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EDITORIAL

Hydrogen Sulfide: A Rescue Molecule for Mucosal Defence and Repair

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In the past decade, hydrogen sulfide (H_2S) has taken on something of a new identity. Long recognized as an industrial pollutant and environmental toxin, H_2S is now known to be produced throughout the body and to regulate important functions in most organs and tissues [1–3]. In the digestive system, H_2S exerts potent anti-inflammatory actions, regulates blood flow and smooth muscle tone, modulates epithelial secretion and promotes healing of ulcers [4, 5]. Indeed, many of the actions of H_2S overlap with those of nitric oxide (NO), another gaseous mediator recognized mainly as a pollutant and toxin before its physiological importance was elucidated [1–4].

H_2S also bears some similarity to NO with respect to its synthetic pathways in mammals. Like NO, H_2S is synthesized from an amino acid (L-cysteine), and this can occur via three (at least) enzyme pathways. Inhibitors of these pathways are available for use in experimental settings, but they are imperfect, lacking specificity for the target enzymes. A number of H_2S donors are available for assessing the effects of this mediator in experimental settings, including some derived from natural products, such as garlic [3, 5].

Like NO, H_2S is an important mediator of gastric mucosal defence (Table 1) [5]. Inhibition of endogenous H_2S synthesis increases the susceptibility of the mucosa to damage induced by nonsteroidal anti-inflammatory drugs (NSAIDs), for example [6, 7]. On the other hand, exogenous H_2S donors can increase the resistance of the mucosa to injury [5–7]. Moreover, H_2S synthesis is markedly up-regulated after mucosal injury occurs, and it contributes significantly to promoting the healing of the injured tissue [8, 9]. H_2S donors can accelerate ulcer healing in experimental models [8, 9]. There is emerging evidence that H_2S plays an important role in promoting resolution of inflammation, in part by up-regulating cyclooxygenase-2 expression [9].

In the current issue of this journal, Mard et al. [10] report that administration of H_2S just prior to an episode of ischemia–reperfusion can dose-dependently protect the stomach of the rat from damage. Protection could similarly be afforded through administration of L-cysteine, the precursor for H_2S synthesis. Further evidence that H_2S played a pivotal role in the maintenance of mucosal integrity during ischemia–reperfusion was the observation that suppression of endogenous H_2S synthesis, with propargylglycine, resulted in a significant exacerbation of gastric injury.

The authors suggest that it is the suppression of mRNA expression and plasma levels of pro-inflammatory cytokines that accounts for the reduction of gastric damage when the rats were pre-treated with an H_2S donor or L-cysteine. One cannot exclude the possibility that the reduced cytokine expression/production occurred, at least in part, as a consequence of the reduced gastric injury, though H_2S has been shown to reduce pro-inflammatory cytokine expression/synthesis in other in vivo models, including colitis [9, 11, 12].

The reduced gastric injury observed in the study of Mard et al. [10] may have been attributable to effects of H_2S on any of a number of components of mucosal defence, including bicarbonate secretion [13] and mucosal blood flow [6] (see summary in Table 1). A number of recent studies suggest that the ability of H_2S to maintain mitochondrial function in the face of challenges such as ischemia may underlie some of the beneficial effects of this

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Table 1 Mechanisms underlying the gastro-protective effects of hydrogen sulfide

Effect	Mechanism
Maintenance and/or elevation of gastric mucosal blood flow [2, 6]	Vasodilation (K^+-ATP channels)
Stimulation of bicarbonate secretion [13]	Sensory afferent stimulation
Reduced pro-inflammatory cytokine expression/release [11, 12]	Inhibition of Nf-KB
Increased prostaglandin synthesis [9]	Up-regulation of COX-2
Reduced of leukocyte-endothelial adherence [17]	Reduced adhesion molecule expression
Decreased reactive oxygen metabolite production [18–20]	Maintenance of mitochondrial function
Enhanced tissue repair [8, 21]	Promotion of angiogenesis

mediator. This has been elegantly demonstrated by Elrod et al. [14] using an experimental model of myocardial ischemia–reperfusion. H_2S was found to reduce myocardial inflammation and to preserve mitochondrial structure and function in this model. Thus, oxidative phosphorylation can be maintained during a period of ischemia, with reduced generation of reactive oxygen species, thereby reducing tissue injury [14]. Over-expression of one of the key enzymes for H_2S synthesis (cystathionine-βsynthase) in cardiac tissue greatly reduced the extent of tissue injury, as did administration of an H_2S donor [14, 15].

Part of the protective effect of H_2S may be related to its ability, like NO [16], to suppress leukocyte adherence to the vascular endothelium [17], a crucial event in the pathogenesis of ischemia–reperfusion injury that contributes to prolonged impairment of tissue perfusion after the ischemic period. The more quickly blood flow can be restored to the mucosa, the less tissue injury will occur. With less post-ischemic leukocyte adherence within post-capillary venules, blood flow is less impaired.

The study of Mard et al. [10] focused on ischemia–reperfusion injury in the stomach. H_2S is produced and contributes to mucosal defence throughout the GI tract [5]. H_2S may also serve as an important energy source in the GI tract, particularly in the colon [18, 19]. Many species of bacteria within the small and large intestine have the capacity to produce H_2S, which could potentially influence the mucosa. Enterocytes and colonocytes can very effectively metabolize H_2S, limiting its penetrance into the subepithelial compartment [18–20]. However, in a setting of epithelial injury or dysfunction, this "metabolic barrier" capacity may be diminished. A significant question that warrants further investigation is: to what extent can bacterially derived H_2S influence mucosal structure and function? The development of more selective inhibitors of H_2S synthesis and improved methods for measuring H_2S synthesis will greatly enhance our ability to address questions such as these.

Conflict of interest Dr. Wallace is a founder of Antibe Therapeutics Ltd., a company focused on hydrogen sulfide-releasing anti-inflammatory drugs.

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