The protect role of Hydrogen sulfide in gastric injury

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Hydrogen sulfide (H\textsubscript{2}S), a traditionally known toxic gas, is now recognized as a third gasotransmitter and exerts protective effects against various system diseases and cellular injuries. This article put emphasis on the protective effects of H\textsubscript{2}S on gastric injury and the well-known signaling mechanisms underlying these protective effects, based on existing literature. H\textsubscript{2}S, either endogenous or exogenous origin, have protective effect on gastric mucosa injury and can accelerate ulcer healing. H\textsubscript{2}S exert its protective effect through anti-inflammation, anti-oxidative or anti-apoptosis. These features make H\textsubscript{2}S a potential therapeutic value in acute gastric mucosal lesion and a hot point to exploit in the development of new anti-gastric injury drugs.

**Keywords:** hydrogen sulfide; gastric injury; inflammation; oxidative stress, apoptosis

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**Introduction**

Hydrogen sulfide (H\textsubscript{2}S) is a colorless and rotten egg shell gas, with flammable and water/lipid-soluble characteristic. Though H\textsubscript{2}S traditionally known for centuries as a noxious and toxic gas, now it is recognized as a third gasotransmitter after carbon monoxide and nitric oxide (NO), and plays multiple physiological and pathological functions in various body systems [1-3]. Endogenous H\textsubscript{2}S is formed largely (but not totally) by the enzyme cystathionine β-synthase in the nerve system cells, and cystathionine γ-lyase (CSE) in other organic cells, utilizing l-cysteine and/or homocysteine as substrate [4]. In mammalian serum, the physiological concentrations of sulfide production are believed to be 30-100 μmol/L range, whereas in brain, the physiological concentrations of sulfide production can be as high as 160 μM [5]. H\textsubscript{2}S have toxic effects on some organs when sulfide production concentrations are above 250 μM. A wide range of researches have confirmed the protective effects of H\textsubscript{2}S against various stimuli-triggered injuries in many organs including the heart, brain, lung, liver and even gastrointestinal tract [6-10]. Here, I focus on the protective effects of H\textsubscript{2}S on gastric injury and the well-known mechanisms underlying them.

**H2S & gastric injury**

Gastric mucosa injury is a common phenomenon that can be induced by luminal agents or by gastric ischemia-reperfusion injury. In physiological conditions, H\textsubscript{2}S like NO, can be produced by the gastric mucosa and contributes to gastric ability to resist damage induced by endogenous luminal agents [11]. But it’s functions more than that. Numerous studying have proved that H\textsubscript{2}S also is an important mediator of mucosal defense under pathological gastric injury. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the common causes of gastric ulceration and...
bleeding [12]. Endogenous H$_2$S generations are often inhibited and thus increased the susceptibility of the mucosa to damage induced by NSAIDs [13, 14]. Exogenous H$_2$S, conversely, alleviated the severity of NSAID-induced damage [14]. Furthermore, hybrid NSAIDs which release H$_2$S do not cause stomach ulcers, but enhanced ulcer healing [15]. Ischemiareperfusion is the other important clinical problem contributing for gastric injury. At 2007, Yonezawa et al first proved that oral administration of sodiumhydro sulfide (NaHS), an H$_2$S donor, at 0.01μmol per rat had significant protective effect against ischemia-reperfusion induced mucosal injury [16]. Mard et al and Cui et al also confirmed the protective effect of H$_2$S on gastric ischemia-reperfusion [10, 17]. The total area of gastric lesions significantly decreased following of NaHS or L-cysteine administration, but increased by pretreatment with DL-propargylglycine (PAG), a famous CSE inhibitor [10, 16, and 17]. In the recently published paper in European Journal of Pharmacology, our group first reported that NaHS concentration-dependently suppressed IR-induced cellular injury [18]. Not only exogenous H$_2$S exerted protect effect, but also the endogenous H$_2$S. Human gastric epithelial cells overexpressing CSE gene, a H$_2$S generating enzymes, were more resistant to ischemia/reperfusion induced cell injury, but this effect was abolished by PAG. These studies all proved H$_2$S have protective effect on gastric mucosa injury.

**The mechanisms involved in H$_2$S protective effect**

Although results from different labs support that H$_2$S exert protective effects against gastric injury, versatile mechanisms have been proposed in these studies. All these mechanisms will be discussed in here shortly.

**Anti-inflammatory effect**

Though some studies have showed that exogenous H$_2$S has a pro-inflammatory effect in various inflammatory models such as lipopolysaccharide induced endotoxemia and acute pancreatitis [19], others have reported its anti-inflammatory effects [20-22]. At now, it is well accepted that high concentration and fast-releasing rate of H$_2$S results in a pro-inflammatory effect, whereas low concentration and slow releasing rate of H$_2$S results in anti-inflammatory effect [23, 24].

Inflammation is one of important contributors to gastric injury. The induction of circulating leukocytes adhere to vascular endothelium is the initial step for leukocytes migrating to injury sites. H$_2$S is a potent inhibitory effect on leukocyte adherence to the vascular endothelium and on transmigration of leukocytes across the endothelium. It is supported by the facts that alleviation of endogenous H$_2$S synthesis led to a prompt increase in leukocyte adherence to the vascular endothelium [25]. Except this, infiltration of leukocytes to injury/inflammation sites is also reduced by H$_2$S [26]. Various H$_2$S donors, at micromolar concentrations, reduced carrageenan induced leukocyte infiltration significantly, while inhibitors of endogenous H$_2$S synthesis enhanced leukocyte infiltration [25]. The H$_2$S- induced reduction of leukocyte adherence may be attributable to direct effects on the decreasing expression of intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen (LFA) [27]. When H$_2$S generation is inhibited, ICAM-1 and on LFA-1 expression is enhanced [11].

Leukocytes infiltration and subsequent proinflammatory cytokines and chemokines often mediate many gastric injuries. IL-6, TNF-α, IL-1β and NO are most used markers for gastric epithelial cell inflammation. We have detected that NaHS and L-cysteine significantly lowered IL-6, TNF-α, and NO secretions. NF-κB is an important pro-inflammation factor [18]. The p65 protein is one of the most abundant subunits of NF-κB [28]. Its intranuclear translocation is the central step of NF-κB activation. We have confirmed that NaHS pretreatment significantly inhibited NF-κB p65 activation in gastric epithelial cells after ischemia-reperfusion induced injury. This implied the anti-inflammatory effects of H$_2$S in gastric injury. Nilkantha et al have reported that the p65 subunit of NF-κB can be sulphydrated by H$_2$S at cysteine-38 [29]. Perhaps also through this pathway, H$_2$S inhibited NF-κB activation and inflammation factors secretions.

**Antioxidant effect**

Oxidative stress is an imbalance between the systemic production and clearance of reactive oxygen species (ROS), thus induce cells an overabundance of reactive free radicals. These reactive free radicals attack on DNA, lipids, and proteins, and eventually lead to cell death. Oxidative stress is involved in the pathogenesis of gastric injury. Hydrogen sulfide has been confirmed to produce antioxidant effects in various systems [30, 31]. H$_2$S reduces malondialdehyde (MDA) level in ischemia-reperfusion induced injury, indicating NaHS protective effects on IR-induced lipid peroxidation. Depletion of cellular glutathione (GSH) and superoxide dismutase-1 (SOD-1) also results in the accumulation of reactive oxygen species and accelerates tissue injury. H$_2$S donors increase SOD1 expression and GSH activity in both NASID and ischemia-reperfusion induced gastric injury, indicating that H$_2$S provides protective effects through anti-oxidative stress [18, 32]. Nuclear factor E2-related factor 2 (Nrf2) is the primary cellular defense against the cytotoxic effects of oxidative stress and ECH-associated protein 1 (Keap1) acts as a negative regulator of Nrf2. Under stressed conditions, Nrf2 dissociates with Keap1, translocate to the nuclear and initiates the gene expression of anti-oxidant enzymes. We and others all reported that H$_2$S could s-sulphydrate Keap1 at cysteine-151, which interfere its interaction with Nrf2,
thus dissociated Nrf-2 from Keap1 and unregulated Nrf-2 activity \[18, 33\]. Through this way, H\(\textsubscript{2}\)S decreased ROS accumulation under gastric injury conditions.

**Antiapoptotic effect**

Cell apoptosis also is one of important elements of gastric injuries. H\(\textsubscript{2}\)S exerted its anti-apoptotic effects in many systems, including the circulatory and nervous system \[34, 35\]. In the recently, we used Hoechst33342 staining for detecting cell apoptosis. Cells with condensed or fragmented nuclei were identified as apoptosis cells. NaHS significantly reduced gastric cell after ischemia-reperfusion treatment. The data imply that H\(\textsubscript{2}\)S protects against gastric damage also by preventing cell apoptosis. Mitochondrial injury and caspase activity is an important mechanism for cell apoptosis. Through until now, no one detected the relationship with H\(\textsubscript{2}\)S and mitochondrial injury in gastric epithelial cells, H\(\textsubscript{2}\)S prevents mitochondrial membrane potential loss and decreased caspases activities are often reported in other systems \[36, 37\]. So we can highly speculate that H\(\textsubscript{2}\)S also exert anti-apoptotic effect through these pathways in gastro.

**Conclusions**

Plenty of evidence support that endogenous or exogenous H\(\textsubscript{2}\)S, at physiological concentrations, have protective effect on gastric mucosa injury and can accelerate ulcer healing. H\(\textsubscript{2}\)S exert its protective effect through complex mechanisms including inhibit leukocyte adherence and inflammation factors secretions, decrease ROS accumulation and increase anti-oxidant enzymes expressions, or avoid cell apoptosis. These mechanism can either alone or mix together. These features make H\(\textsubscript{2}\)S a potential therapeutic value in acute gastric mucosal lesion. Moreover, until now, NSAIDs are among the most commonly used anti-inflammatory drugs, but the significant side effect of these drugs is gastric ulcer. Through its protective in gastro, H\(\textsubscript{2}\)S also is a hot point to exploit in the development of new anti-gastric injury drugs.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

**References**


