

Basic Study

Hydrogen sulfide attenuates gastric mucosal injury induced by restraint water-immersion stress *via* activation of K_{ATP} channel and NF- κ B dependent pathway

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Abstract

AIM

To explore the effect of hydrogen sulfide (H₂S) on restraint water-immersion stress (RWIS)-induced gastric lesions in rats and the influence of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway on such an effect.

METHODS

Male Wistar rats were randomly divided into a control group, a physiological saline (PS) group, a sodium hydrosulfide (NaHS) group, a glibenclamide (GI) group, GI plus NaHS group, a pyrrolidine dithiocarbamate (PDTC) group, and a PDTC plus NaHS group. Gastric mucosal injury was induced by RWIS for 3 h in rats, and gastric mucosal damage was analyzed after that. The PS, NaHS (100 μ mol/kg body weight), GI (100 μ mol/kg body weight), GI (100 μ mol/kg or 150 μ mol/kg body weight) plus NaHS (100 μ mol/kg body weight), PDTC (100 μ mol/kg body weight), and PDTC (100 μ mol/kg body weight) plus NaHS (100 μ mol/kg body

weight) were respectively injected intravenously before RWIS.

RESULTS

RWIS induced serious gastric lesions in the rats in the PS pretreatment group. The pretreatment of NaHS (a H₂S donor) significantly reduced the damage induced by RWIS. The gastric protective effect of the NaHS during RWIS was attenuated by PDTC, an NF- κ B inhibitor, and also by glibenclamide, an ATP-sensitive potassium channel blocker, in a dose-dependent manner.

CONCLUSION

These results suggest that exogenous H₂S plays a protective role against RWIS injury in rats, possibly through modulation of K_{ATP} channel opening and the NF- κ B dependent pathway.

Key words: Hydrogen sulfide; Nuclear factor kappa B; Gastric mucosal injury; Restraint water-immersion stress; Adenosine triphosphate-sensitive potassium

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Core tip: In this study, the authors demonstrate that exogenous hydrogen sulfide plays a protective role against restraint water-immersion stress injury in rats possibly through modulation of adenosine triphosphate-sensitive potassium channel opening and the nuclear factor kappa-light-chain-enhancer of activated B cells dependent pathway.

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INTRODUCTION

Restraint water-immersion stress (RWIS), considered to be a mixture of physical and psychological stress, can induce anxiety, hypothermia, and severe gastric dysfunction including gastric hypercontractility, gastric acid hypersecretion, and gastric mucosal lesions within a few hours^[1-4]. This model is used to study the mechanism of gastric mucosal lesions induced by stress and filter drugs in clinical trials. As is well known, not only is gastric stress ulcers common complication in patients with clinical critical disease, but also the number of primary gastric stress ulcers seen continues to increase with the fierce competition and pressure common in modern society. Thus, clarifying the mechanism that causes gastric mucosal lesions as a

result of RWIS and looking for ways to reduce these lesions are very important to prevent and cure gastric stress damage in the clinical setting.

Recent studies suggest that hydrogen sulfide (H₂S) is the third gaseous mediator in mammals after nitric oxide (NO) and carbon monoxide (CO) and that it regulates a range of physiological and pathological processes in the nervous system, cardiovascular system, respiratory system, and digestive system, and regulates metabolism and immunity, etc^[5-11].

Recent studies on rats suggest that H₂S can protect the gastric mucosa, possibly through mechanisms that involve anti-oxidant and anti-inflammatory actions^[12], but the effect of H₂S on gastric mucosa damage induced by RWIS still needs further research. Previous reports have shown that H₂S regulates a range of physiological and pathological processes involving K_{ATP} channels. Hydrogen sulfide has been shown to protect gastric epithelial cells from ischemia-reperfusion injury by Keap1 S-sulfhydration, mitogen-activated protein kinase (MAPK) dependent anti-apoptosis, and the NF- κ B dependent anti-inflammation pathway^[13]. Therefore, in this study, we evaluated the effect of H₂S on RWIS-induced gastric lesions in rats and the influence of K_{ATP} channels and the NF- κ B dependent pathway on this effect.

MATERIALS AND METHODS

Animal and drug preparation

Experiments were performed on male Wistar rats (220-280 g) purchased from the Experimental Animal Center of Shandong University. Animals were maintained in a temperature-controlled environment with a 12-h light/dark cycle. They were allowed free access to food and water for one week. Prior to the experiments, the animals were fasted for 24 h but allowed free access to water. All procedures performed were according to the guidelines of the International Association for the Study of Pain^[14] and were approved by the Experimental Animal Ethical Association in Qi Lu Normal University.

Chemicals used and their sources were as follows^[15]: sodium hydrosulfide (NaHS, 100 μ mol/kg body weight), glibenclamide (GI, 100 or 150 μ mol/kg body weight), and pyrrolidine dithiocarbamate (PDTC, 100 μ mol/kg body weight), purchased from Sigma (Saint Louis, MO, United States). NaHS and PDTC were dissolved in 0.9% saline, but GI was dissolved in dimethyl sulfoxide. All chemicals were injected intraperitoneally (IP) before inducing RWIS.

Experimental group and protocol

The rats were randomly divided into 7 groups with 13 rats per group: (1) in the control group, the rats were not stressed under otherwise identical conditions; (2) in the physiological saline (PS) group, the rats were given RWIS for 3 h after pretreatment with IP injection of PS; (3) in the NaHS group, the rats were given RWIS for 3 h after pretreatment with IP injection of



Figure 1 Representative of the degree of gastric mucosal damage induced by restraint water-immersion stress. A: Representative of the degree of gastric mucosal damage in the control group; B: Representative of the degree of gastric mucosal damage in the physiological saline group; C: Representative of the degree of gastric mucosal damage in the NaHS group.

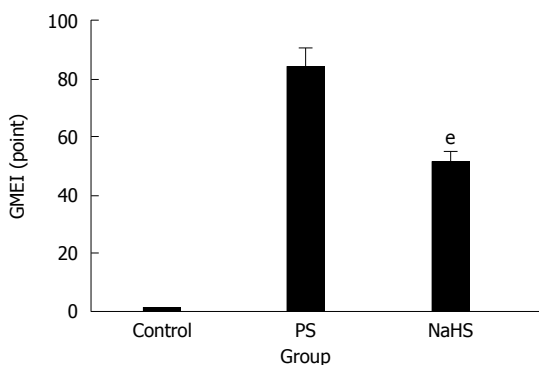


Figure 2 Gastric mucosal erosion index of the control, physiological saline and NaHS groups. ^e $P < 0.001$. GMEI: Gastric mucosal erosion index; PS: Physiological saline.

NaHS (100 $\mu\text{mol/kg}$ body weight); (4) in the GI group, the rats were given RWIS for 3 h after pretreatment with IP injection of GI (100 $\mu\text{mol/kg}$ body weight); (5) in the GI plus NaHS group, the rats were given RWIS for 3 h after pretreatment with IP injection of GI (100 or 150 $\mu\text{mol/kg}$ body weight) and NaHS; (6) in the PDTC group, the rats were given RWIS for 3 h after pretreatment with IP injection of PDTC (100 $\mu\text{mol/kg}$ body weight); and (7) in the PDTC plus NaHS group, the rats were given RWIS for 3 h after pretreatment with IP injection of PDTC (100 $\mu\text{mol/kg}$ body weight) and NaHS.

In the RWIS groups, after light ether anesthesia, the four limbs of each rat were gently bound on a wooden board securely using medical adhesive tape. After the rats were conscious, they were vertically immersed in cold water ($21^\circ\text{C} \pm 1^\circ\text{C}$) to the level of the xiphoid for 3 h. All of the experiments were terminated by a bolus IP injection of sodium pentobarbital (100 mg/kg body weight). Then the abdomen of each rat was opened, and the stomach was removed and fixed with 1% formalin. The gastric lesions were examined with a light microscope, and a scoring system was used to assess the gastric mucosal erosion index (GMEI) of each rat^[16]. Scores were given according to the length of lesions: \leq

1 mm = 1 point, 1 to \leq 2 mm = 2 points, and so on. The score was multiplied by 2 when the damage was more than 1 mm in width. The cumulative scores of all lesions in a rat served as the GMEI of that rat.

Statistical analysis

All values were analyzed using SPSS13.0 software (SPSS Inc.) and presented as mean \pm SE. Statistical analysis was performed by the Student *t*-test. Significance was accepted at the level of $P < 0.05$.

RESULTS

Effect of NaHS on RWIS-induced gastric mucosal injury

The mucosal surface of the control group was smooth, and no significant abnormality in the gastric mucosa was observed under the light microscope (Figure 1A). However, significant hemorrhage and edema and several erosions of varying depths and sizes were observed on the surface of the mucosa of the RWIS groups (Figure 1B and C). The GMEI was 1.54 ± 0.27 points in the control group, 84.38 ± 6.34 points in the PS group (compared with the control group, $P < 0.001$), and 51.23 ± 4.08 points in the NaHS group (compared with the control group, $P < 0.001$) (Figure 2).

Compared with the PS group, the injury area and the extent of mucosal damage significantly decreased in the NaHS group (Figure 1B and C). The GMEI in the NaHS group was obviously lower than that in the PS group (51.23 ± 4.08 points vs 84.38 ± 6.34 points, $P < 0.001$) (Figure 2).

GI prevented the protective effect of NaHS on RWIS-induced gastric mucosal injury in a dose-dependent manner

The gastric protective effect of NaHS during RWIS was abolished by GI, an ATP-sensitive potassium channel K_{ATP} blocker (Figure 3). Under the light microscope, the GMEIs in the GI (100 $\mu\text{mol/kg}$ body weight) plus NaHS group and the GI (150 $\mu\text{mol/kg}$ body weight) plus NaHS group were much higher than those in the NaHS

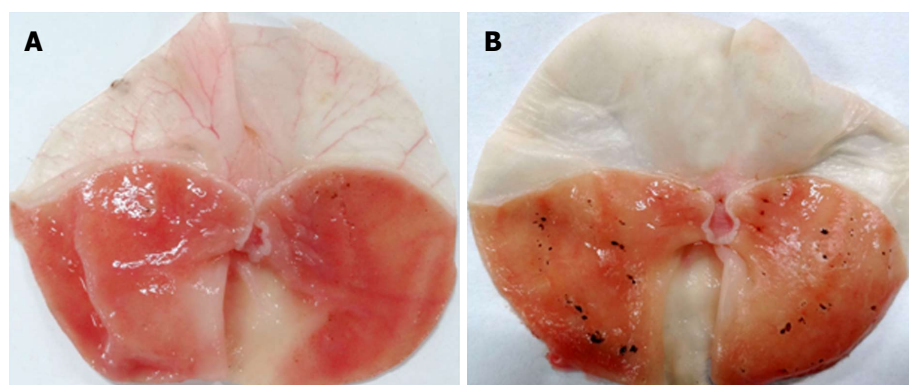


Figure 3 Representative of the degree of gastric mucosal damage in the NaHS group (A) and the glibenclamide + NaHS group (B).

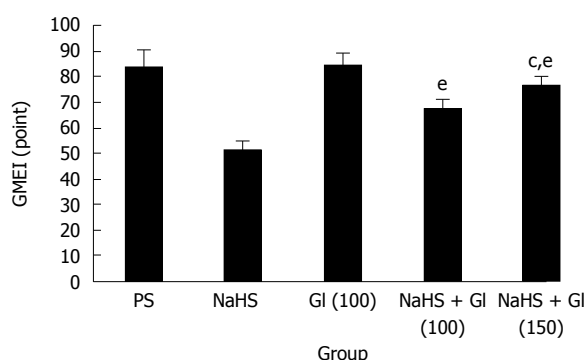


Figure 4 Gastric mucosal erosion index in the NaHS group and the glibenclamide + NaHS group. GI + NaHS group vs the NaHS group, $^aP < 0.001$; GI (100 $\mu\text{mol/kg}$ body weight) plus NaHS group vs the GI (150 $\mu\text{mol/kg}$ body weight) + NaHS group, $^bP < 0.05$. GMEI: Gastric mucosal erosion index; PS: Physiological saline; GI: Glibenclamide.

group (67.92 ± 4.63 points and 76.92 ± 4.71 points vs 51.23 ± 4.08 points, $P < 0.001$). The GMEI in the GI (100 $\mu\text{mol/kg}$ body weight) plus NaHS group was lower than that in the GI (150 $\mu\text{mol/kg}$ body weight) plus NaHS group ($P < 0.05$) (Figure 4). These results suggest that GI prevented the protective effect of NaHS on RWIS-induced gastric mucosal injury in a dose-dependent manner.

PDTC weakened the protective effect of NaHS on RWIS-induced gastric mucosal injury

The gastric protective effect of NaHS during RWIS was weakened by PDTC, an NF- κ B inhibitor (Figure 5). Under the light microscope, the GMEI in the PDTC (100 $\mu\text{mol/kg}$ body weight) plus NaHS group was higher than that in the NaHS group (65.00 ± 4.01 points vs 51.23 ± 4.08 points, $P < 0.001$) (Figure 6). These results suggest that PDTC weakened the protective effect of NaHS on RWIS-induced gastric mucosal injury.

DISCUSSION

In this study, significant hemorrhage and edema and several erosions of varying depths and sizes were

observed on the surface of the mucosa in the RWIS groups. The occurrence of RWIS-induced gastric mucosal erosion is possibly related to a number of factors, including excessive production of oxygen free radicals in the mucosa^[12,17], leukocyte infiltration^[18], decreased release of nitric oxide^[19], gastric hypercontractility, gastric acid hypersecretion, and gastric mucosa ischemia caused by a reduction in the gastric mucosal blood flow.

H₂S is formed in mammalian cells by the activity of two pyridoxal phosphate-dependent enzymes: cystathionine- γ -lyase and cystathionine- β -synthase^[20]. NaHS, as a H₂S donor, dissociates in vivo into sodium ions and sulfhydryl group ions, and the latter bind with hydrogen ions to generate H₂S. Thus, H₂S and NaHS are in dynamic equilibrium^[21]. Previous work has demonstrated that H₂S has anti-inflammatory and antioxidant activities^[22]. The gastroprotective effect of endogenous H₂S against gastric ischemia-reperfusion injury may be mediated by enhancing the anti-oxidative capacity through increasing glutathione and superoxide dismutase to reduce free radical production^[21]. In this study, NaHS significantly attenuates gastric mucosal injury induced by restraint water-immersion stress. We surmise that the mechanism is possibly through antioxidant and anti-inflammatory actions.

Previous reports showed that ATP-sensitive potassium K_{ATP} channels regulate a range of physiological and pathological processes. Dawe *et al.*^[23] found that H₂S in the hypothalamus decreases blood pressure and heart rate by a K_{ATP} channel-dependent mechanism in freely moving rats. Data support the hypothesis that endogenous H₂S produces cardiovascular inhibition functions in the nucleus of solitary tract, mainly mediated by K_{ATP} channel regulation or/and glutamate receptors^[24]. Exogenous H₂S plays a protective role against gastric ischemia-reperfusion injury in rats possibly through modulation of K_{ATP} channel opening^[25]. Here, we have shown that GI, an ATP-sensitive potassium channel blocker, reversed the protective effect of NaHS on RWIS-induced gastric damage in a dose-dependent manner. These results suggest that H₂S plays a protective role against gastric RWIS injury in rats, possibly through

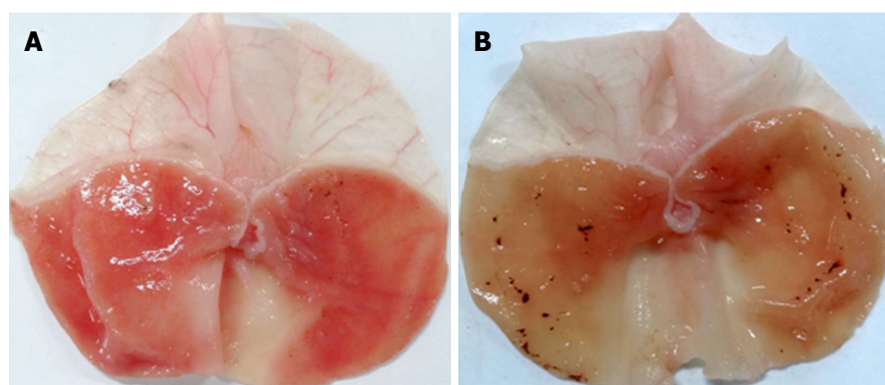


Figure 5 Representative of the degree of gastric mucosal damage in the NaHS group (A) and pyrrolidine dithiocarbamate + NaHS group (B).

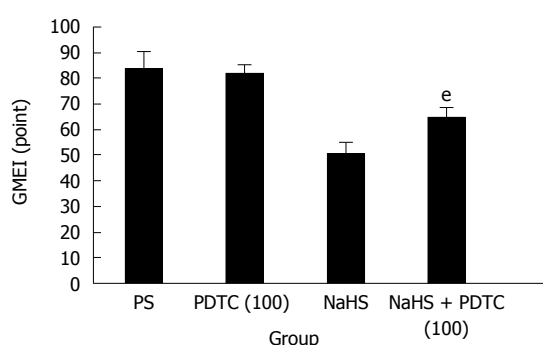


Figure 6 Gastric mucosal erosion index in the NaHS group and PDTC + NaHS group. ^e $P < 0.001$. GMEI: Gastric mucosal erosion index; PDTC: Pyrrolidine dithiocarbamate; PS: Physiological saline.

modulation of K_{ATP} channel opening mechanisms. Data have demonstrated that the H_2S -induced relaxation of mesenteric artery beds was mediated by ATP-sensitive K^+ (K_{ATP}) channel activity in vascular smooth muscle cells^[26]. Therefore, we speculate that on the one hand, H_2S , by opening K_{ATP} channels, relaxes gastric mucosal blood vessels and increases gastric mucosal blood flow. This reduces the damage caused by RWIS by accelerating the removal of harmful substances. On the other hand, H_2S , by opening the K_{ATP} channels, increases the K^+ efflux, which attenuates RWIS-induced gastric mucosal injury by hyperpolarizing the oxyntic cell membrane to reduce gastric acid secretion.

H_2S is a small gas molecule, which can freely pass through a variety of biological membranes, target a wide range, which may affect multiple signaling pathways such as mitogen-activated protein kinase (MAPK) signaling pathways, NF- κ B signal through-road, and phosphoinositide 3-kinase (PI3K) and its downstream molecules, serine/threonine protein kinase AKT (PI3K/AKT)^[27,28]. Hydrogen sulfide protected gastric epithelial cells from ischemia-reperfusion injury by Keap1 s-sulfhydration, MAPK dependent anti-apoptosis, and the NF- κ B dependent anti-inflammation pathway^[13]. Our study results show that PDTC, an NF- κ B inhibitor, reversed the protective effect of NaHS

on RWIS-induced gastric damage, which suggests that H_2S plays a protective role against gastric RWIS injury in rats, possibly through an NF- κ B dependent anti-inflammation mechanism.

In conclusion, the results of this study suggest that H_2S plays a protective role against RWIS-induced gastric mucosal injury in rats, possibly through modulation of K_{ATP} channel opening and through the NF- κ B dependent pathway.

COMMENTS

Background

Recent studies suggest that hydrogen sulfide (H_2S) is the third gaseous mediator in mammals after nitric oxide and carbon monoxide and that it modulates a range of physiological and pathological processes. H_2S has been found throughout the gastrointestinal tract, but little is known about the effect of H_2S on restraint water-immersion stress (RWIS)-induced gastric lesions in rats and the influence of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway on such an effect.

Research frontiers

Previous reports have shown that H_2S is a small gas molecule, which may not only regulate a range of physiological and pathological processes involving K_{ATP} channels, but also affect multiple signaling pathways, such as mitogen-activated protein kinase signaling pathways, NF- κ B signal through-road, and phosphoinositide 3-kinase and its downstream molecules serine/threonine protein kinase. In this study, the authors demonstrate that exogenous H_2S plays a protective role against RWIS injury in rats possibly through modulation of K_{ATP} channel opening and the NF- κ B dependent pathway.

Innovations and breakthroughs

This is the first study to report that exogenous H_2S plays a protective role against RWIS injury in rats possibly through modulation of K_{ATP} channel opening and the NF- κ B dependent pathway.

Applications

This study may provide a future strategy for therapeutic intervention in case of stress gastric lesions by helping understand the mechanism of action of H_2S on RWIS-induced gastric lesions.

Terminology

In the gastrointestinal tract, cystathionine- β -synthase and cystathionine- γ -lyase are mainly responsible for endogenous H_2S synthesis. H_2S is involved in gastric motility, gastric acid secretion, and gastric mucosal injury.

Peer-review

This is a well written and planned study demonstrating the protective effects of H₂S in gastric stress lesions in rats. The protective effects of H₂S seem to arise from modulation of K_{ATP} channel and the NF-κB dependent pathway.

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