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 (H₂S) in the gastrointestinal system is reviewed. Bacterial, host and pharmaceutical-derived H₂S are all considered and presented according to the physiological or pathophysiological effects of the gaseous signal molecule. These subjects include the toxicology of intestinal H₂S with emphasis on bacterial-derived H₂S, especially from sulfate-reducing bacteria, the role of endogenous and exogenous H₂S in intestinal inflammation, and the roles of H₂S 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 H₂S in this system; recent findings have expanded the potential molecular targets for H₂S 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 H₂S. It is clear from the current literature that the long-appreciated relationship between H₂S and the gastrointestinal tract continues to be strong as we endeavor to unravel its mysteries.

Introduction

Hydrogen sulfide (H₂S) is intimately connected with the gastrointestinal system. Early biochemists, microbiologists, and physiologists recognized H₂S 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 H₂S 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 H₂S in privy gas (88). It is likely not surprising to most people that early chemists consider that digestion in the large intestine is the same chemical process as putrefaction. The biological origin of H₂S gas was solidified when Gayon described the ability of isolated bacteria to generate H₂S 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 H₂S by intestinal bacteria.

This manuscript is designed to comprehensively review the current literature regarding the effects of H₂S 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.
Bacterial H₂S, Intestinal H₂S Toxicology, and Cancer

Microbial origins of H₂S 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 H₂S via the desulfhydration of cysteine or serum proteins by subgingival bacteria, including *Peptostreptococcus anaerobius*, *M. prevotii*, *Eubacterium limosum*, *Centipedia periodontii*, *Selenomonas artemidis*, *Prevotella intermedia*, *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 H₂S by *Helicobacter pylori*, the pathogen responsible for gastritis. While it is clear that *H. pylori* can produce H₂S 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 H₂S from *H. pylori* during gastritis is not clear, but is likely a major contributor to the bacterium’s defense against oxidative attack (101).

*Desulfovoccus*, *Desulfonema*, *Desulfosarcina*, *Desulfobacter*, *Desulfobulbus*, and *Desulfovirbio* are *ß*-Proteobacteria genera that utilize sulfate as a terminal electron acceptor in the production of ATP to produce H₂S. *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 *Desulfovirbio* and *Archaea* species belonging to the genera *Archaeoglobus*, *Thermocladium*, and *Caldicellulosa* that are also capable of dissimilatory sulfate reduction with *Desulfotomaculum* species being the most robust (41).

H₂S 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 *x*-ketobutyrate can be used as electron donors for the SRB described above to generate even more H₂S. 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 H₂S *via* the expression of the iron flavoprotein sulfite reductase.

H₂S is the major sulfur-containing constituent of cecal and rectal gas and can reach concentrations as high as 40 μM.
(1000 ppm) (103). Because of numerous lethal exposures to H₂S from sewage and farm workers, the toxicity of H₂S, 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 H₂S 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 H₂S on intestinal cells, more specifically, cultured colonic epithelial cells are reviewed (Fig. 3). Sodium hydroxysulfide (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). H₂S causes 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 H₂S 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 H₂S and that butylhydroxyanisole, a radical scavenger, reduces DNA damage induced by H₂S 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 H₂S (6). In addition to causing DNA
H2S and Intestinal Epithelial Cells

H2S exerts numerous toxic effects on cultured gastrointestinal epithelial cells. Damage, H2S 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 colon epithelial cells is inhibited by NaHS with an IC50 of 0.32 μM with concurrent reductions in oxygen consumption (55). Despite these findings that support the toxic effects of H2S, it does not alter the membrane integrity of isolated pig colonic crypts (56).

The toxic effects of exogenous H2S have led some to propose luminal H2S 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 H2S (described above) suggest a potential causative role for the gas in cancer biology. Support for this concept comes from observations that H2S 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, H2S 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 H2S, 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 H2S 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).

H2S and Intestinal Inflammation

The role of H2S in intestinal inflammation is complex and at times contradictory (Fig. 4). Some experimental and clinical data suggest that H2S 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, H2S 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 H2S 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 H2S, 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 H2S 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 H2S 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 H2S is delivered (28, 68, 115), or significantly worsen when endogenous H2S production is inhibited (115). A potential mechanism of the anti-inflammatory effects of H2S is the ability of luminal H2S to modify secreted defensin activity (97).

Further support for an anti-inflammatory role of H2S comes from a number of studies conducted outside the colon. As has been demonstrated in the heart and central nervous system, exogenous H2S has a protective role in models of intestinal ischemia (37, 60, 66, 126, 127). H2S protects the gastric mucosa in models of ethanol-induced gastritis (15, 70). Exogenous H2S 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 H2S,
mostly by the efforts of John Wallace and colleagues, is the protective role for both endogenous and exogenous H$_2$S against nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis (11, 27, 113, 114). These studies are culminating in the development of therapeutics designed to release H$_2$S 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 H$_2$S (180 l 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 l mol/kg) (18, 100). To confuse this issue further, both sides in this debate have demonstrated that inhibiting the endogenous production of H$_2$S inhibits leukocyte trafficking in mesenteric arteries (124) and conversely, delivering exogenous H$_2$S enhances leukocyte trafficking (18, 124). Completely opposite effects on leukocyte trafficking have been demonstrated in models of carrageenan-induced hindpaw inflammation, aspirin-induced gastric ulceration, and air pouch-induced inflammation, where inhibition of endogenous H$_2$S enhanced leukocyte migration, and exogenous H$_2$S (100 l mol/kg) reduced leukocyte migration (27, 121). One study has also demonstrated that nanomolar concentrations of H$_2$S can potentiate T lymphocyte activation (72). Because T cells are capable of both potentiating and resolving inflammation depending on polarization, it is possible that H$_2$S 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 H$_2$S 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 H$_2$S are likely to resolve what is at present often conflicting and confusing data.

**Endogenous H$_2$S 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-$\gamma$-lyase generate H$_2$S from the amino acid cysteine (59). There

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**FIG. 4. H$_2$S and inflammation.** The literature describes both pro-inflammatory and anti-inflammatory effects of endogenously produced and exogenously delivered H$_2$S.
is a robust mechanism that removes H\textsubscript{2}S 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\textsubscript{2}S is incorporated into proteins in the mouse colon neuromuscular layers (58).

The first work on the role of H\textsubscript{2}S 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\textsubscript{2}S (40, 109). Unlike the cardiovascular system, identifying the molecular mechanisms that contribute to H\textsubscript{2}S-induced smooth muscle relaxation has been more difficult. There are studies that have demonstrated a partial contribution of the ATP-sensitive potassium (K\textsubscript{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\textsubscript{ATP} channels in H\textsubscript{2}S-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\textsubscript{2}S 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\textsubscript{2}S and suggests that H\textsubscript{2}S 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\textsubscript{2}S inhibits pacemaker activity in ICC (83) and interacts with nitric oxide in regulating functional pacemaker activity (120). H\textsubscript{2}S stimulates the proliferation of ICC through the phosphorylation of AKT (42). H\textsubscript{2}S activates voltage-gated sodium channels (NaV1.5) 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\textsubscript{2}S contributes to resting membrane potential and spontaneous contractions in the rat colon as cystathionine-\gamma-lyase and cystathionine-\beta-synthase inhibitors are able to reduce H\textsubscript{2}S production, depolarize smooth muscle cells, and increase the frequency of contractions in muscle strips (33). Functional assessments in awake mice demonstrate that H\textsubscript{2}S enhances the gastric motility. The neural and muscular components of the peristaltic reflex, one pattern of gastrointestinal motility, are illustrated with observed actions of H\textsubscript{2}S on these components. There is little evidence that luminal (bacterial) H\textsubscript{2}S contributes directly to the neuromuscular components of motility as the epithelial cells efficiently oxidize H\textsubscript{2}S 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.
emptying of liquids via K\textsubscript{ATP} and transient receptor potential V1 (TRPV1) channels (71).

**H\textsubscript{2}S 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 H\textsubscript{2}S, but it should be noted that there is significant interaction in this system of H\textsubscript{2}S with nitric oxide and carbon monoxide. Exogenous H\textsubscript{2}S 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 demonstrates that H\textsubscript{2}S 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, H\textsubscript{2}S relaxes gastric arterioles at high concentrations via K\textsubscript{ATP}-dependent and independent mechanisms, but also contracts gastric arterioles at low concentrations by inhibiting NO release (51). Other neurogenic effects of H\textsubscript{2}S 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 H\textsubscript{2}S on epithelial cells, a subsequent study in the rat colon demonstrates that H\textsubscript{2}S 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, H\textsubscript{2}S stimulates the

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**FIG. 6.** H\textsubscript{2}S and intestinal secretion. H\textsubscript{2}S 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 H₂S in the physiological response of the duodenum to stomach acid (44). An early work in this area described that H₂S delivered to the isolated intestinal loop of the dog reduced the absorption of glucose without affecting xylose absorption (64).

Many direct effects of H₂S on epithelial cells were discussed above in the section regarding H₂S 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 H₂S 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 H₂S in this system are suggested by the finding that cysteine enhances ileal mucosal growth following ileal resection in rats (98). The breakdown products of H₂S, thiosulfate, and sulfate inhibit the transport of selenium across monolayers of the transformed epithelial cell, Caco-2 (52), suggesting that not only H₂S, 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 H₂S on different and new epithelial cell lines.

**FIG. 7.** H₂S and gastrointestinal nociception. H₂S 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 H₂S. 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 N-type calcium channels (69). The chelation of zinc usually bound to N-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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Abbreviations Used

CM = circular muscle
H2S = hydrogen sulfide
ICC = interstitial cells of Cajal
IPANs = intrinsic afferent neurons
KATP 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