H₂S attenuates sepsis-induced cardiac dysfunction via a PI3K/Akt-dependent mechanism

JIANPING LIU¹, JIANHUA LI², PEIGANG TIAN², BAHÄER GULI², GUOPENG WENG¹, LEI LI¹ and QINGHONG CHENG²

¹Department of Critical Care Medicine, Medical School of Shihezi University; ²Department of Critical Care Medicine, The First Affiliated Hospital, School of Medicine, Shihezi University, Shihezi, Xinjiang 832008, P.R. China

Received August 25, 2018; Accepted February 8, 2019

DOI: 10.3892/etm.2019.7440

Abstract. The heart is the most vulnerable target organ in sepsis, and it has been previously reported that hydrogen sulfide (H₂S) has a protective role in heart dysfunction caused by sepsis. Additionally, studies have demonstrated that the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway has a protective function during sepsis. However, the potential association between H₂S and PI3K/Akt in sepsis-induced cardiac dysfunction is unclear. Therefore, the PI3K inhibitor LY294002 was used to investigate the role of PI3K/Akt signaling in the protective effects of H₂S during sepsis-induced myocardial injury. A rat sepsis model was established using cecal ligation and puncture (CLP) surgery. Sodium hydrosulfite, a H₂S donor, was administered intraperitoneally (8.9 µmol/kg), and serum myocardial enzyme levels, inflammatory cytokine levels, cardiac histology and cardiomyocyte apoptosis were assessed to determine the extent of myocardial damage. The results demonstrated that exogenous H₂S reduced serum myocardial enzyme levels, decreased the levels of the inflammatory factors tumor necrosis factor (TNF)-α and interleukin (IL)-6, and increased the level of anti-inflammatory IL-10 following CLP. Staining of histological sections demonstrated that myocardial damage and cardiomyocyte apoptosis were alleviated by the administration of exogenous H₂S. Western blot analysis was used to detect phosphorylated and total PI3K and Akt levels, as well as NF-κB, B-cell lymphoma-2, Bcl-2-associated X protein (Bax) and caspase levels, and the results demonstrated that H₂S significantly increased PI3K and Akt phosphorylation. This indicated that the PI3K/Akt signaling pathway was activated by H₂S. Additionally, H₂S reduced Bax and caspase expression, indicating that apoptosis was inhibited, and decreased NF-κB levels, indicating that inflammation was reduced. Furthermore, the PI3K inhibitor LY294002 eliminated the protective effects of H₂S. In conclusion, the results of the current study suggest that exogenous H₂S activates PI3K/Akt signaling to attenuate myocardial damage in sepsis.

Introduction

Sepsis is a pathophysiological syndrome caused by infection and is a major public health problem (1). Its incidence rate has been reported to be 535 cases per 100,000 person-years and rising; in-hospital mortality remains high at 25-30% (2). Despite advances in care, sepsis is a major cause of mortality and critical illness in intensive care units worldwide (3). The heart is the most vulnerable organ during sepsis, and ~50% of patients with sepsis develop heart dysfunction (4,5). Hydrogen sulfide (H₂S) has been confirmed to serve an important role in the physiological and pathological processes of various systems, including the circulatory, nervous and respiratory systems (6). H₂S has a protective role in cells as a regulator of vascular tone, inflammatory responses and the clearance of reactive oxygen species, and it may even reduce the risk of myocardial ischemia (7,8). Multiple studies have confirmed that an appropriate dose of H₂S has cardiac protective effects (7,9,10), which may be associated with anti-apoptotic, anti-inflammatory and anti-oxidative mechanisms (11). A previous study by the present research team demonstrated that low doses of H₂S are able to improve the cardiac dysfunction caused by sepsis (12); however, the specific mechanisms involved are not clear.

Phosphoinositide-3-kinases (PI3Ks) are a conserved family of signaling transducers involved in the regulation of cell proliferation and survival. In studies of the mechanisms of cardiac dysfunction caused by sepsis, the PI3K/protein kinase B (Akt) signaling pathway has been proposed to have a key role in the development of dysfunction (13,14). Previous studies have revealed that PI3K and its downstream mediator, Akt, serve a role in sepsis via the regulation of cell activation, inflammation and apoptosis (15-17). Additionally, studies have...
demonstrated that H₂S is involved in the PI3K/Akt signaling pathway in pancreatitis and myocardial ischemia (18-20). However, it is unclear whether the protective effect of H₂S against myocardial damage during sepsis is associated with the PI3K/Akt pathway. Therefore, the current study used cecal ligation and puncture (CLP) to induce a rat model of sepsis, and the effect and mechanism of H₂S on myocardial injury in sepsis were evaluated by the administration of H₂S and inhibitors of PI3K in this model.

Materials and methods

Reagents. Sodium hydrosulfide (NaHS) was purchased from Sigma-Aldrich (Merck KGaA; Darmstadt, Germany; cat. no. 161527). LY294002 (a PI3K inhibitor) was purchased from ApexBio (Houston, TX, USA; cat. no. 8250-200 mg). Akt, phospho (p)-Akt and caspase-3 antibodies were obtained from Abcam (Cambridge, MA, USA; cat. nos. ab179463, ab192623 and ab13847, respectively). PI3K, p-PI3K and nuclear factor-κB (NF-κB) antibodies were obtained from Cell Signaling Technology, Inc. (Danvers, MA, USA; cat. nos. 4249, 4228 and 8242, respectively). B-cell lymphoma-2 (Bcl-2) and Bcl-2-associated X protein (Bax) antibodies were obtained from Boster Biological Technology, Ltd. (Wuhan, China; cat. nos. BA0412 and BA0315-2, respectively). Peroxidase-conjugated AffiniPure goat anti-rabbit immunoglobulin G (IgG), peroxidase-conjugated AffiniPure goat anti-mouse IgG and mouse anti-β-actin monoclonal antibodies were obtained from OriGene Technologies, Inc. (Beijing, China; cat. nos. ZB-2301, ZB-2305 and TA-09, respectively). In situ Cell Death Detection kit, POD was obtained from Roche Diagnostics GmbH (Mannheim, Germany; cat. no. 11684817910). Rat troponin I (TnI), interleukin (IL)-10, IL-6 and tumor necrosis factor-α (TNF-α) ELISA kits were provided by Elabscience Biotechnology Co., Ltd. (Wuhan, China; cat. nos. E-EL-R0055c, E-EL-R0016c, E-EL-R0015c and E-EL-R0019c, respectively).

Experimental animals. Adult male Sprague Dawley rats (7-8 weeks old; body weight 211.58±11.42 g) were provided by the animal center of Xinjiang Medical University [Urumqi, China; animal use license no. SYXK (Sinkiang) 2011-010101]. The animals were housed in cages with pathogen-free conditions, and free access to food and water, under a 12-h light/dark cycle at a room temperature of 22°C with 45% humidity, and normal air conditions (21% O₂, 78% N₂ and 0.03% CO₂). Chloral hydrate (350 mg/kg; intraperitoneal injection) was used to anesthetize rats for surgery and blood collection. Subsequently, rapid cervical dislocation was used to sacrifice the animals painlessly. All experimental protocols in this study complied with the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health (1996) and were approved by the Animal Protection and Use Committee of Shihezi University (Shihezi, China).

Animal model. Prior to surgery, all mice were fasted for 8 h, with water freely available. The CLP procedure was performed as previously described (21). Briefly, the rats were anesthetized with chloral hydrate and then secured to a sterile operating table. Under aseptic conditions, a 2-cm incision was made in the abdomen, and the cecum was exposed layer by layer. Prior to ligation of the cecum, feces were gently squeezed to the distal end of the cecum, then the cecum was ligated with a thin wire, and the cecum was pierced with an 18-gauge needle. Any remaining contents were extruded through the puncture site. Subsequently, the cecum was pushed back into the abdominal cavity, the abdominal cavity was closed and the layers were sutured. The sham group underwent the same procedure without CLP. All rats were resuscitated using 0.9% sodium chloride brine (subcutaneous injection, ~40 ml/kg), and following surgery, rats were returned their cages with free access to food and water.

Experimental grouping. Rats (n=56) were randomly divided into 7 groups as follows: Sham group, underwent exposure of the cecum, but not ligation and perforation; sham + NaHS group, received the sham procedure and was administered a 2-ml/kg intraperitoneal administration of 8.9 µmol/kg NaHS 1 h following the surgery; sham + LY294002 group, underwent the sham procedure and was administered a 2-ml/kg intraperitoneal injection of 40 mg/kg LY294002 following the surgery; CLP group, treated with the CLP surgery; CLP + NaHS group, underwent CLP and was administered NaHS (dosage and method as in the sham + NaHS group); CLP + LY294002 group, underwent CLP and was administered LY294002 following the surgery (dosage and method as in the sham + LY294002 group); CLP + NaHS + LY294002 group, underwent CLP and was administered an intraperitoneal injection of NaHS and LY294002 at the aforementioned doses. The doses of LY294002 and NaHS were selected according to previous studies (5,12). Following the procedures, all the rats were free to drink and eat, and 12 h later they were anesthetized again. The rat abdominal cavity was opened and blood was obtained from the abdominal aorta. Following coagulation, blood samples were centrifuged (3,500 x g, 15 min) and clear supernatants were collected. A portion of each serum sample was sent to the First Affiliated Hospital of Shihezi University for the measurement of creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH). The remaining samples were frozen at -80°C for subsequent analysis. The rats were sacrificed by cervical dislocation immediately after blood collection. Heart tissue was obtained immediately after sacrifice. Half of each heart tissue sample was sent to the First Affiliated Hospital of Shihezi University for the measurement of creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH). The remaining samples were frozen at -80°C for subsequent analysis. The rats were sacrificed by cervical dislocation immediately after blood collection. Heart tissue was obtained immediately after sacrifice. Half of each heart tissue sample was fixed in paraformaldehyde (4%) for histomorphological analysis, and the other half was stored at -80°C for Western blot analysis and other experiments.

Measurements of CK-MB, LDH and cardiac TnI (cTnI) levels in serum. Serum CK-MB and LDH levels in the rats were measured using an automatic biochemical analyzer (Modular DPP H7600; Roche Diagnostics, Basel, Switzerland). An ELISA kit was used to measure serum cTnI levels according to the manufacturer's instructions.

Measurement of inflammatory cytokines in serum. ELISA kits were used to determine the TNF-α, IL-6 and IL-10 levels in serum according to the manufacturer's instructions.

Measurement of H₂S levels. H₂S levels in serum were detected using a H₂S testing kit purchased from Nanjing Institute of
Bioengineering (Nanjing, China). H$_2$S reacts with zinc acetate, N,N-dimethylphenylenediamine and ammonium ferric sulfate in the kit to form methylene blue, which has a maximum absorption peak at 665 nm. The H$_2$S content was calculated by determining the absorbance value of methylene blue, and the plasma H$_2$S level is expressed in µmol/l.

**Histological analysis.** The tissue fixed in paraformaldehyde was conventionally embedded, sliced (4-µm thick) and dewaxed with xylene, then washed with ethanol at various levels. Subsequently, sections were stained with hematoxylin and eosin (H&E) at room temperature for ~2 min, dehydrated, dewaxed and sealed. Finally, images of sections were captured using an optical microscope (Olympus Corporation, Tokyo, Japan).

Western blot analysis. The frozen myocardial tissue was lysed with lysis buffer (cat. no. R0030; Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) on ice, and following protein extraction, a NanoDrop spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to determine the concentration of tissue proteins. A total of 10 µl of protein samples (40 mg/ml) were separated by SDS-PAGE using 10% gels, and then transferred to a polyvinylidene fluoride membrane. The membrane was blocked with 5% bovine serum albumin (cat. no. 4240GR100; BioRoxx; NeoFROXX GmbH, Hesse, Germany) for 2 h at room temperature. Membranes were incubated with antibodies against Akt (1:800 dilution), p-Akt (1:800 dilution), NF-κB (1:800 dilution), p-Igκ (1:800 dilution), p-Igκ (1:800 dilution), Bcl-2 (1:200 dilution), Bax (1:200 dilution), caspase-3 (1:500 dilution) and β-actin (1:1,000 dilution) at 4°C for 12-18 h. The membranes were then washed six times in TBS-Tween (5 min each time), and incubated with horseradish peroxidase-conjugated HRP (HRP) for 1 h at room temperature (β-actin was detected using HRPO-conjugated goat anti-mouse secondary antibody under the same conditions). Following incubation, the membranes were washed six times over a total of 30 min. The membranes were reacted with an enhanced chemiluminescence reagent (cat. no. WBKLS0100; EMD Millipore, Billerica, MA, USA) and developed using X-ray film. The band intensities were quantified using ImageJ software (Java 1.6.0.24; version 1.51k; National Institutes of Health, Bethesda, MD, USA).

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Apoptosis of myocardial cells was determined by a TUNEL assay using the in situ Cell Death Detection kit, POD. Slices (4-µm thick) of heart tissue were incubated in a 68°C oven for 1 h, and then dewaxed in xylene and gradient alcohol. The sliced tissue was then washed three times with PBS (5 min each wash). After washing, the sections were placed in hydrogen peroxide and soaked for 10 min. Subsequently, further washes with PBS were performed, and then sections were steamed in a pressure cooker for 5 min with citrate buffer at pH 6.0, and washed again three times with PBS (5 min each wash). Samples were incubated with 50 µl TUNEL reaction mixture (1:12) at 37°C for 1 h in the dark. The slides were then rinsed three times with PBS, 50 µl POD substrate was added to each section, and the samples were incubated at 37°C for 30 min in the dark. Following incubation, the sections were washed three times with PBS, and then 50 µl diaminobenzidine coloring solution was added dropwise, and the color development was stopped with distilled water when an appropriate degree of coloration was achieved. The sections were counterstained with hematoxylin for 2 min, then dehydrated in alcohol and sealed with neutral gum. Finally, a light microscope was used to calculate the apoptotic index. Dark brown staining indicated TUNEL-positive cells, and five high power fields of the slices were randomly selected to calculate the proportion of positive cells.

**Statistical analysis.** Each experiment was repeated three times. All data were analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). All data are expressed as the mean ± standard error. The data were analyzed using one-way analysis of variance followed by least significant difference tests. P<0.05 was considered to indicate a statistically significant difference.

**Results**

Confirmation of the rat model of sepsis. The rats in the CLP group exhibited the behavioral characteristics of sepsis, including malaise, fever, chills, piloerection, generalized weakness and reduced gross motor activity, as well as weight loss and increased proinflammatory cytokine levels in the serum. One mortality in the CLP group and two in the CLP + LY294002 group were observed.

Effects of NaHS on myocardial enzyme serum levels. As presented in Fig. 1, CK-MB, LDH and cTnI concentrations exhibited no significant differences among the sham, sham + NaHS and sham + LY groups. There was a significant increase in serum CK-MB, LDH and cTnI in the CLP group compared with the sham group, and rats in the NaHS treatment group exhibited reductions in CK-MB, LDH and cTnI levels compared with those in the CLP group. However, these reductions were attenuated by LY294002 (a PI3K/Akt pathway-specific inhibitor).

NaHS reduces inflammatory reactions in septic rats. Inflammatory factors were measured in the serum of model rats. Following CLP, the levels of the inflammatory factors TNF-α, IL-6 and IL-10 in the serum of rats were increased significantly compared with those in the sham group (P<0.05; Fig. 2). The administration of NaHS decreased the levels of TNF-α and IL-6 in the serum compared with those in the CLP group (P<0.05), whereas the level of IL-10 was significantly increased. However, the administration of LY294002 eliminated the effects of NaHS (P<0.05 vs. CLP + NaHS group; Fig. 2).

H$_2$S levels. Although level of H$_2$S was increased in the CLP group, there was no significant difference in H$_2$S levels between the CLP and sham groups. Following the administration of NaHS, the serum H$_2$S content was increased significantly compared with that in the CLP group (P<0.05; Fig. 3). This finding indicated that the administration of NaHS increases serum H$_2$S content (Fig. 3).
NaHS alleviates myocardial damage caused by sepsis. H&E staining demonstrated that the sham group had normal myocardial fiber morphology and a regular arrangement of myocardial cells, with no abnormalities of the interstices and microvessels (Fig. 4). However, myocardial cells were disordered in the CLP group, with broken myocardial fibers, and parts of the myocardium exhibited vacuolization changes and inflammatory cell infiltration. The administration of NaHS reduced the degree of myocardial damage, and LY294002 eliminated the protective effect of NaHS (Fig. 4).

NaHS reduces myocardial apoptosis in septic rats. TUNEL staining was performed to investigate the effect of NaHS on myocardial apoptosis in rats with sepsis (Fig. 5). Myocardial apoptosis was significantly increased in the CLP group compared with the sham group (P<0.05). However, following the administration of NaHS, the apoptosis rate of cardiomyocytes was significantly reduced compared with that in the CLP group, and LY294002 treatment reversed these alterations (Fig. 5).

Effect of NaHS on PI3K, Akt, NF-κB, Bcl-2, Bax and caspase-3. The p-PI3K/PI3K and p-Akt/Akt ratios, and the levels of NF-κB, Bcl-2, Bax and caspase-3 were determined using western blot analysis to further understand the protective mechanism of NaHS against the myocardial injury caused by sepsis. The p-PI3K/PI3K and p-Akt/Akt ratios, and NF-κB, Bax and caspase-3 levels were increased by CLP compared with those in the sham group, whereas the level of Bcl-2...
was decreased (Figs. 6 and 7). Following the administration of NaHS, the phosphorylation of PI3K and Akt was further increased and the expression of Bcl-2 was increased compared with that in the CLP group, whereas the expression levels of NF-κB, Bax and caspase-3 were decreased. The addition of LY294002 eliminated these NaHS-induced effects.

**Discussion**

As reported in our previous study, exogenous H₂S can improve sepsis-induced heart dysfunction (12). In the current study, exogenous H₂S significantly reduced the expression of myocardial injury markers (CK-MB, LDH and cTnI), reduced the expression of pro-inflammatory factors (TNF-α and IL-6) and induced the expression of the anti-inflammatory factor IL-10 following CLP. Furthermore, the apoptosis of cardiomyocytes was reduced by H₂S in the CLP-induced sepsis model. However, the effects of exogenous H₂S on myocardial injury in sepsis were counteracted by the PI3K signaling pathway inhibitor LY294002, indicating that the PI3K/Akt signaling pathway may partially mediate the effect of H₂S.

Sepsis is caused by a dysfunctional response to infection in the host, resulting in life-threatening organ dysfunction (22). Sepsis has high morbidity and mortality rates, and significant treatment costs in developed and developing countries (23). During sepsis, various factors, including cytokines, eicosanoids, reactive oxygen species and nitrogen species, accelerate the development of the symptoms observed in patients with sepsis and cause severe systemic inflammatory reactions, which can ultimately lead to multiple organ failure (24). The heart is one of the most vulnerable target organs in sepsis (4,5). Currently, there is no specific treatment for sepsis-induced cardiac insufficiency.

H₂S is one of a family of gaseous signaling molecules, which includes nitric oxide (NO) and carbon monoxide. H₂S is typically considered to be a toxic gas; however, in the past 30 years, the understanding of the effects H₂S has changed markedly (25). Numerous in vitro and in vitro experiments
have demonstrated that H₂S has protective effects in various tissues and cells (26-28). Abdelrahman et al (29) reported that H₂S has a protective effect on CLP-induced cardiac dysfunction, by reducing tachycardia, mortality, serum CK-MB, cTnI, C-reactive protein and LDH, and cardiac and aortic malondialdehyde levels. Chen et al (30) demonstrated that the exogenous administration of NaHS ameliorated septic-induced renal dysfunction by inhibiting inflammation and oxidative stress through the Toll-like receptor 4/NACHT, LRR and PYD domains-containing protein 3 signaling pathway. Furthermore, Ahmad et al (31) reported that the intraperitoneal injection of an appropriate dose of H₂S improved the survival rate of septic rats and reduced the inflammatory reaction. This finding is supported by the results of the present study, demonstrating that the exogenous administration of NaHS ameliorated sepsis by attenuating inflammation during septic shock. Due to the increase in iNOS expression, the level of NO is also increased, which can induce cystathionine γ-lyase expression, resulting in higher H₂S levels (35). No significant difference in H₂S level between the sham and CLP groups was observed and, although the production of endogenous H₂S was increased following the occurrence of sepsis, the increase was not significant. Following the administration of exogenous NaHS, a statistically significant increase in the serum level of H₂S was detected, indicating that the administration of NaHS produced the desired effect.

CK, CK-MB and LDH are indicators used for the diagnosis and detection of myocardial injury (36,37). cTnI and cTnT have high specificity, and Tn levels are directly proportional to the degree of myocardial damage (38). In the current study, the analysis of serum myocardial injury markers in each group revealed that myocardial enzymes were significantly elevated in the sepsis group, indicating that sepsis had an adverse effect on the myocardium. The intraperitoneal injection of NaHS reduced the serum myocardial enzyme level. Similar changes in Tn levels were observed. H&E staining of the heart tissue revealed that the sham-operated group exhibited tightly arranged myocardial fibers with uniform coloring, and no edema, congestion or
Following CLP, the presence of edema, degeneration and myocardial fiber breakage was observed in parts of the myocardial tissue. Interstitial blood vessels were congested and inflammatory cells had infiltrated the tissue. The administration of NaHS reduced the degree of myocardial damage compared with that in the sepsis group. The results of Abdelrahman et al. (29) support the findings of the present study.

Following the onset of sepsis, a large amount of endotoxin is released, causing a series of pro-inflammatory factor cascades to be activated, including TNF-α and IL-1 (39,40). Among the pro-inflammatory cytokines, TNF-α induces cardiomyocyte apoptosis (41). A previous study reported that the infusion of TNF-α monoclonal antibodies to septic mice transiently improves ventricular function, suggesting that TNF-α may reduce damage to the myocardium during sepsis (42). Another study demonstrated that the inflammation and apoptosis induced during sepsis is associated with the production and release of reactive oxygen species and inflammatory mediators. These substances may be involved in the activation of inducible pathways, such as NF-κB (43). Additionally, sepsis induces the expression of iNOS, which in turn produces high levels of NO. Excessive NO may cause cytotoxicity due to an increase in peroxynitrite, which can lead to cardiac dysfunction (44). In the current study, the CLP-induced inflammatory responses and
cytotoxicity were characterized by elevated levels of TNF-α, IL-6, CK-MB and LDH in serum. Bcl-2 was decreased, and Bax and caspase levels were increased by CLP, and the TUNEL assay confirmed that the apoptosis rate was increased following CLP. These results indicated that CLP induced inflammation and apoptosis. Furthermore, the administration of NaHS to rats that received CLP reduced the levels of the inflammatory response markers in the serum and reduced cardiomyocyte apoptosis. These results indicated that H₂S ameliorated the degree of sepsis-induced myocardial damage, potentially via anti-inflammatory and anti-apoptotic effects.

In numerous studies of sepsis, PI3K and downstream Akt have been demonstrated to be involved in the regulation of cell activation, inflammation and apoptosis (5,45,46). Studies have reported that heat shock protein protein A12B and heat shock protein 27 can attenuate cardiac dysfunction caused by endotoxins. The mechanism of this effect may be associated with the activation of PI3K/Akt (47,48). Additionally, other studies have demonstrated that H₂S activates the PI3K/Akt pathway (18,49). The results of the current study suggest that the exogenous administration of H₂S significantly increases PI3K and Akt phosphorylation in rats with CLP-induced sepsis. In order to confirm this hypothesis, a PI3K/Akt pathway specific inhibitor, LY294002, was used. The results revealed that the anti-inflammatory and anti-apoptotic effects of H₂S were eliminated by the intraperitoneal injection of LY294002 in the model rats.

H₂S has been widely used in animal studies; however, it is not clear whether H₂S has beneficial or damaging effects in vivo. Currently, clinical experiments have confirmed that H₂S is anti-inflammatory, reduces myocardial fibrosis and protects the myocardium (50). However, different H₂S donors may have different mechanisms of action (51). Future studies are required to investigate the specific mechanisms of H₂S donors in complex cardiovascular signaling pathways.

In conclusion, the present study demonstrated that exogenous H₂S therapy provides an important protective effect against sepsis-induced myocardial damage via activation of the PI3K/Akt pathway. H₂S inhibits inflammation and apoptosis, and reduces myocardial dysfunction during sepsis.

Acknowledgements

Not applicable.

Funding

This study was supported by a grant from XPCC Science and Technology Research and Achievement Transformation Project (grant no. KC0038).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JPL, JHL and QC jointly conceived and designed this study. JPL, GW and LL conducted the animal experiment. JPL analyzed the data and completed the first draft. JHL, PT, BG and QC reviewed and improved the paper. PT and BG revised the manuscript critically for important intellectual content. All authors read and approved the manuscript.

Ethics approval and consent to participate

The present study was approved by the Animal Protection and Use Committee of Shihezi University (Shihezi, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315: 801-810, 2016.
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC and Reinhart K; International Forum of Acute Care Trialists: Assessment of Global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 193: 259-272, 2016.
3. Vincent JL, Marshall JC, Namendys-Silva SA, VinFrancisco B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njmji H, et al: Assessment of the worldwide burden of critical illness: The intensive care over nations (ICON) audit. Lancet Respir Med 2: 380-386, 2014.
4. Zaky A, Deem S, Bendjeldi Y and Treggiari MM: Characterization of cardiac dysfunction in sepsis: An ongoing challenge. Shock 41: 12-24, 2014.
5. An R, Zhao L, Xi C, Li H, Shen G, Liu H, Zhang S and Sun L: Melatonin attenuates sepsis-induced cardiac dysfunction via a PI3K/Akt-dependent mechanism. Basic Res Cardiol 111: 8, 2016.
6. Stein A and Bailey SM: Redox Biology of Hydrogen Sulfide: Implications for Physiology, Pathophysiology and Pharmacology. Redox Biol 1: 32-39, 2013.
7. Shen Y, Shen Z, Luo S, Guo W and Zhu YZ: The cardioprotective effects of hydrogen sulfide in heart diseases: From molecular mechanisms to therapeutic potential. Oxid Med Cell Longev 2015: 925167, 2015.
8. Hu Y, Chen X, Pan TT, Neo KL, Lee SW, Khin ES, Moore PK, Bian JS: Cardioprotection induced by hydrogen sulfide preconditioning involves activation of ERK and PI3K/Akt pathways. Pflugers Arch 455: 607-616, 2008.
9. Dommarruma E, Trivedi RK and Lefer DJ: Protective Actions of H2S in acute myocardial infarction and heart failure. Compr Physiol 7: 583-602, 2017.
10. Patel VB, McLean BA, Chen X and Oudit GY: Hydrogen sulfide: An old gas with new cardioprotective effects. Clin Sci (Lond 128: 121-323, 2015.
11. Calvert JW, Coetzee WA and Lefer DJ: Novel insights into hydrogen sulfide-mediated cytoprotection. Antioxid Redox Signal 12: 1203-1217, 2010.
12. Li X, Cheng Q, Li J, He Y, Tian P and Xu C: Significance of hydrogen sulfide in sepsis-induced myocardial injury in rats. Exp Ther Med 14: 2153-2161, 2017.
13. Zhai J and Guo Y: Paeoniflorin attenuates cardiac dysfunction in endotoxicemic mice via the inhibition of nuclear factor-κB. Biomed Pharmacother 80: 200-206, 2016.
14. Zhao P, Wang Y, Zeng S, Lu J, Jiang TM and Li YM: Protective effect of astragalside IV on lipopolysaccharide-induced cardiac dysfunction via downregulation of inflammatory signaling in mice. Immunopharmacol Immunotoxicol 37: 428-433, 2015.
15. Luo K, Long H, Xu B and Luo Y: Apelin attenuates postburn sepsis via a phosphatidylinositol 3-kinase/protein kinase B dependent mechanism: A randomized animal study. Int J Surg 21: 22-27, 2015.
16. Williams DL, Li C, Ha T, Ozment-Skelton T, Kalbleisch JC, Preiszer J, Brooks L, Breuel K and Schweitzer JB: Modulation of the phosphoinositide 3-kinase pathway alters innate resistance to polymicrobial sepsis. J Immunol 172: 449-458, 2004.

17. Sun N, Wang H, Ma L, Lei P and Zhang Q: Ghrelin attenuates brain injury in septic mice via PI3K/Akt signalling activation. Brain Res Bull 124: 278-285, 2016.

18. Shao M, Zhuo C, Jiang R, Chen G, Shan J, Ping J, Tian H, Wang L, Lin C and Hu L: Protective effect of hydrogen sulphide against myocardial hypertrophy in mice. Oncotarget 8: 22344-22352, 2017.

19. Tamizhselvi R, Moore PK and Bhatia M: Hydrogen sulfide acts as a mediator of inflammation in acute pancreatitis: In vitro studies using isolated mouse pancreatic acinar cells. J Cell Mol Med 11: 315-326, 2007.

20. Liu Y, Liao R, Qiang Z and Zhang C: Pro-inflammatory cytokine-driven PI3K/Akt/Spl signalling and H2S production facilitates the pathogenesis of severe acute pancreatitis. Biosci Rep 37: pii: BSR20160483, 2017.

21. Ritrisch D, Huber-Lang MS, Flierl MA and Ward PA: Immunodenervation of experimental sepsis by cecal ligation and puncture. Nat Proto 4: 31-36, 2009.

22. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 43: 304-377, 2017.

23. Cohen J: The immunopathogenesis of sepsis. Nature 420: 885-891, 2002.

24. Kosir M and Podbregar M: Advances in the diagnosis of sepsis: Hydrogen sulfide as a prognostic marker of septic shock severity. Ejjfcse 28: 134-141, 2017.

25. Lavu M, Bhushan S and Lefer DJ: Hydrogen sulfide-mediated cardioprotection: Mechanisms and therapeutic potential. Clin Sci (Lond) 120: 219-229, 2011.

26. Zhang M, Shan H, Wang T, Liu W, Wang Y, Wang L, Zhang L, Chang P, Dong W, Chen X and Tao L: Dynamic change of hydrogen sulfide after traumatic brain injury and its effect in mice. Neurochem Res 38: 714-725, 2013.

27. Li L, Xiao T, Li F, Li Y, Zeng O, Liu M, Liang B, Li Z, Chu C, Zhang M, Shan H, Wang T, Liu W, Wang L, Zhang L, Chao R, Liu Y, Zhang H, Vray B and Preiser JC: Hydrogen sulfide reduces renal tissue fibrosis by regulating autophagy in diabetic rats. Mol Med Rep 16: 1715-1722, 2017.

28. Bhatia M, Wong FL, Fu D, Lau HY, Mochchhal SM and Moore PK: Role of hydrogen sulfide in acute pancreatitis and associated lung injury. FASEB J 19: 623-629, 2005.

29. Abdelrahman BS, El-Awady MS, Nader MA and Ammar EM: Hydrogen sulfide ameliorates cardiovascular dysfunction induced by cecal ligation and puncture in rats. Hum Exp Toxicol 34: 953-964, 2015.

30. Chen Y, Jin S, Teng X, Hu Z, Zhang Z, Qiu X, Tian D and Wu Y: Hydrogen Sulphide Attenuates LPS-Induced Acute Kidney Injury by Inhibiting Inflammation and Oxidative Stress. Oxid Med Cell Longev 2018: 671212, 2018.

31. Ahmad A, Druzhyna N and Szabo C: Delayed treatment with hydrogen sulfide protects against sepsis by inhibiting Toll-like receptor via phosphoinositide 3-kinase activation. J Infect Dis 209: 1668-1677, 2014.

32. Gao M, Ha T, Zhang X, Wang X, Liu L, Kalbleisch J, Singh K, Williams D and Li C: The Toll-like receptor inhibitor ligand, CpG oligodeoxynucleotide, attenuates cardiac dysfunction in polymicrobial sepsis, involving activation of both phosphoinositide 3 kinase/Akt and extracellular-signal-related kinase signaling. J Pharmacol Exp Ther 357: 99-115, 2015.

33. Zhou H, Qian J, Li C, Li J, Zhang X, Ding Z, Gao X, Han Z, Cheng Y and Liu L: Attenuation of cardiac dysfunction by HSPA12B in endotoxin-induced sepsis in mice through a PI3K-dependent mechanism. Cardiovasc Res 89: 109-118, 2011.

34. You W, Min X, Zhang X, Qian B, Pang S, Ding Z, Li C, Gao X, Di R, Cheng Y and Liu L: Cardiac-specific expression of heat shock protein 27 attenuated endotoxin-induced cardiac dysfunction and mortality in mice through a PI3K/Akt-dependent mechanism. Shock 32: 108-117, 2009.

35. Tamizhselvi R, Sun J, Koh YH and Bhatia M: Effect of hydrogen sulfide on the phosphatidylinositol 3-kinase-protein kinase B pathway and on caerulein-induced cytokine production in isolated mouse pancreatic acinar cells. J Pharmacol Exp Ther 329: 1166-1177, 2009.

36. Hackfort BT and Mishra PK: Emerging role of hydrogen sulfide-microRNA crosstalk in cardiovascular diseases. Am J Physiol Heart Circ Physiol 310: H802-H812, 2016.

37. Chatzianastasiou A, Bilić SI, Andreoudi I, Efentakis P, Kaluderic N, Wood ME, Whiteman M, Di Lisa F, Daiber A, Manolopoulos VG, et al: Cardioprotection by H2S Donors: Nitric oxide-dependent and independent mechanisms. J Pharmacol Exp Ther 358: 431-440, 2016.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.