FORUM REVIEW ARTICLE

Hydrogen Sulfide Signaling in the Gastrointestinal Tract

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Abstract

Significance: The current literature regarding the effects of the gaseous signal molecule hydrogen sulfide (H_2S) in the gastrointestinal system is reviewed. Bacterial, host and pharmaceutical-derived H_2S are all considered and presented according to the physiological or pathophysiological effects of the gaseous signal molecule. These subjects include the toxicology of intestinal H_2S with emphasis on bacterial-derived H_2S , especially from sulfate-reducing bacteria, the role of endogenous and exogenous H_2S in intestinal inflammation, and the roles of H_2S in gastrointestinal motility, secretion and nociception. **Recent Advances:** While its pro- and anti-inflammatory, smooth muscle relaxant, prosecretory, and pro- and antinociceptive actions continue to remain the major effects of H_2S in this system; recent findings have expanded the potential molecular targets for H_2S in the gastrointestinal tract. **Critical Issues:** Numerous discrepancies remain in the literature, and definitive molecular targets in this system have not been supported by the use of competitive antagonism. **Future Directions:** Future work will hopefully resolve discrepancies in the literature and identify molecular targets and mechanisms of action for H_2S . It is clear from the current literature that the long-appreciated relationship between H_2S and the gastrointestinal tract continues to be strong as we endeavor to unravel its mysteries. *Antioxid. Redox Signal.* 20, 818–830.

Introduction

HYDROGEN SULFIDE (H_2S) is intimately connected with the gastrointestinal system. Early biochemists, microbiologists, and physiologists recognized H_2S as a product of digestive processes and studied its properties. While the perception of malodorous sulfur was certainly clear and present in antiquity as evidenced by the actual location of Gehenna, or hell, as the garbage dump of vial sulfur odors in Ben Hinnom just outside Ancient Jerusalem (61), or the description of rotten eggs, or “uria” by Aristotle (5), the first clear account of H_2S that distinguishes it from other malodorous sulfur gases, such as methyl mercaptan (“rotten cabbage”) or sulfur dioxide (“burnt sulfur”), comes from the description of the Italian physician Ramazzini in 1713 of the eye irritation in sewer cleaners caused by chronic exposure to H_2S in privy gas (88). It is likely not surprising to most people that early descriptions of H_2S come from accounts of the contents or products of the mammalian intestines as H_2S is a well-recognized constituent of flatus.

In 1777, the Swedish chemist, Carl Wilhelm Scheele, provided the first systematic study of H_2S gas (94). Using the

knowledge of Scheele, chemists of the late 18th and early 19th centuries, including Justis Leibig, recognized H_2S as a common constituent of putrefaction and the intestines, which remain anaerobic, and yet, generate copious H_2S gas after death, became a common observational and experimental preparation. In his classic text, Lehmann described the culmination of several studies in the first half of the 19th century that observed H_2S as a constituent of intestinal gas before postmortem putrefaction (54). The small amount of H_2S in normal flatus made early chemists consider that digestion in the large intestine is the same chemical process as putrefaction. The biological origin of H_2S gas was solidified when Gayon described the ability of isolated bacteria to generate H_2S from albuminous material (31). This experiment, during the advent of microbiology, started a considerable flurry of taxonomical and biochemical studies in the late 19th century and first half of the 20th century regarding the enzymatic production of H_2S by intestinal bacteria.

This manuscript is designed to comprehensively review the current literature regarding the effects of H_2S in the gastrointestinal system (Fig. 1). Current data are organized into five major themes and will be discussed with special emphasis regarding current areas of controversy.

Hydrogen Sulfide in the Gastrointestinal System

FIG. 1. Hydrogen sulfide (H_2S) exerts numerous effects on the gastrointestinal system.

Bacterial H_2S , Intestinal H_2S Toxicology, and Cancer

Microbial origins of H_2S are typically well understood but remain quite active areas of research in microbial biochemistry (Fig. 2). Oral malodor or halitosis is known to arise from the production of volatile sulfur compounds in the oral cavity, respiratory tract or the blood (106). Halitosis of oral origin is well understood and, in part, arises from the release of H_2S via the desulfhydration of cysteine or serum proteins by subgingival bacteria, including *Peptostreptococcus anaerobius*, *Micros prevotii*, *Eubacterium limosum*, *Centipedia periodontii*, *Selenomonas artemidis*, *Prevotella intermedia*, *Prevotella loescheii*, *Porphyromonas gingivalis*, *Treponema denticola*, and several *Bacteroides* species, among them *B. forsythus* (62). There is controversy regarding halitosis that may arise from the production of H_2S by *Helicobacter pylori*, the pathogen responsible for gastritis. While it is clear that *H. pylori* can produce H_2S via cysteine and methionine desulfhydration (53), some cohorts following *H. pylori* eradication have improved halitosis (39, 43), while another did not (107). The effect of copious H_2S from *H. pylori* during gastritis is not clear, but is likely a major contributor to the bacterium's defense against oxidative attack (101).

Desulfococcus, *Desulfonema*, *Desulfosarcina*, *Desulfobacter*, *Desulfobulbus*, and *Desulfovibrio* are δ -Proteobacteria genera that utilize sulfate as a terminal electron acceptor in the production of ATP to produce H_2S . *Desulfovibrio* account for 66% and *Desulfobulbus* account for 16% of all sulfate-reducing

bacteria (SRB) in the human colon. These two genera are capable of using molecular hydrogen, an oxidation product of short-chain fatty acids produced by fermentation of undigested carbohydrates, as the electron donor for energy production (32). There are Firmicutes species belonging to the genera *Desulfotomaculum*, *Desulfosporomusa*, and *Desulfosporosinus* and Archaea species belonging to the genera *Archaeoglobus*, *Thermocladium*, and *Calditerrivirga* that are also capable of dissimilatory sulfate reduction with *Desulfotomaculum* species being the most robust (41).

H_2S can also accumulate in the lumen of the colon from bacteria that degrade the sulfur-containing amino acids cysteine and methionine (via conversion to homocysteine), through the expression of desulfhydrases. These bacteria have a varied phylogeny and as a whole are relatively understudied but include members of the groups *Enterococci*, *Enterobacteria*, and *Clostridia*, including *Escherichia coli* (10). Interestingly, the products of desulfhydration, including pyruvate and α -ketobutyrate can be used as electron donors for the SRB described above to generate even more H_2S . In addition, there is a small contribution of assimilatory sulfite-reducing γ -Proteobacteria, including *Salmonella*, *Enterobacteria*, and *Klebsiella*, Firmicutes, including *Bacillus* and *Staphylococcus* and numerous Bacteroidetes species to the production of luminal H_2S via the expression of the iron flavoprotein sulfite reductase.

H_2S is the major sulfur-containing constituent of cecal and rectal gas and can reach concentrations as high as $40 \mu M$

Desulfhydration

Dissimilatory Sulfate Reduction

Assimilatory Sulfite Reduction

FIG. 2. Bacterial H_2S . Bacterial sources of H_2S in the lumen of the gastrointestinal tract occurs *via* three biochemical pathways: desulfhydration, dissimilatory sulfate reduction, and assimilatory sulfite reduction.

(~1000 ppm) (103). Because of numerous lethal exposures to H_2S from sewage and farm workers, the toxicity of H_2S , primarily *via* the lung as the route of absorption, is well documented (9) and include toxic effects on lung, heart, vascular, and brain tissues. Among the most well known toxic effects of H_2S is the noncompetitive inhibition of oxygen binding to cytochrome C oxidase (17), which inhibits cellular respiration in all tissue but seems particularly sensitive in respiratory centers of the brain (9), although a lung site of action has been put forth as a more probable site for acute toxicity (2). For the purpose of this manuscript, the toxic potential of H_2S on intestinal cells, more specifically, cultured colonic epithelial cells are reviewed (Fig. 3). Sodium hydrosulfide (NaHS, 0.2–5 mM) increases the proliferation in non-transformed rat intestinal epithelial cells (IEC-18-cells) (20), but 1 mM NaHS decreases proliferation of an immortalized colon epithelial cell (YAMC cells) and a panel of colon cancer cell lines (HT-29, SW1116, and HCT116 cells) (118). H_2S cau-

ses DNA damage in colonic cancer cells (HT-29-C1.16E cells) at concentrations of 250 μM , although only when DNA repair is inhibited (8). Evidence that intracellular signaling is not required for H_2S to induce genotoxicity, is the observation that naked nuclei from Chinese hamster ovary cells treated with 1 mM sulfide demonstrated similar DNA damage. What is somewhat confusing is that the number of oxidized bases is increased after exposure to the highly reductive H_2S and that butylhydroxyanisole, a radical scavenger, reduces DNA damage induced by H_2S suggesting perhaps the involvement of mitochondrial radical production (7). In rat normal gastric epithelial cells (RGM1 cells), low concentrations of NaHS (0.5–1 mM) augments hydrogen peroxide-induced toxicity, while a higher concentration (1.5 mM) protects the cells from oxidative damage (119). In nontransformed human intestinal epithelial cells (FHs 74 Int cells), the expression of cell-cycle progression genes, inflammation genes, and DNA repair genes were modulated by H_2S (6). In addition to causing DNA

FIG. 3. H_2S and intestinal epithelial cells. H_2S exerts numerous toxic effects on cultured gastrointestinal epithelial cells.

damage, H_2S prevents the oxidation of butyrate and other short chain fatty acids in colonocytes, reducing nutritional support for colonocytes resulting in reduced absorption of sodium, reduced secretion of mucin, and a shorter life of the colonocytes (46, 74, 76, 89–91). As in other tissues, cytochrome C oxidase from colonic epithelial cells is inhibited by NaHS with an IC_{50} of $0.32 \mu M$ with concurrent reductions in oxygen consumption (55). Despite these findings that support the toxic effects of H_2S , it does not alter the membrane integrity of isolated pig colonic crypts (56).

The toxic effects of exogenous H_2S have led some to propose luminal H_2S as a causative factor in both intestinal cancers and chronic intestinal inflammation. The former will be discussed here, while the latter will be discussed in the following section. Genotoxic effects of H_2S (described above) suggest a potential causative role for the gas in cancer biology. Support for this concept comes from observations that H_2S detoxifying genes are reduced in colorectal cancer (6), disulfide levels are increased in transplanted animal tumors (14), and fecal sulfide levels are increased in a sigmoid colon cancer group compared to disease-free controls (47). Mucosal biopsies of sigmoidal rectum exposed to $1 mM$ NaHS causes hyperproliferation with an expansion of the proliferative zone (16). In addition, H_2S forces cell cycle entry of nontransformed rat epithelial cells (20) and increases the proliferation of the transformed epithelial cell line, Caco-2 (45). What is difficult to resolve is the conflicting evidence that diallyl sulfide and carbon disulfide, which may potentially have similar mechanisms of action as H_2S , have potent antiproliferative effects and inhibit carcinogen-induced DNA damage in colonic, gastric, and esophageal epithelial cells (36, 77, 84, 116, 117). S-propargyl-cysteine, a H_2S donor, is proapoptotic and causes cell cycle arrest in gastric cancer (SGC-7901) cells. In addition, S-propargyl-cysteine reduces the growth of tumor implants in nude mice (65).

H_2S and Intestinal Inflammation

The role of H_2S in intestinal inflammation is complex and at times contradictory (Fig. 4). Some experimental and clinical data suggest that H_2S may be implicated in the etiology of

ulcerative colitis, or at least serve to increase the risk of relapse. Ulcerative colitis is a mucosal inflammation of the colon with widespread epithelial cell damage and accumulation of neutrophils and eosinophils with crypt abscesses. As discussed above, H_2S has many deleterious effects on intestinal epithelial cells, including reduced nutrition for colonocytes [for review see Refs. (86, 92)]. In some studies, fecal sulfide levels are increased in patients with ulcerative colitis (57, 85) and effective treatment of relapsed inflammation is associated with a reduction in sulfide levels (26). Increased sulfide levels are also observed in the trinitrobenzene sulfonic acid-induced murine colitis (115). Perhaps increased sulfide levels are due to reduced levels of rhodanese, or thiol methyltransferase, which is involved in H_2S detoxification that has been demonstrated in human ulcerative colitis (75, 92) and dextran sodium sulfate induced colitis in mice (108). In addition, some investigators have suggested that widely used animal models of ulcerative colitis, with similar features of epithelial damage to ulcerative colitis, are due to increased availability of indigestible sulfate as a substrate for SRB (10).

Because of the toxic effects of H_2S , the SRB have long been recognized as candidates in the etiology of ulcerative colitis but fecal and mucosal biopsy analysis of bacterial populations have failed to definitively implicate any change in SRB populations in the disease (93). It seems as though chronic pouchitis, a common condition that develops after total abdominal colectomy with ileal pouch anal anastomosis for the treatment for ulcerative colitis, is following the trail that its parent disease blazed. Ileal pouches accumulate more H_2S when pouchitis is active *versus* remitted states (81), and SRBs colonize pouches of patients who undergo total abdominal colectomy with ileal pouch anal anastomosis for the treatment for ulcerative colitis but not in patients that have had the procedure for familial adenomatous polyposis in which cases the incidence of pouchitis is low (25). However, like ulcerative colitis, there is no correlation between populations of SRBs and mucosal inflammation (85, 99).

Evidence against H_2S having a causative role in ulcerative colitis comes from a study that failed to demonstrate elevated fecal sulfide levels in the disease state (73) and animals models of colitis that fail to show improvement when bacterial sulfide is scavenged with bismuth (29), significantly improve when exogenous H_2S is delivered (28, 68, 115), or significantly worsen when endogenous H_2S production is inhibited (115). A potential mechanism of the anti-inflammatory effects of H_2S is the ability of luminal H_2S to modify secreted defensive proteins. *Via* reduction of disulfide bonds, H_2S releases trefoil factor 3 (TFF3), which plays a key role in mucosal regeneration and repair processes, from its cosecreted disulfide-linked partner IgG Fc binding protein (1). In addition, recent evidence suggests that H_2S reduces the sulfur groups of β -defensin which increases the potency of its antimicrobial activity (97).

Further support for an anti-inflammatory role of H_2S comes from a number of studies conducted outside the colon. As has been demonstrated in the heart and central nervous system, exogenous H_2S has a protective role in models of intestinal ischemia (37, 60, 66, 126, 127). H_2S protects the gastric mucosa in models of ethanol-induced gastritis (15, 70). Exogenous H_2S causes hypothermia which is thought to contribute to its effect of reducing stress-induced gastric ulcers (63). The most prolific work regarding the anti-inflammatory actions of H_2S ,

FIG. 4. H₂S and inflammation. The literature describes both pro-inflammatory and anti-inflammatory effects of endogenously produced and exogenously delivered H₂S.

mostly by the efforts of John Wallace and colleagues, is the protective role for both endogenous and exogenous H₂S against nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis (11, 27, 113, 114). These studies are culminating in the development of therapeutics designed to release H₂S from NSAIDs to combat the gastric ulcer side effects of the most widely used class of pain medications (112).

While some investigators demonstrate that exogenous H₂S ($\sim 180 \mu\text{mol/kg}$) increases lung injury after cecal ligation and puncture, a model for sepsis (4, 122–124) others demonstrate improvement with only a slightly smaller dose ($100 \mu\text{mol/kg}$) (18, 100). To confuse this issue further, both sides in this debate have demonstrated that inhibiting the endogenous production of H₂S inhibits leukocyte trafficking in mesenteric arteries (124) and conversely, delivering exogenous H₂S enhances leukocyte trafficking (18, 124). Completely opposite effects on leukocyte trafficking have been demonstrated in models of carageenan-induced hindpaw inflammation, aspirin-induced gastric ulceration, and air pouch-induced inflammation, where inhibition of endogenous H₂S enhanced leukocyte migration, and exogenous H₂S ($100 \mu\text{mol/kg}$) reduced leukocyte migration (27, 121). One study has also demonstrated that nanomolar concentrations of H₂S can potentiate T lymphocyte activation (72). Because T cells are ca-

pable of both potentiating and resolving inflammation depending on polarization, it is possible that H₂S can potentiate both pro- and anti-inflammatory effects through an action on T lymphocytes depending on which way any particular model is polarized.

As this section hopefully demonstrates, the role of H₂S in intestinal inflammation is far from clear. But with increased works put forth by numerous established gas biologists, and those investigators new to the field, nuances between models, understanding of dose-dependent and release rate- and duration-dependent effects as well as definitive identification of multiple molecular targets for H₂S are likely to resolve what is at present often conflicting and confusing data.

Endogenous H₂S and Gastrointestinal Motility

The neuromuscular layers of the gastrointestinal tract contain the afferent, interneuronal, and efferent neurons and the effector smooth muscle cells that are capable of intrinsic neurogenic reflex control as well as myogenic control of motility (Fig. 5). When the neuromuscular layers of the mouse colon are isolated in a sterile manner without the luminal bacterial contents, the neurons, which express cystathionine- γ -lyase generate H₂S from the amino acid cysteine (59). There

FIG. 5. Endogenous H_2S modulates gastrointestinal motility. The neural and muscular components of the peristaltic reflex, one pattern of gastrointestinal motility, are illustrated with observed actions of H_2S on these components. There is little evidence that luminal (bacterial) H_2S contributes directly to the neuromuscular components of motility as the epithelial cells efficiently oxidize H_2S to thiosulfate and sulfate which is removed *via* the portal circulation. ICC, interstitial cells of Cajal; LM, longitudinal muscle; MP, myenteric plexus; CM, circular muscle; SMP, submucosal plexus; MUC, mucosa; IPANs, intrinsic afferent neurons.

is a robust mechanism that removes H_2S in this system, partially through the degradation to thiosulfate through sulfide quinone reductase and partially through the degradation to sulfate (58). There is little evidence that sulfur from exogenously delivered H_2S is incorporated into proteins in the mouse colon neuromuscular layers (58).

The first work on the role of H_2S on gastrointestinal smooth muscle was a relaxation of guinea pig ileum smooth muscle that is augmented by cyanide and nitroprusside, but reversed relaxations caused by nitric oxide (50). Further studies demonstrated that, like the cardiovascular system, gastrointestinal smooth muscle from different regions and species are relaxed by exogenous delivery of H_2S (40, 109). Unlike the cardiovascular system, identifying the molecular mechanisms that contribute to H_2S -induced smooth muscle relaxation has been more difficult. There are studies that have demonstrated a partial contribution of the ATP-sensitive potassium (K_{ATP}) channel to intestinal smooth muscle relaxation in the guinea pig antrum (125), rat jejunum (78), and the human, rat and mouse jejunum and colon (30). In addition, there are studies that demonstrate a lack of effect of K_{ATP} channels in H_2S -mediated intestinal smooth muscle relaxations in the mouse gastric fundus (21), mouse distal colon (22), the rat jejunum (48), rat ileum (79), and guinea pig taenia caecum (19). These studies have suggested a role for voltage-gated potassium channels, myosin light chain phosphatase, mitochondria, or have failed to identify a molecular mechanism of action.

Importantly, H_2S has an inhibitory role on spontaneous and agonist-mediated rhythmic contractile activity. A key finding was the demonstration that this occurs across species and in distinct gastrointestinal regions (30). Recent work from rainbow trout (*Oncorhynchus mykiss*) and coho salmon (*Oncorhynchus kisutch*) suggest that this pan-intestinal inhibitory effect also occurs in nonmammalian vertebrates as well (24). This latter work has demonstrated that hypoxia has similar effects to exogenous H_2S and suggests that H_2S may act as cellular oxygen sensor in the gastrointestinal tract. Spontaneous rhythmic contractions of the gastrointestinal tract are dependent on a cell type known as interstitial cells of Cajal (ICC), which generate intrinsic pacemaker potentials. In isolated ICC of the mouse small intestine, H_2S inhibits pacemaker activity in ICC (83) and interacts with nitric oxide in regulating functional pacemaker activity (120). H_2S stimulates the proliferation of ICC through the phosphorylation of AKT (42). H_2S activates voltage-gated sodium channels ($Na_v1.5$) in circular smooth muscle cells from the human jejunum (102) which play a role in propagating pacemaker activity. A recent study demonstrated that endogenous H_2S contributes to resting membrane potential and spontaneous contractions in the rat colon as cystathionine- γ -lyase and cystathionine- β -synthase inhibitors are able to reduce H_2S production, depolarize smooth muscle cells, and increase the frequency of contractions in muscle strips (33). Functional assessments in awake mice demonstrate that H_2S enhances the gastric

emptying of liquids *via* K_{ATP} and transient receptor potential V1 (TRPV1) channels (71).

H₂S and Epithelial Cell Function, Including Neurogenic Secretion

Recent reviews have summarized current knowledge of all gaseous signal molecules involved in regulating small intestinal (105) and colonic ion secretion (87). In this review, I will discuss only H₂S, but it should be noted that there is significant interaction in this system of H₂S with nitric oxide and carbon monoxide. Exogenous H₂S has a prosecretory neuromodulator effect in isolated mucosal/submucosal preparations of the guinea pig and human colon (Fig. 6). Further pharmacological dissection of this effect demonstrate that H₂S likely acts on TRPV1 receptors expressed by spinal afferent neurons that innervate the mucosa which release substance P

to activate intrinsic submucosal secretomotor neurons that stimulate secretion *via* acetylcholine acting on mucosal epithelial cells (49, 96). It should be noted here that secretomotor neurons of the submucosal plexus are also involved in vasodilatation of submucosal arterioles to facilitate nutrient absorption. Like other cardiovascular regions, H₂S relaxes gastric arterioles at high concentrations *via* K_{ATP} -dependent and independent mechanisms, but also contracts gastric arterioles at low concentrations by inhibiting NO release (51). Other neurogenic effects of H₂S on intestinal vasodilator responses are likely to be found. While the studies in human, guinea pig, and mouse colonic secretion find no role for direct effects of H₂S on epithelial cells, a subsequent study in the rat colon demonstrates that H₂S increases anion secretion that is only partially blocked by tetrodotoxin, while the remaining response is *via* both apical and basolateral potassium channels (38). In the intact duodenum of the rat, H₂S stimulates the

FIG. 6. H₂S and intestinal secretion. H₂S is prosecretory *via* direct epithelial and indirect neural mechanisms. CNS, central nervous system.

release of bicarbonate from Brunner's glands *via* increased release of prostaglandins and nitric oxide. In addition, an inhibitor of cystathionine- γ -lyase reduces acid-induced bicarbonate secretion suggesting a role for endogenous H_2S in the physiological response of the duodenum to stomach acid (44). An early work in this area described that H_2S delivered to the isolated intestinal loop of the dog reduced the absorption of glucose without affecting xylose absorption (64).

Many direct effects of H_2S on epithelial cells were discussed above in the section regarding H_2S toxicology. Mucosal epithelial cells have the functional role of not only transporting nutrients, but also in forming a barrier to potential luminal pathogens. Cysteine enhances barrier function in salmonella-infected rats independent of its role in glutathione production

(111) suggesting that H_2S may enhance barrier function. Bismuth which effectively removes luminal sulfide (82, 104) also reduces the invasion of epithelial cells by enteroinvasive bacteria (35) and thiol and disulfide compounds inhibit the secretory response of *E. coli* heat stable enterotoxin (34). Further protective roles of H_2S in this system are suggested by the finding that cysteine enhances ileal mucosal growth following ileal resection in rats (98). The breakdown products of H_2S , thiosulfate, and sulfate inhibit the transport of selenium across monolayers of the transformed epithelial cell, Caco-2 (52), suggesting that not only H_2S , but also its catabolic products may have roles in the function of intestinal epithelial cells. Work in this area is growing at a fast pace as more investigators study the effects of H_2S on different and new epithelial cell lines.

FIG. 7. H_2S and gastrointestinal nociception. H_2S modulates nociceptive reflexes of the gastrointestinal tract through several identified molecular targets, including the TRPV1 receptor, TRPA1 receptor and T-type voltage-gated calcium channels (VGCC). There are both pro-nociceptive and anti-nociceptive actions of H_2S . TRP, transient receptor potential.

H₂S and Gastrointestinal Nociception

H₂S modulates nociceptive sensitivity of the gastrointestinal tract (Fig. 7). Studies in the human and guinea pig colon suggest a role for TRPV1 receptors on spinal afferent neurons in the response to exogenous H₂S (49, 96) which has also been reviewed (95). Interestingly, H₂S has an antinociceptive effect for the spinal and supraspinal visceromotor response and decreases spinal Fos immunoreactivity in response to colonic distension (23). On the other hand, studies have also demonstrated a pronociceptive effect of H₂S on visceromotor responses to colonic distension *via* the activation of T-type calcium channels (69). The chelation of zinc usually bound to T-type calcium channels by H₂S, appears to be a key step in their activation in colonic afferents (67, 68). Support for a pronociceptive role of H₂S comes from the demonstration that H₂S directly activates jejunal mesenteric afferents (49). In addition to TRPV1 receptors, H₂S activates TRPA1 receptors (3, 80). TRPA1 receptors are partially responsible for mechanosensitive responses of afferent neurons in mouse colon (12, 13). Recent evidence suggests that H₂S acts on TRPA1 directly in colonic afferent neurons to enhance nociceptive function (110).

Conclusion

While the role of H₂S in gastrointestinal physiology is becoming clearer, it is by no means clear. There are a plethora of targets for H₂S in this system and numerous complimentary and conflicting studies. While studies in the last century focused on the toxicology of H₂S in the gut, and found roles for H₂S from bacterial sources in gastrointestinal diseases, studies in the last decade have focused on endogenous host H₂S and are finding numerous physiological effects of this gaseous signal molecule. The major effects of H₂S in this system continue to remain both pro- and anti-inflammatory, smooth muscle relaxation, prosecretory, and pro- and antinociceptive. Future work will hopefully resolve discrepancies in the literature and identify molecular targets and mechanisms of action for H₂S. One thing is clear; the intimate relationship between H₂S and the gastrointestinal tract continues to be strong as we persist to unravel its mysteries.

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References

1. Albert TK, Laubinger W, Muller S, Hanisch FG, Kalinski T, Meyer F, and Hoffmann W. Human intestinal TFF3 forms disulfide-linked heteromers with the mucus-associated FCGBP protein and is released by hydrogen sulfide. *J Proteome Res* 9: 3108–3117, 2010.
2. Almeida AF and Guidotti TL. Differential sensitivity of lung and brain to sulfide exposure: a peripheral mechanism for apnea. *Toxicol Sci* 50: 287–293, 1999.
3. Andersson DA, Gentry C, and Bevan S. TRPA1 has a key role in the somatic pro-nociceptive actions of hydrogen sulfide. *PLoS One* 7: e46917, 2012.
4. Ang SF, Sio SW, Mochhala SM, MacAry PA, and Bhatia M. Hydrogen sulfide upregulates cyclooxygenase-2 and prostaglandin E metabolite in sepsis-evoked acute lung injury via transient receptor potential vanilloid type 1 channel activation. *J Immunol* 187: 4778–4787, 2011.
5. Aristotle. *On the Generation of Animals*. English & Greek, 1953, *Generation of animals, with an English translation by Peck AL*. Cambridge, MA: Harvard University Press; London, W. Heinemann Ltd., 1953.
6. Attene-Ramos MS, Nava GM, Muellner MG, Wagner ED, Plewa MJ, and Gaskins HR. DNA damage and toxicogenomic analyses of hydrogen sulfide in human intestinal epithelial FHs 74 Int cells. *Environ Mol Mutagen* 51: 304–314, 2010.
7. Attene-Ramos MS, Wagner ED, Gaskins HR, and Plewa MJ. Hydrogen sulfide induces direct radical-associated DNA damage. *Mol Cancer Res* 5: 455–459, 2007.
8. Attene-Ramos MS, Wagner ED, Plewa MJ, and Gaskins HR. Evidence that hydrogen sulfide is a genotoxic agent. *Mol Cancer Res* 4: 9–14, 2006.
9. Beauchamp RO, Jr., Bus JS, Popp JA, Boreiko CJ, and Andjelkovich DA. A critical review of the literature on hydrogen sulfide toxicity. *Crit Rev Toxicol* 13: 25–97, 1984.
10. Blachier F, Davila AM, Mimoun S, Benetti PH, Atanasiu C, Andriamihaja M, Benamouzig R, Bouillaud F, and Tome D. Luminal sulfide and large intestine mucosa: friend or foe? *Amino Acids* 39: 335–347, 2010.
11. Blackler R, Syer S, Bolla M, Ongini E, and Wallace JL. Gastrointestinal-sparing effects of novel NSAIDs in rats with compromised mucosal defence. *PLoS One* 7: e35196, 2012.
12. Brierley SM, Castro J, Harrington AM, Hughes PA, Page AJ, Rychkov GY, and Blackshaw LA. TRPA1 contributes to specific mechanically activated currents and sensory neuron mechanical hypersensitivity. *J Physiol* 589: 3575–3593, 2011.
13. Brierley SM, Hughes PA, Page AJ, Kwan KY, Martin CM, O'Donnell TA, Cooper NJ, Harrington AM, Adam B, Liebrechts T, Holtmann G, Corey DP, Rychkov GY, and Blackshaw LA. The ion channel TRPA1 is required for normal mechanosensation and is modulated by algogenic stimuli. *Gastroenterology* 137: 2084–2095, 2009.
14. Calcutt G and Ting SM. The acid soluble disulphide and mixed disulphide levels of some normal tissues and transplanted tumours. *Br J Cancer* 24: 599–602, 1970.
15. Chavez-Pina AE, Tapia-Alvarez GR, and Navarrete A. Inhibition of endogenous hydrogen sulfide synthesis by PAG protects against ethanol-induced gastric damage in the rat. *Eur J Pharmacol* 630: 131–136, 2010.
16. Christl SU, Eisner HD, Dusel G, Kasper H, and Scheppach W. Antagonistic effects of sulfide and butyrate on proliferation of colonic mucosa: a potential role for these agents in the pathogenesis of ulcerative colitis. *Dig Dis Sci* 41: 2477–2481, 1996.
17. Cooper CE and Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. *J Bioenerg Biomembr* 40: 533–539, 2008.
18. Dal-Secco D, Cunha TM, Freitas A, Alves-Filho JC, Souto FO, Fukada SY, Grespan R, Alencar NM, Neto AF, Rossi MA, Ferreira SH, Hothersall JS, and Cunha FQ. Hydrogen sulfide augments neutrophil migration through enhancement of adhesion molecule expression and prevention of CXCR2 internalization: role of ATP-sensitive potassium channels. *J Immunol* 181: 4287–4298, 2008.
19. Denizalti M, Durlu-Kandilci NT, Bozkurt TE, and Sahin-Erdemli I. Hydrogen sulphide inhibits carbachol-induced

- contractile responses in beta-escin permeabilized guinea-pig taenia caecum. *Eur J Pharmacol* 658: 229–235, 2011.
20. Deplancke B and Gaskins HR. Hydrogen sulfide induces serum-independent cell cycle entry in nontransformed rat intestinal epithelial cells. *FASEB J* 17: 1310–1312, 2003.
 21. Dhaese I and Lefebvre RA. Myosin light chain phosphatase activation is involved in the hydrogen sulfide-induced relaxation in mouse gastric fundus. *Eur J Pharmacol* 606: 180–186, 2009.
 22. Dhaese I, Van Colen, I, and Lefebvre RA. Mechanisms of action of hydrogen sulfide in relaxation of mouse distal colonic smooth muscle. *Eur J Pharmacol* 628: 179–186, 2010.
 23. Distrutti E, Sediari L, Mencarelli A, Renga B, Orlandi S, Antonelli E, Roviezzo F, Morelli A, Cirino G, Wallace JL, and Fiorucci S. Evidence that hydrogen sulfide exerts antinociceptive effects in the gastrointestinal tract by activating KATP channels. *J Pharmacol Exp Ther* 316: 325–335, 2006.
 24. Dombkowski RA, Naylor MG, Shoemaker E, Smith M, DeLeon ER, Stoy GF, Gao Y, and Olson KR. Hydrogen sulfide (H₂S) and hypoxia inhibit salmonid gastrointestinal motility: evidence for H₂S as an oxygen sensor. *J Exp Biol* 214: 4030–4040, 2011.
 25. Duffy M, O'Mahony L, Coffey JC, Collins JK, Shanahan F, Redmond HP, and Kirwan WO. Sulfate-reducing bacteria colonize pouches formed for ulcerative colitis but not for familial adenomatous polyposis. *Dis Colon Rectum* 45: 384–388, 2002.
 26. Edmond LM, Hopkins MJ, Magee EA, and Cummings JH. The effect of 5-aminosalicylic acid-containing drugs on sulfide production by sulfate-reducing and amino acid-fermenting bacteria. *Inflamm Bowel Dis* 9: 10–17, 2003.
 27. Fiorucci S, Antonelli E, Distrutti E, Rizzo G, Mencarelli A, Orlandi S, Zanardo R, Renga B, Di SM, Morelli A, Cirino G, and Wallace JL. Inhibition of hydrogen sulfide generation contributes to gastric injury caused by anti-inflammatory nonsteroidal drugs. *Gastroenterology* 129: 1210–1224, 2005.
 28. Fiorucci S, Orlandi S, Mencarelli A, Caliendo G, Santagada V, Distrutti E, Santucci L, Cirino G, and Wallace JL. Enhanced activity of a hydrogen sulphide-releasing derivative of mesalamine (ATB-429) in a mouse model of colitis. *Br J Pharmacol* 150: 996–1002, 2007.
 29. Furne JK, Suarez FL, Ewing SL, Springfield J, and Levitt MD. Binding of hydrogen sulfide by bismuth does not prevent dextran sulfate-induced colitis in rats. *Dig Dis Sci* 45: 1439–1443, 2000.
 30. Gallego D, Clave P, Donovan J, Rahmati R, Grundy D, Jimenez M, and Beyak MJ. The gaseous mediator, hydrogen sulphide, inhibits *in vitro* motor patterns in the human, rat and mouse colon and jejunum. *Neurogastroenterol Motil* 20: 1306–1316, 2008.
 31. Gayon U. Note de M.U. Gayon presentee par M. Pasteur. *Comp Rend Acad Sci* 85: 1074–1076, 1877.
 32. Gibson GR. Physiology and ecology of the sulphate-reducing bacteria. *J Appl Bacteriol* 69: 769–797, 1990.
 33. Gil V, Gallego D, and Jimenez M. Effects of inhibitors of hydrogen sulphide synthesis on rat colonic motility. *Br J Pharmacol* 164: 485–498, 2011.
 34. Greenberg RN, Dunn JA, and Guerrant RL. Reduction of the secretory response to *Escherichia coli* heat-stable enterotoxin by thiol and disulfide compounds. *Infect Immun* 41: 174–180, 1983.
 35. Gump DW, Nadeau OW, Hendricks GM, and Meyer DH. Evidence that bismuth salts reduce invasion of epithelial cells by enteroinvasive bacteria. *Med Microbiol Immunol* 181: 131–143, 1992.
 36. Hadjiolov D, Fernando RC, Schmeiser HH, Wiessler M, Hadjiolov N, and Pirajnov G. Effect of diallyl sulfide on aristolochic acid-induced forestomach carcinogenesis in rats. *Carcinogenesis* 14: 407–410, 1993.
 37. Henderson PW, Weinstein AL, Sung J, Singh SP, Nagineni V, and Spector JA. Hydrogen sulfide attenuates ischemia-reperfusion injury in *in vitro* and *in vivo* models of intestine free tissue transfer. *Plast Reconstr Surg* 125: 1670–1678, 2010.
 38. Hennig B and Diener M. Actions of hydrogen sulphide on ion transport across rat distal colon. *Br J Pharmacol* 158: 1263–1275, 2009.
 39. Hoshi K, Yamano Y, Mitsunaga A, Shimizu S, Kagawa J, and Ogiuchi H. Gastrointestinal diseases and halitosis: association of gastric *Helicobacter pylori* infection. *Int Dent J* 52 Suppl 3: 207–211, 2002.
 40. Hosoki R, Matsuki N, and Kimura H. The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide. *Biochem Biophys Res Commun* 237: 527–531, 1997.
 41. Hristova KR, Mau M, Zheng D, Aminov RI, Mackie RI, Gaskins HR, and Raskin L. Desulfotomaculum genus- and subgenus-specific 16S rRNA hybridization probes for environmental studies. *Environ Microbiol* 2: 143–159, 2000.
 42. Huang Y, Li F, Tong W, Zhang A, He Y, Fu T, and Liu B. Hydrogen sulfide, a gaseous transmitter, stimulates proliferation of interstitial cells of Cajal via phosphorylation of AKT protein kinase. *Tohoku J Exp Med* 221: 125–132, 2010.
 43. Ierardi E, Amoroso A, La NT, Francavilla R, Castellaneta S, Marrazza E, Monno RA, and Francavilla A. Halitosis and *Helicobacter pylori*: a possible relationship. *Dig Dis Sci* 43: 2733–2737, 1998.
 44. Ise F, Takasuka H, Hayashi S, Takahashi K, Koyama M, Aihara E, and Takeuchi K. Stimulation of duodenal HCO₃(-) secretion by hydrogen sulphide in rats: relation to prostaglandins, nitric oxide and sensory neurones. *Acta Physiol (Oxf)* 201: 117–126, 2011.
 45. Jonas CR, Ziegler TR, Gu LH, and Jones DP. Extracellular thiol/disulfide redox state affects proliferation rate in a human colon carcinoma (Caco2) cell line. *Free Radic Biol Med* 33: 1499–1506, 2002.
 46. Jorgensen J and Mortensen PB. Hydrogen sulfide and colonic epithelial metabolism: implications for ulcerative colitis. *Dig Dis Sci* 46: 1722–1732, 2001.
 47. Kanazawa K, Konishi F, Mitsuoka T, Terada A, Itoh K, Narushima S, Kumemura M, and Kimura H. Factors influencing the development of sigmoid colon cancer. Bacteriologic and biochemical studies. *Cancer* 77: 1701–1706, 1996.
 48. Kasperek MS, Linden DR, Farrugia G, and Sarr MG. Hydrogen sulfide modulates contractile function in rat jejunum. *J Surg Res* 175: 234–242, 2012.
 49. Krueger D, Foerster M, Mueller K, Zeller F, Slotta-Huspenina J, Donovan J, Grundy D, and Schemann M. Signaling mechanisms involved in the intestinal pro-secretory actions of hydrogen sulfide. *Neurogastroenterol Motil* 22: 1224–1220, 2010.
 50. Kruszyna H, Kruszyna R, and Smith RP. Cyanide and sulfide interact with nitrogenous compounds to influence the relaxation of various smooth muscles. *Proc Soc Exp Biol Med* 179: 44–49, 1985.
 51. Kubo S, Kajiwarra M, and Kawabata A. Dual modulation of the tension of isolated gastric artery and gastric mucosal

- circulation by hydrogen sulfide in rats. *Inflammopharmacology* 15: 288–292, 2007.
52. Leblondel G, Mauras Y, Cailleux A, and Allain P. Transport measurements across Caco-2 monolayers of different organic and inorganic selenium: influence of sulfur compounds. *Biol Trace Elem Res* 83: 191–206, 2001.
 53. Lee H, Kho HS, Chung JW, Chung SC, and Kim YK. Volatile sulfur compounds produced by *Helicobacter pylori*. *J Clin Gastroenterol* 40: 421–426, 2006.
 54. Lehmann CG. Contents of the intestinal canal. In: *Physiological Chemistry*, Vol 2. Translated by Day GE. London: Harrison and Sons, St. Martin's Lane, 1853, pp. 121–153.
 55. Leschelle X, Goubert M, Andriamihaja M, Blottiere HM, Couplan E, Gonzalez-Barroso MD, Petit C, Pagniez A, Chaumontet C, Mignotte B, Bouillaud F, and Blachier F. Adaptive metabolic response of human colonic epithelial cells to the adverse effects of the luminal compound sulfide. *Biochim Biophys Acta* 1725: 201–212, 2005.
 56. Leschelle X, Robert V, Delpal S, Mouille B, Mayeur C, Martel P, and Blachier F. Isolation of pig colonic crypts for cytotoxic assay of luminal compounds: effects of hydrogen sulfide, ammonia, and deoxycholic acid. *Cell Biol Toxicol* 18: 193–203, 2002.
 57. Levine J, Ellis CJ, Furne JK, Springfield J, and Levitt MD. Fecal hydrogen sulfide production in ulcerative colitis. *Am J Gastroenterol* 93: 83–87, 1998.
 58. Linden DR, Furne J, Stoltz GJ, Abdel-Rehim MS, Levitt MD, and Szurszewski JH. Sulphide quinone reductase contributes to hydrogen sulphide metabolism in murine peripheral tissues but not in the CNS. *Br J Pharmacol* 165: 2178–2190, 2012.
 59. Linden DR, Sha L, Mazzone A, Stoltz GJ, Bernard CE, Furne JK, Levitt MD, Farrugia G, and Szurszewski JH. Production of the gaseous signal molecule hydrogen sulfide in mouse tissues. *J Neurochem* 106: 1577–1585, 2008.
 60. Liu Y, Kalogeris T, Wang M, Zuidema MY, Wang Q, Dai H, Davis MJ, Hill MA, and Korthuis RJ. Hydrogen sulfide preconditioning or neutrophil depletion attenuates ischemia-reperfusion-induced mitochondrial dysfunction in rat small intestine. *Am J Physiol Gastrointest Liver Physiol* 302: G44–G54, 2012.
 61. Lodge JP. Fire and Brimstone. *Ann NY Acad Sci* 502: 76–82, 1987.
 62. Loesche WJ and Kazor C. Microbiology and treatment of halitosis. *Periodontol* 2000 28: 256–279, 2002.
 63. Lou LX, Geng B, Du JB, and Tang CS. Hydrogen sulphide-induced hypothermia attenuates stress-related ulceration in rats. *Clin Exp Pharmacol Physiol* 35: 223–228, 2008.
 64. Ludany G, Cserevny J, and Handel M. [The effect of the hydrogen sulfide on intestinal sugar resorption]. *Arch Int Pharmacodyn Ther* 91: 25–31, 1952.
 65. Ma K, Liu Y, Zhu Q, Liu CH, Duan JL, Tan BK, and Zhu YZ. H₂S donor, S-propargyl-cysteine, increases CSE in SGC-7901 and cancer-induced mice: evidence for a novel anti-cancer effect of endogenous H₂S? *PLoS One* 6: e20525, 2011.
 66. Mard SA, Neisi N, Solgi G, Hassanpour M, Darbor M, and Maleki M. Gastroprotective effect of NaHS against mucosal lesions induced by ischemia-reperfusion injury in rat. *Dig Dis Sci* 57: 1496–1503, 2012.
 67. Matsunami M, Kirishi S, Okui T, and Kawabata A. Chelating luminal zinc mimics hydrogen sulfide-evoked colonic pain in mice: possible involvement of T-type calcium channels. *Neuroscience* 181: 257–264, 2011.
 68. Matsunami M, Kirishi S, Okui T, and Kawabata A. Hydrogen sulfide-induced colonic mucosal cytoprotection involves T-type calcium channel-dependent neuronal excitation in rats. *J Physiol Pharmacol* 63: 61–68, 2012.
 69. Matsunami M, Tarui T, Mitani K, Nagasawa K, Fukushima O, Okubo K, Yoshida S, Takemura M, and Kawabata A. Luminal hydrogen sulfide plays a pronociceptive role in mouse colon. *Gut* 58: 751–761, 2009.
 70. Medeiros JV, Bezerra VH, Gomes AS, Barbosa AL, Lima-Junior RC, Soares PM, Brito GA, Ribeiro RA, Cunha FQ, and Souza MH. Hydrogen sulfide prevents ethanol-induced gastric damage in mice: role of ATP-sensitive potassium channels and capsaicin-sensitive primary afferent neurons. *J Pharmacol Exp Ther* 330: 764–770, 2009.
 71. Medeiros JV, Bezerra VH, Lucetti LT, Lima-Junior RC, Barbosa AL, Tavares BM, Magalhaes PJ, Santos AA, Cunha FQ, Soares PM, and Souza MH. Role of KATP channels and TRPV1 receptors in hydrogen sulfide-enhanced gastric emptying of liquid in awake mice. *Eur J Pharmacol* 693: 57–63, 2012.
 72. Miller TW, Wang EA, Gould S, Stein EV, Kaur S, Lim L, Amarnath S, Fowler DH, and Roberts DD. Hydrogen sulfide is an endogenous potentiator of T cell activation. *J Biol Chem* 287: 4211–4221, 2012.
 73. Moore J, Babidge W, Millard S, and Roediger W. Colonic luminal hydrogen sulfide is not elevated in ulcerative colitis. *Dig Dis Sci* 43: 162–165, 1998.
 74. Moore JW, Babidge W, Millard S, and Roediger WE. Effect of sulphide on short chain acyl-CoA metabolism in rat colonocytes. *Gut* 41: 77–81, 1997.
 75. Moore JW, Babidge WJ, Millard SH, and Roediger WE. Thiolmethyltransferase activity in the human colonic mucosa: implications for ulcerative colitis. *J Gastroenterol Hepatol* 12: 678–684, 1997.
 76. Moore JW, Millard S, Babidge W, Rowland R, and Roediger WE. Hydrogen sulphide produces diminished fatty acid oxidation in the rat colon *in vivo*: implications for ulcerative colitis. *Aust N Z J Surg* 67: 245–249, 1997.
 77. Nagabhushan M, Line D, Polverini PJ, and Solt DB. Anticarcinogenic action of diallyl sulfide in hamster buccal pouch and forestomach. *Cancer Lett* 66: 207–216, 1992.
 78. Nagao M, Duenes JA, and Sarr MG. Role of hydrogen sulfide as a gasotransmitter in modulating contractile activity of circular muscle of rat jejunum. *J Gastrointest Surg* 16: 334–343, 2012.
 79. Nagao M, Linden DR, Duenes JA, and Sarr MG. Mechanisms of action of the gasotransmitter hydrogen sulfide in modulating contractile activity of longitudinal muscle of rat ileum. *J Gastrointest Surg* 15: 12–22, 2011.
 80. Ogawa H, Takahashi K, Miura S, Imagawa T, Saito S, Tominaga M, and Ohta T. H(2)S functions as a nociceptive messenger through transient receptor potential ankyrin 1 (TRPA1) activation. *Neuroscience* 218: 335–343, 2012.
 81. Ohge H, Furne JK, Springfield J, Rothenberger DA, Madoff RD, and Levitt MD. Association between fecal hydrogen sulfide production and pouchitis. *Dis Colon Rectum* 48: 469–475, 2005.
 82. Ohge H, Furne JK, Springfield J, Sueda T, Madoff RD, and Levitt MD. The effect of antibiotics and bismuth on fecal hydrogen sulfide and sulfate-reducing bacteria in the rat. *FEMS Microbiol Lett* 228: 137–142, 2003.
 83. Parajuli SP, Choi S, Lee J, Kim YD, Park CG, Kim MY, Kim HI, Yeum CH, and Jun JY. The inhibitory effects of hydrogen sulfide on pacemaker activity of interstitial cells of

- cajal from mouse small intestine. *Korean J Physiol Pharmacol* 14: 83–89, 2010.
84. Park HS, Kim GY, Choi IW, Kim ND, Hwang HJ, Choi YW, and Choi YH. Inhibition of matrix metalloproteinase activities and tightening of tight junctions by diallyl disulfide in AGS human gastric carcinoma cells. *J Food Sci* 76: T105–T111, 2011.
 85. Pitcher MC, Beatty ER, and Cummings JH. The contribution of sulphate reducing bacteria and 5-aminosalicylic acid to faecal sulphide in patients with ulcerative colitis. *Gut* 46: 64–72, 2000.
 86. Pitcher MC and Cummings JH. Hydrogen sulphide: a bacterial toxin in ulcerative colitis? *Gut* 39: 1–4, 1996.
 87. Pouokam E, Steidle J, and Diener M. Regulation of colonic ion transport by gasotransmitters. *Biol Pharm Bull* 34: 789–793, 2011.
 88. Ramazzini B. *De Morbis Artificum English. Diseases of Workers* (the Latin text of 1713 revised, with translation and notes by Wright WC). Birmingham, AL: Classics of Medicine Library, 1983.
 89. Roediger WE and Babidge WJ. Nitric oxide effect on colonocyte metabolism: co-action of sulfides and peroxide. *Mol Cell Biochem* 206: 159–167, 2000.
 90. Roediger WE, Duncan A, Kapaniris O, and Millard S. Reducing sulfur compounds of the colon impair colonocyte nutrition: implications for ulcerative colitis. *Gastroenterology* 104: 802–809, 1993.
 91. Roediger WE, Duncan A, Kapaniris O, and Millard S. Sulphide impairment of substrate oxidation in rat colonocytes: a biochemical basis for ulcerative colitis? *Clin Sci (Lond)* 85: 623–627, 1993.
 92. Roediger WE, Moore J, and Babidge W. Colonic sulfide in pathogenesis and treatment of ulcerative colitis. *Dig Dis Sci* 42: 1571–1579, 1997.
 93. Rowan FE, Docherty NG, Coffey JC, and O'Connell PR. Sulphate-reducing bacteria and hydrogen sulphide in the aetiology of ulcerative colitis. *Br J Surg* 96: 151–158, 2009.
 94. Scheele CW. *Chemical Observations and Experiments on Air and Fire, ... with a Prefatory Introduction by Torben Bergman*, Translated from the German by Forster JR... To which are Added Notes by Richard Kirwan... with a Letter to Him from Joseph Priestley. London: J. Johnson, 1780.
 95. Schemann M and Grundy D. Role of hydrogen sulfide in visceral nociception. *Gut* 58: 744–747, 2009.
 96. Schicho R, Krueger D, Zeller F, Von Weyhern CW, Frieling T, Kimura H, Ishii I, De GR, Campi B, and Schemann M. Hydrogen sulfide is a novel prosecretory neuromodulator in the Guinea-pig and human colon. *Gastroenterology* 131: 1542–1552, 2006.
 97. Schroeder BO, Wu Z, Nuding S, Groscurth S, Marcinowski M, Beisner J, Buchner J, Schaller M, Stange EF, and Wehkamp J. Reduction of disulphide bonds unmasks potent antimicrobial activity of human beta-defensin 1. *Nature* 469: 419–423, 2011.
 98. Shyntum Y, Iyer SS, Tian J, Hao L, Mannery YO, Jones DP, and Ziegler TR. Dietary sulfur amino acid supplementation reduces small bowel thiol/disulfide redox state and stimulates ileal mucosal growth after massive small bowel resection in rats. *J Nutr* 139: 2272–2278, 2009.
 99. Smith FM, Coffey JC, Kell MR, O'Sullivan M, Redmond HP, and Kirwan WO. A characterization of anaerobic colonization and associated mucosal adaptations in the undiseased ileal pouch. *Colorectal Dis* 7: 563–570, 2005.
 100. Spiller F, Orrico MI, Nascimento DC, Czaikoski PG, Souto FO, Alves-Filho JC, Freitas A, Carlos D, Montenegro MF, Neto AF, Ferreira SH, Rossi MA, Hothersall JS, Assreuy J, and Cunha FQ. Hydrogen sulfide improves neutrophil migration and survival in sepsis via K⁺ ATP channel activation. *Am J Respir Crit Care Med* 182: 360–368, 2010.
 101. Stent A, Every AL, and Sutton P. *Helicobacter pylori* defense against oxidative attack. *Am J Physiol Gastrointest Liver Physiol* 302: G579–G587, 2012.
 102. Strega PR, Bernard CE, Kraichely RE, Mazzone A, Sha L, Beyder A, Gibbons SJ, Linden DR, Kendrick ML, Sarr MG, Szurszewski JH, and Farrugia G. Hydrogen sulfide is a partially redox-independent activator of the human jejunum Na⁺ channel, Nav1.5. *Am J Physiol Gastrointest Liver Physiol* 300: G1105–G1114, 2011.
 103. Suarez F, Furne J, Springfield J, and Levitt M. Production and elimination of sulfur-containing gases in the rat colon. *Am J Physiol* 274: G727–G733, 1998.
 104. Suarez FL, Furne JK, Springfield J, and Levitt MD. Bismuth subsalicylate markedly decreases hydrogen sulfide release in the human colon. *Gastroenterology* 114: 923–929, 1998.
 105. Takeuchi K, Aihara E, Kimura M, Dogishi K, Hara T, and Hayashi S. Gas mediators involved in modulating duodenal HCO₃⁻ secretion. *Curr Med Chem* 19: 43–54, 2012.
 106. Tangerman A. Halitosis in medicine: a review. *Int Dent J* 52 Suppl 3: 201–206, 2002.
 107. Tangerman A, Winkel EG, de LL, van Oijen AH, and de Boer WA. Halitosis and *Helicobacter pylori* infection. *J Breath Res* 6: 017102, 2012.
 108. Taniguchi E, Matsunami M, Kimura T, Yonezawa D, Ishiki T, Sekiguchi F, Nishikawa H, Maeda Y, Ishikura H, and Kawabata A. Rhodanese, but not cystathionine-gamma-lyase, is associated with dextran sulfate sodium-evoked colitis in mice: a sign of impaired colonic sulfide detoxification? *Toxicology* 264: 96–103, 2009.
 109. Teague B, Asiedu S, and Moore PK. The smooth muscle relaxant effect of hydrogen sulphide *in vitro*: evidence for a physiological role to control intestinal contractility. *Br J Pharmacol* 137: 139–145, 2002.
 110. Tsubota-Matsunami M, Noguchi Y, Okawa Y, Sekiguchi F, and Kawabata A. Colonic hydrogen sulfide-induced visceral pain and referred hyperalgesia involve activation of both Ca(v)3.2 and TRPA1 channels in mice. *J Pharmacol Sci* 119: 293–296, 2012.
 111. van Ampting MT, Schonewille AJ, Vink C, Brummer RJ, van der Meer R, and Bovee-Oudenhoven IM. Intestinal barrier function in response to abundant or depleted mucosal glutathione in Salmonella-infected rats. *BMC Physiol* 9: 6–9, 2009.
 112. Wallace JL. Building a better aspirin: gaseous solutions to a century-old problem. *Br J Pharmacol* 152: 421–428, 2007.
 113. Wallace JL, Caliendo G, Santagada V, and Cirino G. Markedly reduced toxicity of a hydrogen sulphide-releasing derivative of naproxen (ATB-346). *Br J Pharmacol* 159: 1236–1246, 2010.
 114. Wallace JL, Caliendo G, Santagada V, Cirino G, and Fiorucci S. Gastrointestinal safety and anti-inflammatory effects of a hydrogen sulfide-releasing diclofenac derivative in the rat. *Gastroenterology* 132: 261–271, 2007.
 115. Wallace JL, Vong L, McKnight W, Dickey M, and Martin GR. Endogenous and exogenous hydrogen sulfide promotes resolution of colitis in rats. *Gastroenterology* 137: 569–78, 2009.
 116. Wargovich MJ and Goldberg MT. Diallyl sulfide. A naturally occurring thioether that inhibits carcinogen-induced nuclear damage to colon epithelial cells *in vivo*. *Mutat Res* 143: 127–129, 1985.

117. Wargovich MJ, Woods C, Eng VW, Stephens LC, and Gray K. Chemoprevention of N-nitrosomethylbenzylamine-induced esophageal cancer in rats by the naturally occurring thioether, diallyl sulfide. *Cancer Res* 48: 6872–6875, 1988.
118. Wu YC, Wang XJ, Yu L, Chan FK, Cheng AS, Yu J, Sung JJ, Wu WK, and Cho CH. Hydrogen sulfide lowers proliferation and induces protective autophagy in colon epithelial cells. *PLoS One* 7: e37572, 2012.
119. Yonezawa D, Sekiguchi F, Miyamoto M, Taniguchi E, Honjo M, Masuko T, Nishikawa H, and Kawabata A. A protective role of hydrogen sulfide against oxidative stress in rat gastric mucosal epithelium. *Toxicology* 241: 11–18, 2007.
120. Yoon PJ, Parajuli SP, Zuo DC, Shahi PK, Oh HJ, Shin HR, Lee MJ, Yeum CH, Choi S, and Jun JY. Interplay of hydrogen sulfide and nitric oxide on the pacemaker activity of interstitial cells of cajal from mouse small intestine. *Chonnam Med J* 47: 72–79, 2011.
121. Zanardo RC, Brancaleone V, Distrutti E, Fiorucci S, Cirino G, and Wallace JL. Hydrogen sulfide is an endogenous modulator of leukocyte-mediated inflammation. *FASEB J* 20: 2118–2120, 2006.
122. Zhang H, Moolchala SM, and Bhatia M. Endogenous hydrogen sulfide regulates inflammatory response by activating the ERK pathway in polymicrobial sepsis. *J Immunol* 181: 4320–4331, 2008.
123. Zhang H, Zhi L, Moolchala S, Moore PK, and Bhatia M. Hydrogen sulfide acts as an inflammatory mediator in cecal ligation and puncture-induced sepsis in mice by upregulating the production of cytokines and chemokines via NF-kappaB. *Am J Physiol Lung Cell Mol Physiol* 292: L960–L971, 2007.
124. Zhang H, Zhi L, Moore PK, and Bhatia M. Role of hydrogen sulfide in cecal ligation and puncture-induced sepsis in the mouse. *Am J Physiol Lung Cell Mol Physiol* 290: L1193–L1201, 2006.
125. Zhao P, Huang X, Wang ZY, Qiu ZX, Han YF, Lu HL, Kim YC, and Xu WX. Dual effect of exogenous hydrogen sulfide on the spontaneous contraction of gastric smooth muscle in guinea-pig. *Eur J Pharmacol* 616: 223–228, 2009.
126. Zuidema MY, Peyton KJ, Fay WP, Durante W, and Korthuis RJ. Antecedent hydrogen sulfide elicits an anti-inflammatory phenotype in postischemic murine small intestine: role of heme oxygenase-1. *Am J Physiol Heart Circ Physiol* 301: H888–H894, 2011.
127. Zuidema MY, Yang Y, Wang M, Kalogeris T, Liu Y, Meiningner CJ, Hill MA, Davis MJ, and Korthuis RJ. Antecedent hydrogen sulfide elicits an anti-inflammatory phenotype in postischemic murine small intestine: role of BK channels. *Am J Physiol Heart Circ Physiol* 299: H1554–H1567, 2010.

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Abbreviations Used

CM	=	circular muscle
H ₂ S	=	hydrogen sulfide
ICC	=	interstitial cells of Cajal
IPANs	=	intrinsic afferent neurons
K _{ATP} channel	=	ATP-sensitive potassium channel
LM	=	longitudinal muscle
MP	=	myenteric plexus
MUC	=	mucosa
NSAID	=	non-steroidal anti-inflammatory drug
SMP	=	submucosal plexus
SRB	=	sulfate-reducing bacteria
TFF3	=	trefoil factor 3
TRP	=	transient receptor potential