule in regulating energy metabolism in cells, and suppression of AMPK leads to NF-κB activation which induces inflammatory responses [39,40]. Therefore, we hypothesized that LTL inhibited NF-κB activation by activating AMPK, thereby decreasing inflammation and iNOS expression. We found that LTL prevented the decline of AMPK phosphorylation levels induced by sepsis. To further clarify the role of AMPK in the protective effects of LTL in sepsis, we used CC to inhibit AMPK. We found that CC could abolish the protective effect of LTL. In other words, LTL inhibited inflammatory response and iNOS transcription induced by NF-κB by activating AMPK, thereby improving vasoconstriction and reducing mortality of mice.

Admittedly, Our study was limited by focusing on changes in the aortas of the mice. Arterioles and resistance vessels would be more critical than aortas in regulating the opening and closing of the vascular bed and blood pressure. Therefore, we will focus on the changes in arterioles in our future study. In addition, current study demonstrated that LTL could activate AMPK to inhibit NF-κB to exert its protective role in sepsis. Nevertheless, AMPK has many other roles, such as regulating autophagy, which will be explored in our future study.

All in all, our study shows that LTL activates AMPK to inhibit the NF-κB-induced transcription of inflammatory mediators and iNOS in sepsis, which reverses the decline of α1-adrenergic receptors and up-regulation of iNOS expression, improves vasoconstriction function and blood pressure, and ultimately reduces the incidence of septic shock and mortality of mice.

Author contribution statement

Bin Liu: Performed the experiments; Wrote the paper.

Hailong Su: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Funding statement

This research was funded by Hailong Su personally.

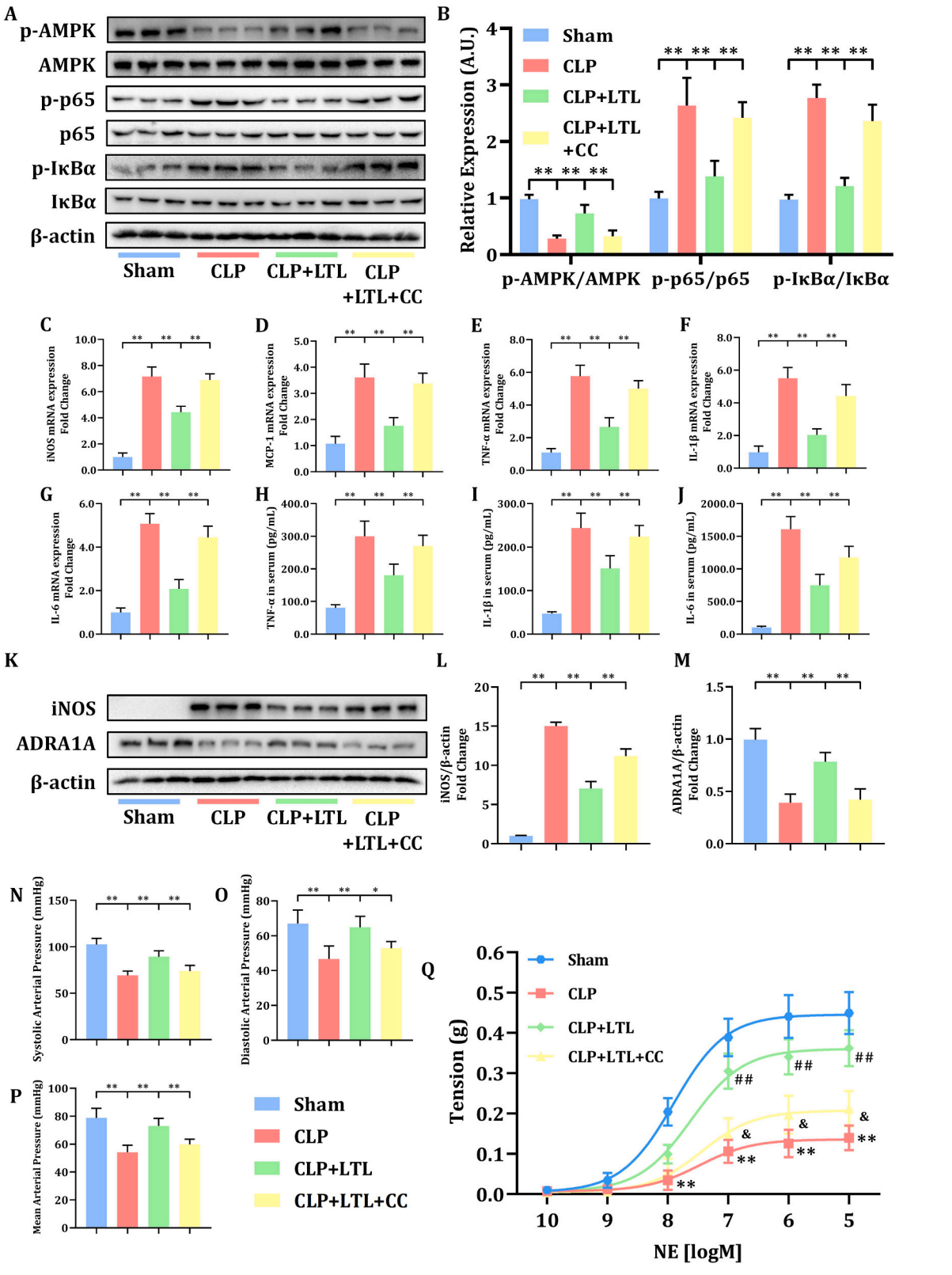

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Fig. 4. AMPK plays a crucial role in the protective effects of LTL against septic vascular hyporeactivity. (A) Western blot was used to examine the expression levels of *p*-AMPK, AMPK, p-p65, p65, *p*-IκBα, IκBα, and β-actin. The original blots are presented in supplementary material. (B) Quantification of *p*-AMPK/AMPK, p-p65/p65, and *p*-IκBα/IκBα. n = 5, $^{**}P < 0.01$. PCR was used to determine the mRNA expression of iNOS (C), MCP-1 (D), TNF-α (E), IL-1β (F), and IL-6 (G). n = 5, $^{**}P < 0.01$. ELISA kit was used to measure the levels of TNF-α (H), IL-1β (I), and IL-6 (J) in serum. n = 5, $^{**}P < 0.01$. (K) Western blot was used to examine the expression levels of iNOS, ADRA1A, and β-actin. The original blots are presented in supplementary material. Quantification of iNOS (L) and ADRA1A (M). n = 5, $^{**}P < 0.01$. SAP (N), DAP (O), and MAP (P) of mice was measured by noninvasive mice tail sphygmomanometer. n = 5, $^{*}P < 0.05$, $^{**}P < 0.01$. (Q) NE-induced vasoconstriction of aortas in all groups. n = 5, $^{**}P < 0.01$ compared with Sham group, $\#\#P < 0.01$ compared with CLP group, $\&P < 0.05$ compared with CLP + LTL group.

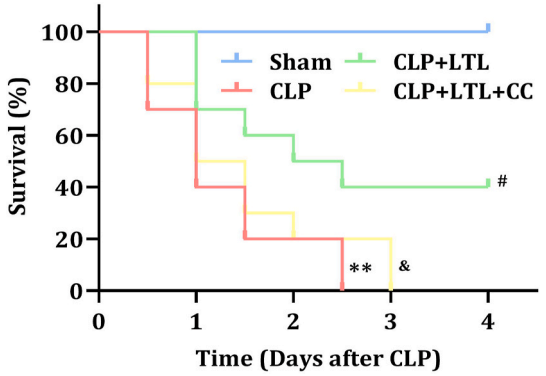

Fig. 5. AMPK plays a vital role in LTL-induced increase in survival rates in septic mice. After CLP surgery, the mice were observed for 4 days without any other operation except LTL and CC administration. n = 10, $^{**}P < 0.01$ compared with Sham group, $\#P < 0.05$ compared with CLP group, $\&P < 0.05$ compared with CLP + LTL group.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e13330.

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