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Effect of hydrogen sulfide on cardiomyocyte apoptosis in rats with myocardial ischemia-reperfusion injury *via* the JNK signaling pathway

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Abstract. – OBJECTIVE: The aim of this study was to explore the influence of hydrogen sulfide (H_2S) on cardiomyocyte apoptosis in rats with myocardial ischemia-reperfusion injury *via* the c-Jun N-terminal kinase (JNK) pathway.

MATERIALS AND METHODS: A total of 60 normal female Sprague-Dawley (SD) rats aged 38 weeks were divided into 3 groups, including the sham operation group (n=20), ischemia group (n=20) and ischemia + sodium hydrosulfide (NaHS) group (n=20). Subsequently, differences in cardiac function, the morphology of myocardial tissues, protein expression of JNK2, the content of plasma H_2S and malondialdehyde (MDA), the activity of superoxide dismutase (SOD), cystathionine-γ-lyase (CSE) and glutathione peroxidase (GSH-Px) were analyzed among rats in all groups.

RESULTS: Left ventricular diastolic pressure (LVDP) and maximum rate of pressure rise/fall (± dP/dtmax) were the highest in of rats of the sham operation group and the lowest in the ischemia group. Meanwhile, they were significantly elevated in the ischemia + NaHS group compared with those in the ischemia group ($p<0.01$). Left ventricular end-diastolic pressure (LVEDP) was the lowest in rats of the sham operation group and the highest in the ischemia group. Similarly, it decreased markedly in the ischemia + NaHS group compared with the ischemia group ($p<0.01$). Compared with the sham operation group, the perinuclear space in the myocardium was gradually larger, the arrangement of fibers became significantly more disordered, and the damage of mitochondrial cristae and membrane was remarkably more severe in rats in the ischemia group. Compared with the ischemia group, the above-mentioned conditions of rat cardiomyocytes were markedly improved ($p<0.01$). Meanwhile, the content of H_2S and activity of CSE in the cardiomyocytes were altered in rats of the ischemia + NaHS group. Western blotting results indicated that, compared with the sham operation group, both the ischemia group and ischemia + NaHS group showed significantly up-regulated protein expression level of phosphorylated JNK2, with the highest level in the ischemia group. The content of MDA in rat myocardial tissues was markedly higher in the ischemia group than that of the ischemia + NaHS group, with the lowest level in the sham operation group ($p<0.01$). Additionally, the activity of SOD and GSH-Px in rat myocardial tissues was remarkably worse in the ischemia group than that of the ischemia + NaHS group, and it was the strongest in the sham operation group ($p<0.01$).

CONCLUSIONS: H_2S inhibits the activity of the JNK pathway, decreases its phosphorylation level and down-regulates the protein expression level of JNK2, thereby protecting against myocardial ischemia-reperfusion injury.

Key Words:
Hydrogen sulfide, JNK, Myocardial ischemia.

Introduction

Due to the decline of physical function, the incidence rate of heart diseases is higher in the elderly. As one of the most common diseases, coronary heart disease can cause myocardial infarction, heart failure and even sudden death[1]. Currently, it has been found that damaged myocardium can be improved with some treatments. Among them, the main approach is myocardial reperfusion, which can reduce the mortality rates of myocardial ischemia-induced diseases. However, myocardial reperfusion has its drawback that it can induce many other diseases such as reperfusion arrhythmia[2-4]. Myocardial ischemia is a common manifestation of coronary heart diseases. Myocardial ischemia-reper-

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fusion injury refers to the phenomenon that the damaged area of ischemic myocardial tissues becomes larger owing to sudden blood circulation[5]. The c-Jun N-terminal kinase (JNK) signaling pathway plays an important role in human bodies. JNK is activated through phosphorylation of its amino acid residue, enabling JNK in rat cells to enter the nucleus[6]. In mammals, JNK proteins are formed *via* binding of JNK 1, 2 and AP-1-like sites[7]. Hydrogen sulfide (H_2S) has been regarded as a colorless poisonous gas with a particular odor. It will destroy the central nervous system once being inhaled by humans or animals[8]. Since the last century, scientists have found that H_2S can induce long-term potentiation in the hippocampus. Large numbers of studies[9,10] have corroborated that H_2S is extensively effective in medical treatment. In viviparous animals, endogenous H_2S is generated *via* the metabolism of sulfur-containing amino acids, such as L-cysteine. In this process, both cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) are key enzymes. In recent years, it has been discovered that H_2S can dilate vessels, regulate myocardial contraction and inhibit the proliferation of vascular smooth muscle cells in the cardiovascular system[11].

Therefore, in the present study, the female SD rat model of myocardial ischemia was first surgically established. The expression level of JNK protein, CSE activity, malondialdehyde (MDA) content and superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity in rat myocardial tissues were detected in the sham operation group, ischemia group and ischemia + sodium hydrosulfide (NaHS) group, respectively. The aim of this study was to investigate the relationships of NaHS, an H_2S donor, and JNK signals with myocardial ischemia symptoms.

Materials and Methods

Animal Modeling and Grouping

A total of 60 female Sprague-Dawley (SD) rats aged 38 weeks and weighing roughly 300 g were purchased. This study was approved by the Animal Ethics Committee of Peking Union Medical College Hospital Animal Center. After anesthesia *via* intraperitoneal injection of anesthetics, 40 rats were placed flatly with the face up. Subsequently, the hair was shaved to expose the abdomen and chest, followed by disinfection using alcohol. The skin between the 2nd and the 5th rib in the left chest was cut to expose the heart. After gently removing the heart, the left coronary artery was ligated by threading under the left atrium and ventricle. Once the operation was completed, the heart of rats was slowly replaced into the body, and the skin was sutured. Finally, cardio-pulmonary resuscitation was performed in rats until they breathed smoothly. This indicated that they could survive.

Experimental rats were divided into three groups, including the sham operation group (healthy rats, n=20), ischemia group (myocardial ischemia model, n=20) and ischemia + NaHS group (myocardial ischemia model + NaHS, n=20). Sham operation group: the abdomen of rats was cut open and sutured without treating the heart. 4 h later, the rats were intra-abdominally injected with normal saline (3 mL/kg). Ischemia group: 4 h after modeling, the rats with injected with normal saline (3 mL/kg) *via* the abdomen. Ischemia + NaHS group: 4 h after modeling, the rats were intra-abdominally injected with NaHS (3 mg/kg). 48 h after operation, rats in the three groups were sacrificed, and the cells were selected as experimental materials.

Instruments and Reagents

NaHS was purchased from Sigma-Aldrich, (St. Louis, MO, USA), PowerLab polygraph from Mettler Toledo (Columbus, OH, USA) and malondialdehyde (MDA) and the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

Observation of Cardiac Function in Rats of Each Group

Blood pressure was measured using PowerLab polygraph. The pressure transducer was connected to the catheter and inserted into the left cervical artery of rats in the three groups. Another catheter was inserted into the right ventricle of female SD rats. Finally, the left ventricular diastolic pressure (LVDP), the maximum rate of pressure rise/fall ($\pm dP/dt_{max}$) and left ventricular end-diastolic pressure (LVEDP) were measured.

Observation of Morphological Changes of Rat Myocardial Tissues

Heart apex tissues of SD rats were selected and cleansed using cold normal saline. Subsequently, the tissues were cut into 8 mm^3 positive-cube

blocks using a special scalpel on the operating table. The blocks were then fixed with 4% glutaraldehyde, washed with dimethylarsinic acid three times, mounted in 1% osmium tetroxide and washed again. Next, the blocks were dehydrated using acetone, soaked in epoxy resin, sliced and stained with uranyl acetate and lead citrate. Finally, the changes in myocardial ultrastructure were observed under a transmission electron microscope.

Determination of Content of Plasma Hydrogen Sulfide (H_2S)

The content of H_2S was measured by removing proteins. Briefly, the tube was added with 0.5 mL of 1% zinc acetate and 0.1 mL of plasma. Subsequently, they were stirred evenly until the zinc acetate precipitation was observed. Then, 0.5 mL of 7.2 mol/L hydrochloric acid containing 20 mmol/L N, N-dimethyl-amphetamine sulfate and 0.4 mL of 1.2 mol/L hydrochloric acid containing 30 mmol/L ferric trichloride were added to the products, followed by incubation at normal temperature for 20 min. Then, the mixture was added with 1 mL of 10% trichloroacetic acid to settle proteins. After centrifugation at 6,000 rpm for 5 min, a clear supernatant solution was obtained. The absorbance of the supernatant was measured using a spectrophotometer, and the content of H_2S was calculated.

Detection of Protein Expression of JNK2 via Western Blotting

After the operation, cardiac tissues were extracted from rats in each group. The tissues were lysed using the protein lysate, followed by centrifugation at 12,000 g for 15 min. The supernatant was collected and added with the protein loading dyes. Next, extracted proteins were separated by dodecyl sulfate, sodium salt-polyacrylamide gel electrophoresis (SDS-PAGE) gel at 80 μg/well and transferred onto membranes at 25°C for 2 h. After washing with a Tris-Buffered Saline and Tween solution (TBST; Sigma-Aldrich, St. Louis, MO, USA), the membranes were sealed in 3% skim milk powder solution. Then, the membranes were incubated with phosphorylated JNK2 (1:1,000) primary antibody at 4°C overnight. After washing with TBST, the membranes were incubated with the corresponding secondary antibody for 1 h. Immunoreactive bands were visualized using diaminobenzidine (DAB) development solution (Solarbio, Beijing, China).

Determination of Cystathionine-γ-Lyase (CSE) Activity in Myocardial Tissues

The right ventricular anterior wall tissues of SD rats were first obtained. After washing with cold normal saline, the tissues were absorbed dry with filter paper. The myocardial tissues of SD rats were weighed using a scale, and precooled 50 mmol/L potassium phosphate buffer (pH=6.8) was added at the weight-to-volume ratio of 10:1. Subsequently, they were stirred evenly and centrifuged for 10 min. Finally, a certain amount of solution was taken to determine the activity of CSE.

Determination of SOD and GSH-Px Activity and MDA Content in Myocardial Tissues

The activity of SOD was measured by the method of xanthine oxidases. Superoxide anion radical (O^{2-}) was produced through the reaction system containing xanthine and xanthine oxidases. Nitrite was then generated through the oxidation reaction between O^{2-} and hydroxylamine. Next, the nitrite was coated with the developer, followed by incubation for a while. It could be observed that the nitrite was purplish red. The absorbance of nitrite was measured using a visible spectrophotometer. MDA in myocardial cells of rats can bind to thiobarbituric acid to produce red substances. Therefore, the content of MDA was determined *via* thiobarbituric acid. GSH-Px reacted with dithionitrobenzoic acid to produce 5-thionitrobenzoate anion. After development using the developer, the product turned yellow. The absorbance at 412 nm was measured, and the activity of GSH-Px was finally calculated.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 13.0 (SPSS, Chicago, IL, USA) software was used for all statistical analysis. *t*-test was performed to compare the differences in the activity of SOD, GSH-Px and CSE and the content of MDA and H_2S among the sham operation group, ischemia group and ischemia + NaHS group. One-way analysis of variance (ANOVA) test was used to compare the differences among different groups, followed by Post-Hoc Test (Least Significant Difference). $p<0.01$ was considered statistically significant.

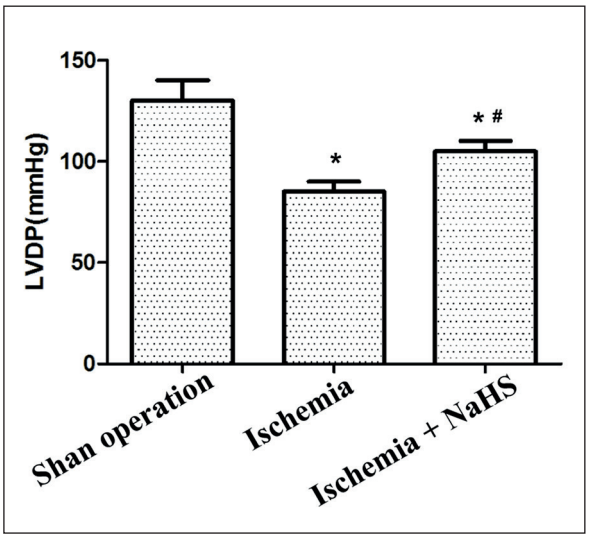

Figure 1. Comparison of LVDP among all groups of rats. *: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

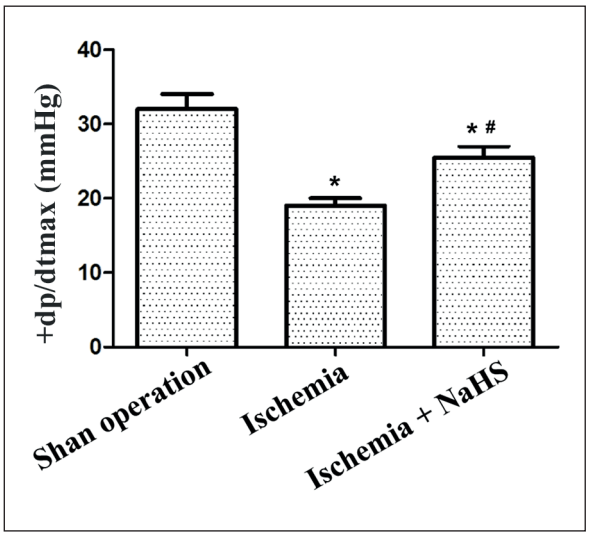

Figure 3. Comparison of $\pm dP/dt_{max}$ among all groups of rats. *: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

Results

Comparison of Cardiac Function Among Rats in All Groups

The rats in the ischemia group showed significantly lower LVDP than the sham operation group ($p<0.01$). However, the LVDP of rats in the ischemia + NaHS group was markedly higher than that of the ischemia group ($p<0.01$). Compared with the sham operation group, the LVEDP of rats was significantly elevated in the ischemia group ($p<0.01$). However, it decreased remarkably in the ischemia + NaHS group when compared with the ischemia group ($p<0.01$). Additionally, $\pm dP/dt_{max}$ was significantly lower in rats of the ischemia group than that of the sham operation group ($p<0.01$). It was evidently higher in the ischemia + NaHS group than the ischemia group ($p<0.01$; Figures 1-3).

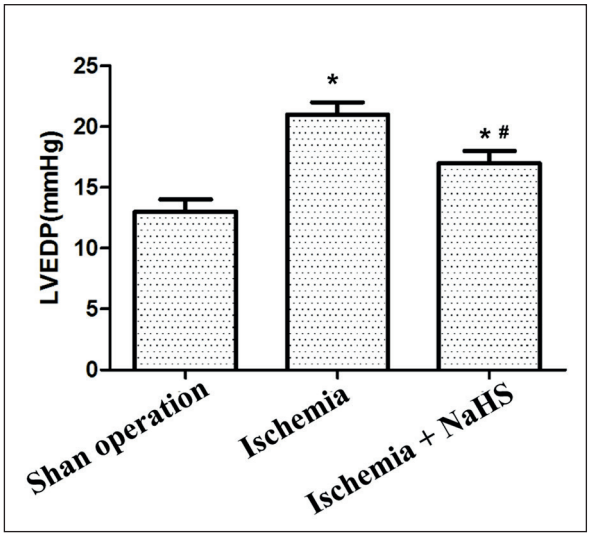

Figure 2. Comparison of LVDEP among all groups of rats. *: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

Morphological Changes in Rat Myocardial Tissues

As shown in Figure 4, compared with the sham operation group, the perinuclear space in the myocardium was significantly larger, the arrangement of fibers was increasingly disorderly and mitochondrial cristae and membrane damage was markedly severer in rats of the ischemia group ($p<0.01$). Moreover, compared with the ischemia group, the ischemia + NaHS group showed significantly alleviated myocardial cell damage, slightly disorderly arranged fibers and mild mitochondrial Matrix edema ($p<0.01$).

Content of Plasma H_2S in Rats

The content of plasma H_2S in rats showed the highest in the sham operation group and the lowest in the ischemia group. After the treatment of NaHS, it was substantially up-regulated in the ischemia group + NaHS group ($p<0.01$; Figure 5).

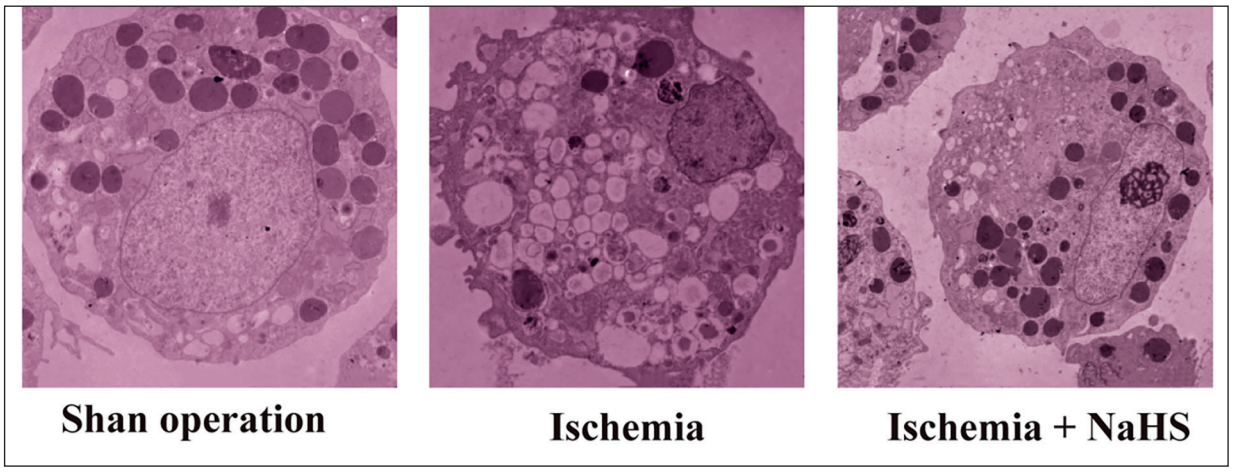

Figure 4. Morphological changes in rat myocardial tissues in the three groups (magnification × 400).

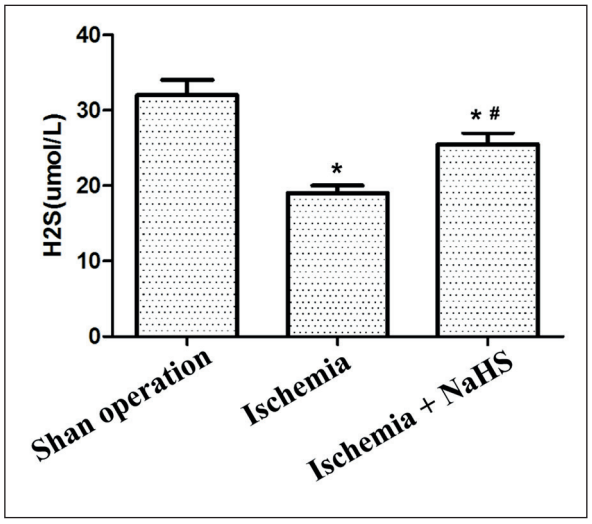

Figure 5. Content of plasma H_2S in all groups of rats. *: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

Protein Expression of JNK2 in Myocardial Cells in Rats of Each Group via Western Blotting

Western blotting results demonstrated that (Figure 6), compared with the sham operation group, the protein expression level of phosphorylated JNK2 was significantly up-regulated in both the ischemia group and ischemia + NaHS group, with the highest in the ischemia group (Table I). These findings implied that NaHS could inhibit the phosphorylation of JNK2 to suppress the activity of the JNK2 pathway.

Changes in the Activity of CSE in Myocardial Tissues of Rats

The activity of CSE in myocardial tissues of rats was the strongest in the sham operation

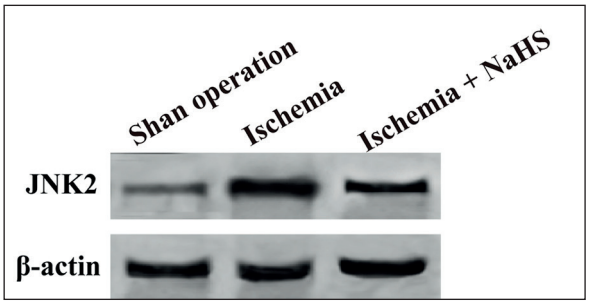

Figure 6. Protein expression level of JNK2 in myocardial tissues in all groups of rats.

Table I. Average optical density and phosphorylation level of JNK2 protein expressed in the myocardial tissues in all groups of rats.

Group	Average optical density	Level of phosphorylation
Sham operation group	156.36 ± 8.45	0.26 ± 0.01
Ischemia group	311.48 ± 9.56*	0.65 ± 0.02*
Ischemia + NaHS group	248 ± 10.95*#	0.39 ± 0.02*#

*: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

group and the lowest in the ischemia group, respectively. Moreover, it was notably up-regulated in the ischemia + NaHS group (p<0.01; Figure 7).

Content of MDA and Changes in the Activity of SOD and GSH-Px in Rat Myocardial Tissues

The content of MDA in myocardial tissues of rats was significantly higher in the ischemia group than the ischemia + NaHS group (p<0.01). No significant differences were observed in the content of MDA between the sham operation group and ischemia + NaHS group. In addition, the activity of SOD and GSH-Px in rat myocardial tissues was markedly worse in the ischemia group than ischemia + NaHS group, with the strongest in the sham operation group (p<0.01; Figures 8-10).

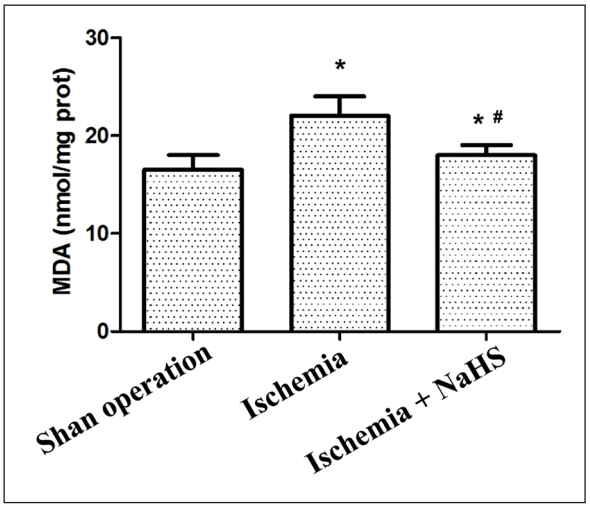

Figure 8. MDA content in myocardial tissues in all groups of rats. *: p<0.01, *vs.* sham operation group and #: p<0.01, *vs.* ischemia group.

Discussion

Myocardial ischemia can cause metabolic dysfunction of cardiomyocytes. Therefore, the wastes produced cannot be discharged, and myocardial damage and necrosis will occur in severe cases. This can eventually affect normal cardiac function[12]. Besides, in real life, the common manifestation of myocardial ischemia is myocardial infarction. Long-term myocardial ischemia can result in the fibrillation of cardiomyocytes, which also gradually triggers other heart diseases and even death in severe cases[13,14]. Myocardial ischemia is attributed to the insufficient blood supply to coronary arteries or blocked the blood supply to these arteries due to some other reasons. Finally, this causes temporary or long-term ischemia to cardiomyocytes. Currently, researchers have focused on the treatment of ischemia with drugs or stem cells in the therapy of myocardial ischemia[15,16]. Meanwhile, drug intervention has been considered to be relatively favorable for the treatment of cardiac ischemia. Furthermore, the

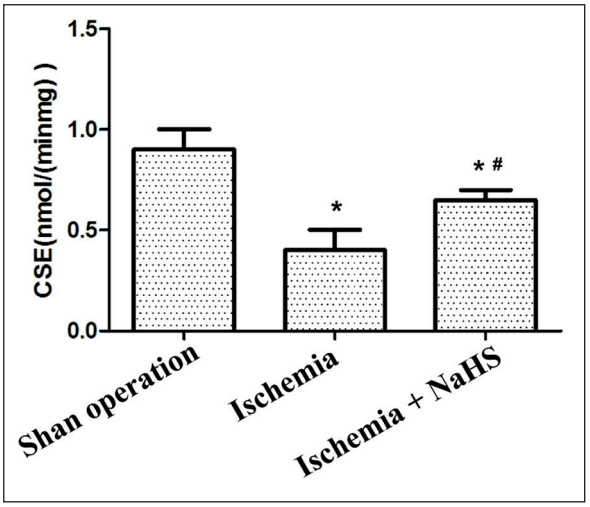

Figure 7. Changes in the activity of CSE in myocardial tissues of rats. *: p<0.01, *vs.* sham operation group and #: p<0.01, *vs.* ischemia group.

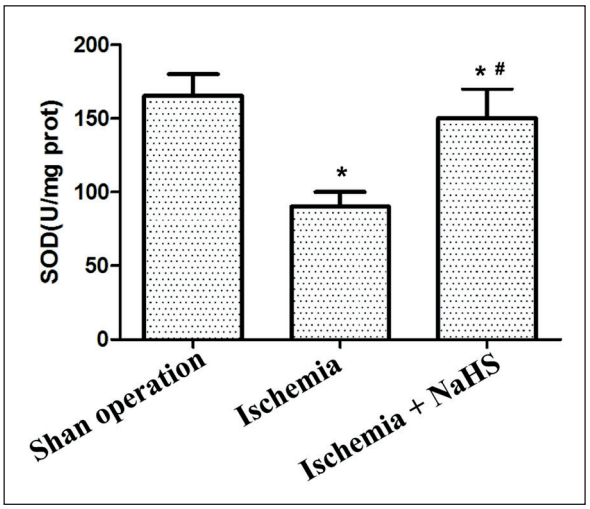

Figure 9. SOD activity in myocardial tissues in all groups of rats. *: p<0.01, *vs.* sham operation group and #: p<0.01, *vs.* ischemia group.

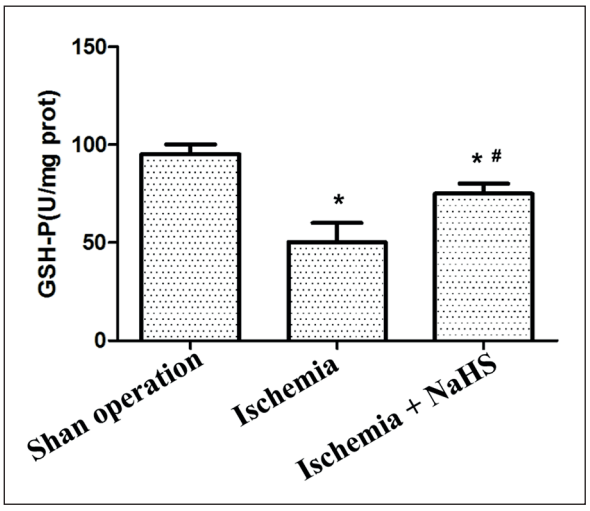

Figure 10. Activity of CSE-Px in myocardial tissues in all groups of rats. *: $p<0.01$, *vs.* sham operation group and #: $p<0.01$, *vs.* ischemia group.

myocardioprotective effect of drug treatment has increasingly attracted much attention from medical community[17].

In this study, we found that compared with the sham operation group, the perinuclear space in the myocardium was gradually larger, the arrangement of fibers became significantly more disordered, and the damage of mitochondrial cristae and membrane was markedly more severe in rats of the ischemia group. Compared with the ischemia group, the above-mentioned conditions of rat cardiomyocytes were remarkably improved in the ischemia + NaHS group ($p<0.01$). It could be concluded that H_2S was able to relieve myocardial ischemia, which was consistent with the findings by Matsui et al[18]. They have previously indicated that acetylation regulates the MKK4-JNK pathway in T cell receptor signaling. LVDP and $\pm$ dP/dt_{max} exhibited the highest in the sham operation group and the lowest in the ischemia group. Meanwhile, they were markedly higher in the ischemia + NaHS group than that of the ischemia group. LVDEP of rats were the lowest in the sham operation group and the highest in the ischemia group, respectively. Meanwhile, it was remarkably lower in the ischemia + NaHS group than that of the ischemia group. Therefore, it was concluded that H_2S had a protective effect on rat cardiomyocytes. Among the three groups, the sham operation group exerted significantly lower content of plasma H_2S and activity of CSE in myocardial tissues than the ischemia group. After adding NaHS, they were markedly elevated in the ischemia + NaHS group ($p<0.01$). Current studies have suggested that during ischemia-reperfusion, the activity of CSE in coronary vascular endothelial tissues is weakened and the production of endogenous H_2S decreases. This may eventually result in oxidative stress damage and aggravate the disease. Our results also detected that the content of H_2S was positively correlated with the activity of CSE. In the present work, the content of MDA in the myocardial tissues of rats was significantly higher in the ischemia group than that of the ischemia + NaHS group ($p<0.01$). Meanwhile, the activity of SOD and GSH-Px in rat myocardial tissues was markedly worse in the ischemia group than ischemia + NaHS group, with the strongest in the sham operation group ($p<0.01$). Lindsey et al[5] have found that the intervention treatment with NaHS reduces the content of MDA. Moreover, this significantly enhances the activity of SOD and GSH-Px in myocardial tissues, thus effectively improving the damage to myocardial ultrastructure. Besides, increased H_2S can relieve the damage to the myocardial structure and cardiac function, as well as weaken lipid peroxidation, thereby alleviating myocardial injuries. These findings are consistent with the conclusion proposed by Kim et al[19]. They have demonstrated that ethyl acetate fraction from persimmon (diospyros kaki) ameliorates cerebral neuronal loss and cognitive deficit *via* the JNK/Akt pathway in TMT-induced mice.

Western blotting results revealed that the protein expression level of phosphorylated JNK2 in myocardial tissues of rats was significantly higher in the ischemia group than the sham operation group. However, it was significantly down-regulated after the administration of NaHS in rats of the ischemia group ($p<0.01$). This suggested that H_2S could inhibit the JNK signaling pathway, thereby playing a protective role. Weakening and repressing the signals in the JNK signaling pathway can lower the risk of death in rat cardiomyocytes[11]. JNK is activated *via* the phosphorylation of its amino acid residue, which then enters the nucleus of cells in rats. The results of this study, illustrated that the JNK pathway was repressed by H_2S to lower the phosphorylation level and the protein expression of JNK2. Furthermore, it could reduce dead cells, thereby protecting against myocardial ischemia in rats. The above data were in line with the findings by Mishra et al[20]. All our findings might bring new insights into the structural dynamics of kinase JNK2.

Conclusions

In summary, H_2S lowered the phosphorylation level of the JNK pathway and down-regulated the protein expression level of JNK2 by inhibiting its activity, thus protecting rats from myocardial ischemia-reperfusion injury.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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