The role of hydrogen sulfide in gastric mucosal damage

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Abstract
Gastrointestinal disease is a major global threat to public health. In the past few decades, numerous studies have focuses on the application of small molecule gases in the disease treatment. Increasing evidence has shown that hydrogen sulfide (H2S) has anti-inflammatory and anti-oxidative effects, and can regulate gastric mucosal blood flow in the gastric mucosa. After gastric mucosa damage, the level of H2S in the stomach decreases. Administration of H2S can protect and repair the damaged gastric mucosa. Therefore, H2S is a new target for the repair and treatment of gastric mucosa damage. In this review, we introduce the roles of H2S in the treatment of gastric mucosa damage and provide the potential strategies for further clinical treatment.

Key words: hydrogen sulfide; gastric mucosa; experimental study; anti-oxidation; anti-inflammation; gastric mucosal blood flow; protective effects; nitric oxide; carbon monoxide

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INTRODUCTION
Gastric mucosal diseases, including gastric ulcers, affect 25–30% of the world’s population. An acute gastric mucosa damage is frequently initiated by alcohol consumption, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) and stress-induced mucosal damage. Currently, the main clinic treatment for this disease is antisecretory drugs such as histamine type 2 receptor antagonists and irreversible proton pump inhibitors. Although effective, long-term use will bring more serious complications and aggravate the condition. In a large number of previous studies, we have found that certain gaseous media are involved in the occurrence, development, and even treatment of diseases, and small molecule gas has been among the most studied biological mediators. Hydrogen sulfide (H2S) is a small gaseous compound, forming the gasotransmitter family with nitric oxide (NO) and carbon monoxide (CO). It influences physiological and pathological processes throughout the body. However, increasing studies have shown that H2S has anti-inflammatory, anti-oxidative, and protective effects in neurological diseases, cardiovascular diseases, hematologic diseases, and urological diseases. The role of H2S in the gastrointestinal system has been lucubrated and received increasing attention. We retrieved studies and clinical trials related to H2S and gastric mucosal damage through literature databases and clinical laboratory platforms, and summarized the influence of H2S in gastric mucosa damage and the potential mechanisms to explore the feasibility of treatment.

HYDROGEN SULFIDE
H2S was first detected in rat brain in 1989. It is metabolized from cysteine by enzymatic reaction in the presence of cystathionine-γ-lyase (CSE), cystathionine-β-synthetase (CBS) and 3-mercaptopyruvate sulfurtransferase. The distributions of the above enzymes are different in different tissues: CBS is mainly expressed in the nervous system, the cardiovascular system only expresses CSE, and the 3-mercaptopyruvate sulfurtransferase is active in erythrocytes and heart cells. Meanwhile, both CBS and CSE are expressed in digestive system. In some tissues, CSE and CBS are both required for H2S synthesis, whereas in others only one of these enzymes is necessary. H2S also has different expressions at different sites of action. According to reports, the level of H2S does not exceed 160 μM in brain, with serum levels of 30–100 μM. H2S has been recognized as a toxic gas for a long time. Recent studies have found that, similar to certain gases, such as NO, H2S is beneficial at physiological concentrations, but beyond a certain limit, it exhibits its toxicological effects. Because of the highly efficient systems for metabolizing, scavenging and sequestering, the concentration of H2S in plasma seldom exceeded the normal range after administration of H2S donors, which lays the foundation for clinical research.

MECHANISMS OF GASTRIC MUCOSA DAMAGE
The mechanisms underlying alcohol, NSAIDs and stress induced gastric injuries have not yet been fully elucidated. This pathology is complex and typically caused by an imbalance agressive and protective factor in the gastric mucosa. In some ways, they are independent of each other and closely related. Ethanol is one of the aggressor factors that inhibits the proliferation of cells, promotes the infiltration of inflammatory cells, and leads to the necrosis. It can increase the level of
oxygen-derived free radicals (reactive oxygen species, ROS) in the stomach tissue and reducing the content of glutathione.\textsuperscript{17,18} While the mechanism of NSAIDs is through the ability to inhibit prostaglandins and cyclooxygenase-1 (an enzyme expressed by gastric epithelial cells), and the synthesis of prostaglandins is inseparable from cyclooxygenase.\textsuperscript{19} In the stomach, prostaglandins play a vital protective role, stimulating the secretion of bicarbonate and mucus, maintaining mucosal blood flow, and regulating mucosal cell turnover and repair.\textsuperscript{20} So the suppression of prostaglandins synthesis results in increased susceptibility to gastric mucosa damage. NSAIDs also can activate neutrophils to adhere to the vascular endothelium, which could lead to obstruction of capillaries, resulting in a reduction in gastric mucosal blood flow and thereby predisposing the mucosa to injury.\textsuperscript{21}

However, whether it is ethanol or NSAIDs, its pathological process is inseparable from oxidative stress response.\textsuperscript{18,22,23} Oxidative stress is believed to be closely related to the formation of gastric ulcers. A major factor in the development of stress ulcer is splanchic hypoperfusion, which results from a number of stress-related effects that may include release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α). Then, overexposure to ROS and TNF-α can trigger caspase-dependent apoptosis, aggravating the damage of the gastric mucosa.\textsuperscript{18} Beside the direct deleterious effect, oxidative stress also can induce inflammatory responses via activation of redox sensitive transcription factors such as nuclear factor-xB (NF-xB).\textsuperscript{24}

**Experimental Studies of Hydrogen Sulfide in Gastric Mucosa Damage**

As we all known, we have to test a large number of animal experiments before clinical application. As for animal tests, we have successfully established animal models of gastric mucosa damage. Due to the toxicity and high solubility of H\textsubscript{2}S, it is uncommon to inhale it directly. So we use other substances to simulate its effect. Sodium hydrosulfide (NaHS) is commonly used in experiments as a source of H\textsubscript{2}S to study the possible physiologic functions. NaHS immediately dissociates and forms the hydrosulfide anion HS\textsuperscript{-}, which then reacts with H\textsuperscript{+} to form H\textsubscript{2}S.\textsuperscript{25} Apply it to the model of gastric mucosa damage to explore the potential mechanisms of H\textsubscript{2}S. By summarizing the experiments, we found that the conclusions between the different experiments are inconsistent. According to some research,\textsuperscript{26-32} NaHS played a protective effect in gastric mucosa damage. NaHS could decrease hemorrhagic damage, edema and epithelial cell loss induced by ethanol.\textsuperscript{26} NaHS played a protective role through modulation of adenosine triphosphate-sensitive potassium channel opening and through the NF-xB dependent pathway.\textsuperscript{27,28} It could reduce the serum level of TNF-α and interleukin-1β to abrogate the inflammatory.\textsuperscript{29,30} It significantly decreased ulcer area\textsuperscript{31} and increased gastric blood flow at ulcer margin.\textsuperscript{30,32} However, Chavez-Pina et al.\textsuperscript{33} reported that H\textsubscript{2}S had no protective effect on the gastric mucosa, which finding was contrary to the former. This may be due to differences in experimental conditions and methods. We analyze several recent experiments related to this gas for gastric mucosa damage in this paper (Table 1), and summarize the outcomes and mechanisms.

### Mechanisms of Hydrogen Sulfide in Gastric Mucosa Damage

**Anti-oxidation**

As mentioned above, oxidative stress is an important cause of gastric mucosa damage. ROS is the harmful specie known to cause the gastric ulcer development. ROS is indicated as an important cause of lipid oxidation, which leads to changes in membrane fluidity and permeability.\textsuperscript{35,36} Cells have different systems to remove ROS, and glutathione is one of the important substances.\textsuperscript{37} Many studies have found that H\textsubscript{2}S can increase the level of glutathione and reduce the content of ROS in the gastric tissue.\textsuperscript{38} As a result, H\textsubscript{2}S may play an anti-oxidation role in the digestive system.

| Study          | Model | Animals/cells | Main results                                                                 |
|----------------|-------|---------------|------------------------------------------------------------------------------|
| Aboubakr et al.\textsuperscript{29} | CRS   | Rats          | NaHS (60 μmol/kg, intraperitoneal injection) reduced the serum level of TNF-α and myeloperoxidase activity, and abrogated the inflammatory and the deleterious responses of gastric mucosa in CRS. |
| Guo et al.\textsuperscript{28}      | Ischemic perfusion | Human gastric epithelial cell | H\textsubscript{2}S exerted its protective effect through reactive oxygen species clearance, inhibition of p38 and JNK dependent cell apoptosis and NF-xB dependent inflammation pathway. |
| Magierowski et al.\textsuperscript{31} | Acetic acid | Rats          | NaHS (10 mg/kg, intragastric administration) significantly decreased ulcer area and increased GBF at ulcer margin. |
| Magierowski et al.\textsuperscript{32} | NSAIDs | Rats          | NaHS (5 mg/kg, intragastric administration) could raise mRNA or protein expression for CSE, COX-1 and decreased mRNA expression for IL-1β level in blood. |
| Magierowski et al.\textsuperscript{34} | WRS    | Rats          | NaHS dose-dependently attenuated severity of WRS-induced gastric lesions, increased GBF and improve gastric microcirculation. |
| Medeiros et al.\textsuperscript{30}  | Ethanol | Mice          | NaHS and Lawesson’s reagent (donors of H\textsubscript{2}S) decreased hemorrhagic damage, edema and epithelial cell loss. |
| Sun et al.\textsuperscript{27}       | WRS    | Rats          | H\textsubscript{2}S played a protective role against WRS-induced gastric mucosal injury in rats, possibly through modulation of K\textsuperscript{+} ATP channel opening and through the NF-xB dependent pathway. |

Note: H\textsubscript{2}S: Hydrogen sulfide; CRS: cold restraint stress; NaHS: sodium hydrosulfide; TNF-α: tumor necrosis factor-α; GBF: gastric blood flow; NSAIDs: non-steroidal anti-inflammatory drugs; CSE: cystathionine-γ-lyase; COX-1: cyclooxygenase-1; IL-1β: interleukin-1β; WRS: water immersion and restraint stress; JNK: c-Jun N-terminal kinase; NF-xB: nuclear factor-xB; K\textsuperscript{+}ATP: ATP-sensitive potassium.
Anti-inflammation
A large number of ROS produced by oxidative stress can activate the NF-kB signaling pathway within the cell, where NF-kB production results in increased levels of cytokines such as interleukin-6 and interleukin-1β. Studies have confirmed that H2S is able to reduce inflammation by suppressing the NF-kB signaling pathway. It is reported that TNF-α was the major proinflammatory cytokine secreted by macrophages during gastric ulcer, which induces injury in a variety of tissues including the gastric mucosa by stimulating neutrophil infiltration into gastric mucosa. H2S also exerts its anti-inflammatory action by inhibiting the level of TNF-α in the stomach. And in the present study, we find that H2S can reduce edema formation, and the action appears to be mediated via adenosine triphosphate-sensitive potassium channels. These findings offer evidences for the powerful anti-inflammation role of H2S.

Regulate gastric mucosal blood flow
According to previous studies, a great deal of evidences described that H2S may regulate gastric microcirculation. H2S induced vasorelaxation in peripheral vessels may be mediated by various mechanisms, including opening of potassium channels, blockade of voltage-gated Ca2+ channels, enhanced production or activity endothelial derived factors. It also can inhibit the expression of leukocyte adhesion molecules and adhesion of leukocytes to the vascular endothelium to increase the blood flow of the gastric mucosa. H2S also activated the transient receptor potential ankyrin 1 receptor, releasing the vasoactive sensory neuropeptides calcitonin gene related peptide and substance P to regulate vasodilation. The endogenous prostaglandin is also a major mediator of H2S-mediated increase in gastric microcirculation.

Additional mechanisms
H2S also can reduce the gastric acid secretion along with pepsin activity and gastric mucosal carbonyl content level with concomitant increase in the gastric juice pH and mucin concentration.

Interaction with carbon monoxide and nitric oxide
In addition to H2S, CO and NO are confirmed to play an important role in the mechanism of mucosal defense and gastroprotection. NO, created from L-arginine and oxygen by NO synthases, is also a pleiotropic neurotransmitter within both the central and peripheral nervous system. Within the stomach, the NO can strengthen the defense function, help maintain the normal physiological state and integrity of the stomach. It can affect the secretion of mucus, increase the blood flow of the gastric mucosa. Like H2S, NO can also play a protective role by reducing oxidative stress. Unlike H2S and NO, CO is more stable. Most biologically relevant CO is produced by the action of heme oxygenase (HMOX). HMOX has been identified with three different phenotypes, of which HMOX-1 is usually expressed in the luminal gastrointestinal tract at a relatively low level. HMOX-1 induction is usually associated with a protective response. New evidence suggests that HMOX-1 is not directly involved in anti-oxidative stress and other reactions, but by up-regulating CO to protect. In terms of its role in gastric mucosa, CO exhibits its anti-inflammatory, anti-apoptotic and anti-oxidant responses in many ways. A large number of studies have found that the three of them interact with each other. For example, H2Sn, generated by the rapid reaction of H2S and NO, could activate transient receptor potential ankyrin 1 channels to modify synaptic activity and cyclic guanosine monophosphate-dependent protein kinase-1α to induce vascular relaxation. However, the way in which the three have previously interacted with each other has not been fully explained. Their protection of the stomach is interrelated and independent. At present, many studies have applied two or three of these gases to a model of gastric mucosal injury to explore whether their mutual effects can also protect the gastric mucosa and its mechanism. We hope that there will be more and more discoveries about them in the future.

CLINICAL APPLICATIONS
Current research on H2S is still at the experimental stage and has not yet been applied to the clinic. The potential value for the clinical application of H2S needs to be further explored through translational research and clinical trials.

CONCLUSION
Through the above introduction, it is believed that H2S may play a potential role in the physiology of the gastrointestinal tract including the gastroprotection of gastric mucosa and possibly exerts a protective effect in other parts of the digestive system. Although some studies have found that the role of H2S is somewhat inconsistent with those mentioned above, which may be caused by differences in dose, mode of action, and type of disease. After acting on the body, H2S does not simply cause the above mechanism. A larger regulatory network will be discovered and explored. Although we have not fully understood its mechanism, we will continue to do a lot of research in the future. H2S is expected to be used to the clinic, providing a more convenient and less side-effect treatment for gastric lesions.
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