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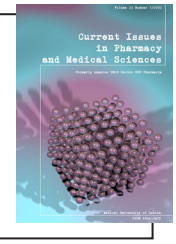

The role of hydrogen sulfide in gastrointestinal tract functioning (review)

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ABSTRACT

Despite a fairly large amount of literature data about the involvement of hydrogen sulfide in physiological and pathophysiological processes, its role in gastrointestinal tract functioning has not been studied sufficiently. This review systematizes and generalizes the mechanisms of H_2S-associated regulation of gastrointestinal secretion and motility on the basis of literature sources processing and own research results. We analysed world professional literature and sources in Google Scholar, PubMed, MedLine, Embase, Cochrane, and data from more than 50 articles and books on the problem were processed in the article. This review gives a synopsis of the H_2S function in the regulation of the secretory and motor-evacuation function, and in stimulating the reparative properties of the digestive tract, and indicates the main mechanisms.

INTRODUCTION

Hydrogen sulfide (H_2S) was synthesized for the first time in 1777 by the Swedish chemist, Carl Wilhelm Scheele, and since then, this molecule has gained considerable significance. Since the end of the 90s of the twentieth century, interest in H_2S has increased considerably in connection with the establishment of its involvement in the regulation of physiological functions in animals and humans [1]. In Nature, this gas is synthesized during decomposition of proteins, which in their turn contain sulfur-containing amino acids, which are also contained in insignificant amounts in the intestines of animals and humans. Normally, its concentration should not exceed 0,1 mg/m^3, and therefore, H_2S remains most dangerous (5 times more toxic than CO) due to its ability to inhibit the processes of tissue respiration by suppressing cytochrome-c-oxidase [2,3]. It has recently become known that this gas is synthesized in humans and animals, and the intensity of synthesis, and, consequently, both the content and the biological effect in different cells of the body – is different [3].

Despite a large amount of literature data on the involvement of this molecule in the physiological and pathophysiological processes, its role in the gastrointestinal tract (GIT) functioning has not been studied thoroughly enough, although in recent years there has been evidence of the ability of H_2S, endogenously synthesized in the GIT, to regulate secretory and motor function, and fulfill pro- and anti-inflammatory, as well as anti- and nociceptive actions [4-7]. Nowadays, H_2S is a recognized member of the family of gas transmitters and is involved in the regulation of vascular tone, neuromodulation, cytoprotection, inflammation, apoptosis and other processes [8-11].

The main substrates for endogenous H_2S in the tissues are sulfur-containing amino acids, L-cysteine and L-homocysteine, its main production enzymes are pyridoxal phosphate -dependent enzymes – cystathionine-β-synthase (CBS, EC 4.2.1.22), cystathionine-γ-lyase (CSE, EC 4.4.1.1), as well as cysteine aminotransferase (CAT, EC 2.6.1.3). The main reactions that ensure the formation of H_2S in the tissues of animals and humans include: 1) desulfuration of L-cysteine to pyruvate with the participation of CSE; 2) condensation of L-homocysteine with L-cysteine and desulfuration of L-cysteine to L-serine with the participation of CBS; 3) transamination of L-cysteine to α-ketoglutarate with the participation of CAT to form 3-mercaptopiruvat, from which H_2S is further released by the participation of 3-mercaptopirovatsulphurtransferase (3-MST, EC 2.8.1.2) [3,12,13].

According to the literature, these enzymes are expressed in the smooth muscle cells of the stomach antral divisions [14], and in the small intestines of rats and mice [15]. Both enzymes are expressed in the neurons of mesenteric nerve nodes of duodenum and small intestine of rats [16].

It is also known that apart from endogenous production, H_2S can be produced exogenously, in particular by intestinal microbiote, notably, by sulfate-reducing bacteria (SRB) [17]. In physiological conditions, H_2S level in the intestine is not

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very high due to the high ability of intestine epithelial cells to metabolize H_2S [18]. However, in case that the integrity of the epithelial barrier is impaired, sufficiently high concentrations of H_2S can be created in the intestine, which may lead to the development of hydrogen sulfide toxic effects in some intestinal diseases.

In the body, H_2S acts as a signaling molecule, a gas transmitter, for which specific receptors are not found. Molecular targets for H_2S are various ion channels, receptors, enzymes and proteins that regulate a wide range of biochemical and physiological processes.

AIM

The aim of the study is to process, systematize, and generalize the mechanisms of H_2S-associated regulation of gastrointestinal activity on the basis of literature sources processing and own research results.

Hydrogen sulfide as antisecretory factor

The work of Mard *et al.* 2014 [19], showed that pharmacological inhibition of CSE by the administration of propargylglycine (PPG) resulted in increased stomach secretion in response to stomach expansion and a simultaneous increase in expression of mRNA H(+)/K(+)-ATPase α-subunit in rats compared to the control. These results confirm the «housekeeping» role of H_2S, which is to maintain the integrity of the gastric mucosa by stimulating bicarbonates secretion [20] and reducing hydrochloric acid release. Moreover, it has been shown that endogenous H_2S simulated the contractility of smooth muscle of the stomach in mice and guinea pigs [21]. Another mechanism that explains the antisecretory function of hydrogen sulfide is its synergistic relationship with NO. Thus, Ise *et al.* [22] showed that intrastomach introduction of Sodium hydrosulfide (NaHS) (donor of H_2S) increased the release of NO in the duodenum of rats. The inhibitory effect of NO on gastric secretion is mediated by direct effect on parietal cells or indirectly through the inhibition of histamine release [23]. At the same time, the antisecretory effect of H_2S significantly decreased after the precondition with N omega-Nitro-L-arginine methyl ester hydrochloride (L-NAME) (NOS inhibitor) and PPG (an inhibitor of CSE). That is, the inhibitory effect of H_2S on gastric secretion may be partially mediated by increasing NO release. Moreover, the inhibitory effect of H_2S on gastric secretion is partially mediated by enhancing endothelial nitric oxide synthase (eNOS) gene expression and simultaneously increasing NO production/release, which leads to antisecretory effects [19].

Another factor that underlies the mechanism of H_2S inhibitory or neutralizing effect on stomach secretion is its effect on cyclooxygenase-2 (COX-2) gene expression. As it is known, hydrogen sulfide increases COX-2 gene expression and production of PGE_2 in isolated cardiomyocytes [24], as well as in the large intestine of rats [25]. Taking into account the antisecretory and antacid properties of prostaglandins, it can be suggested that the reduction of hydrochloric acid synthesis and stomach acidity reduction caused by NaHS are partially associated with increased prostaglandin production.

The study of Zhao *et al*. [23] showed that intravenous administration of NaHS and 5-day administration of L-cysteine substantially reduced expression of mRNA H(+)/K(+)-ATPase α-subunit in rats compared to control animals. Thus, the reduction of mRNA expression of the α-subunit H^+/K^+-ATPase in the stomach can be considered as another possible mechanism of the antisecretory action of NaHS on gastric secretion.

Summing up the aforementioned, it can be stated that H_2S exhibits an antisecretory effect by lowering hydrochloric acid [23] and, simultaneously, has an antacid activity, by increasing bicarbonates production [22].

H_2S and gastrointestinal motility

Endogenous H_2S plays an important role in the regulation of gastrointestinal functions both in physiological and pathophysiological conditions. Numerous results of the studies on the effect of H_2S on gastrointestinal motility describe the multi-vector dose-dependent role of H_2S in different parts of the intestine. This property is compared with the effect of H_2S on the tone of smooth vascular muscles. Thus, despite the fact that, in general, H_2S relaxes smooth muscle of vessels [26], there is evidence that the inhibitory effect of H_2S is only realized at high concentrations, while low concentrations of H_2S increase the contractility of pre-reduced smooth muscle fragments of vessels [27].

Several studies have shown that endogenous H_2S has a dual effect on spontaneous contraction of smooth muscle in the anterior part, namely, low concentrations of H_2S increased basal tone, whereas high concentrations, on the contrary, suppressed spontaneous contractility [14]. A similar effect of NaHS is also described in the stomach of guinea pigs. In addition, NaHS at low concentrations (<200 M) caused membrane potential depolarization, although hyperplasia of the membrane potential and a decrease in the amplitude of slow waves were observed against the background of the inhibitor of the CBS [20]. The mechanisms underlying these relaxant effects are unclear and might include activation of myosin light chain phosphatase, ATP-sensitive potassium channels (KATP), small conductance calcium-activated potassium channels (SKCa) and even sodium channel activation [28]. It was also shown that the effect of hydrogen sulfide on the contractility of smooth muscle cells had been associated with NO. For example, NaHS engenders NO release from inhibitory motor neurons leading to smooth muscle hyperpolarization and relaxation. Considering the fact, that NaHS induced release of NO from nitrosothiols in rat brain homogenates [29], it might be possible that the inhibitory effects observed with NaHS were due to NO release, with subsequent activation of guanylyl cyclase [28]. Recently, it was shown that the interaction between H_2S and NO generated polysulfides (H_2S_n). This molecule could activate transient receptor potential ankyrin 1 channels to modify synaptic activity and cyclic guanosine monophosphate-dependent protein kinase-1α to induce muscular relaxation [30]. On the other hand, it has been demonstrated that the contractile effect of H_2S on the vascular smooth muscle was also associated with NO. H_2S is thought to induce a contractile effect by inhibiting

endothelial nitric oxide synthase (eNOS) or by combining with NO to form a novel nitrosothiol to reduce NO release [31].

The stimulatory effect of H_2S on the stomach musculature is detected in the presence of an inhibitor of voltage-dependent potassium channels, thus, endogenous H_2S directly inhibits the voltage-dependent release of potassium [31]. At the same time, the inhibitory effect of H_2S is reduced in the presence of glibenclamide, the inhibitor of K_{ATP} channels, and endogenous H_2S directly increases the bandwidth of K_{ATP} channels in smooth muscle of vessels, as it was described in some studies [32]. All these results indicate that the H_2S excitatory effect at low concentrations is mediated by inhibition of voltage-dependent potassium channels, whereas the inhibitory effect is mediated through the activation of the KATP channels [14,22]. Medeiros *et al*. [33] described the ability of the H_2S donor to accelerate the release of gastric contents in mice in a dose-dependent manner, which may be due to the relaxing effect of H_2S on muscle of the pyloric sphincter, whereas in the presence of glibenclamide, the antagonist of the vanilloid (TRPV1) receptors of capsazepine, this action was leveled, which indicated the involvement of K_{ATP} channels and TRPV1 receptors located on the nerves afferent to this effect.

Summarizing the above mentioned, H_2S influence on the motor function of the stomach is adapted to the physiological role of its various divisions. So, at the level of the stomach bottom, where the accumulation of food occurs, H_2S has a relaxing effect on the smooth muscle, whereas the stimulating effect of H_2S on the antrum, along with its inhibitory effect on the pyloric sphincter, facilitates stomach emptying. Thus, H_2S is an important stomach activity modulator.

The action of H_2S on intestinal motility has certain specificity and varies according to the intestinal area. In the duodenum of Wistar line rats, NaHS induces biphasic action on spontaneously reduced muscle, when the short-term excitatory effect changes into prolonged relaxation [15]. Such an exciting effect may be the result of vanilloid receptors activation in the afferent nerves due to substance P release and the subsequent activation of smooth muscle cells and smooth muscle contractility. At the same time, the inhibitory effect of NaHS arises from the opening of smooth muscle cell KATP channels. Similar effects of H_2S have been described with respect to the longitudinal muscles of the colon, iliac and large intestine of Wistar line rats [34]. In contrast to them, in the Lewis line rats and mice, NaHS showed suppressive effects on the contractility of smooth muscle [34]. Although ultimately the mechanisms of NaHS-induced inhibition are unknown, it is possibly connected with the difference in regulation of circular and longitudinal muscles contractility, indicating complex function of H_2S in modulating peristalsis of the colon.

In the ileum, most studies show inhibitory effect of H_2S on the motor function of smooth muscle of guinea pig, rabbits and mice [35]. Mechanisms of this effect are still under discussion, but it is believed that this is not the result of K_{ATP} channels opening, but apparently it is due to the effect of hydrogen sulfide on Ca^{2+} – dependent K^+ (SK(Ca)) channels [36].

In addition to intestinal neurons and smooth muscle cells, the object of H_2S-associated regulation of the gastrointestinal motility may be the pacemaker cells – the interstitial cells of Cajal (ICCs). Despite of data lack on CBS and CSE expression in these cells, it has been shown that exogenous H_2S was capable of inhibiting pacemaker activity [37], which may partly explain the inhibitory effect of H_2S on motility of small intestine.

As it was shown in the large intestine of mice, NaHS dose-dependently inhibited the function of spontaneous and pre-reduced smooth muscle, which was not a consequence of the effect on nerve regulation [38], nor was it related to K_{ATP} channels effect and NO content [39]. NaHS also inhibited motor function in the colon of both rats and humans [40]. This effect is significantly reduced in the presence of K_{ATP} channel blockers and small-conductance calcium-activated channels (SKCa), which confirms the involvement of these types of channels to the effects of hydrogen sulfide. In addition, unlike small intestine, NaHS did not change the frequency of slow waves, which rejected the leading role of ICC in the action of H_2S in the colon [41].

Mechanisms of H_2S signaling in the regulation of gastrointestinal motility

In general, the analysis of numerous literature data suggests that H_2S action in the GIT is quite complex and varied (Table 1). Thus, the vector of influence may differ, depending on the site of the digestive tract, the biological species, and others. The generalized mechanism of H_2S-associated regulation of gastrointestinal motility includes that H_2S affects intestinal neurons. In this case, it activates TRPV1 channels in primary afferent neurons and stimulates the release of neurotransmitter [15], or H_2S activates cholinergic neuromuscular transmission [38], which also regulates contractility of CIT musculature. Futhermore, H_2S has a direct effect on channels in smooth muscle cells, such as K_{ATP} channels [39], voltage-dependent K+ channels [26], and also SK_{Ca} channels [28,36]. However, it should be noted that the mechanisms of interaction of hydrogen sulfide with these channels remains unclear.

Table 1. Effect of H_2S on GIT motility and its mechanisms [28]

	Section of GIT	H_2S effect on motility	Mechanism
Stomach	Fundus	Inhibitory effect	Unknown
	Antral part	Stimulating effect	**K**v channels on smooth muscles (-)
		Inhibitory effect	$\mathbf{K_{ATP}}$ channels on smooth muscles (+)
Small intestine	duodenum	Stimulating effect	TRPV1 channels on intestinal nerves (+)
		Inhibitory effect	$\mathbf{K_{ATP}}$ channels on smooth muscles (+)
	jejunum	Inhibitory effect	Unknown
	ileum	Inhibitory effect	$\mathbf{K_{ATP}}$ channels on smooth muscles and on intestinal nerves (+), or
			SK_{Ca} channels on smooth muscles (+)
Large intestine	Large intestine	Inhibitory effect	$\mathbf{K_{ATP}}$ channels (+) or SK_{Ca} channels (+)

(-) – inhibition; (+) – activation

H_2S as a stimulant for regeneration in the GIT

Gastric ulcers, especially induced by nonsteroidal anti-inflammatory drugs, are a great clinical problem, despite the introduction of selective COX-2 inhibitors into clinical

practice. Herein, applying antisecretory medications reduces the risk of developing ulcers and stimulates their healing. Nevertheless, the problem of gastrointestinal bleeding remains unresolved.

Endogenous compounds that can stimulate the healing of stomach ulcers are quite often described. These include PG, epidermal growth factor, fibroblast growth factor and NO [41]. Recently, other gas mediators were included in this list. H_2S is a vasodilator and a neuromodulator [42], and also increases the resistance of stomach mucous membrane (SMM) to the damaging factors [43]. In addition to increasing the resistance of SMM to damage, H_2S is matched with nitric oxide in the ability to inhibit the leukocytes adhesion to vascular endothelium [44], as well as the ability to show analgesic action [45].

Literature data show [46] that H_2S, like NO, has the ability to increase reparative processes in stomach mucous membrane, and the introduction of H_2S donor reduces the timing of healing of ulcers and wounds. It has also been shown that the wound healing effect of hydrogen sulfide on gastric ulcers was a consequence of its vasorelaxing effect, but was not related to K^+ATP channels and NO-dependent mechanisms.

Studies of possible mechanisms for accelerating the healing of ulcers under the influence of H_2S were conducted. It was found that, unlike proton pump inhibitors that also had reparative effects in the stomach and duodenum [47], none of the donor injections of H_2S in wound healing doses affected the volume or pH of gastric juice.

The next step was to study the role of another mechanism of action of H_2S, namely its effect on K^+_{ATP} channels, in the reparative effect on SMM. As it is known, it is through this mechanism that many effects of H_2S, including blood vessel expansion, inhibition of adhesion of leukocytes, visceral analgesia, as well as anti-fluent action, are realized due to the fact that all these effects were inhibited when the K^+_{ATP} channel antagonist (glibenclamide) were introduced and amplified on against his agonist (pinacidil) [45]. However, this mechanism, as evidenced by the results of studies Wallace *et al*. [46], also was not involved in the realization of the reparative effect of H_2S.

According to literature [48], substances containing sulfhydryl groups may exhibit gastroprotective properties, but the mechanism of this action remains unclear. One of the possible mechanisms is the antioxidant action that is mediated through the effect on the level of glutathione in the stomach. Increased blood flow to the periphery of the ulcer, as shown, is important for regeneration processes. Taking into account that H_2S is a vasodilator, it is suggested that this may be one of the mechanisms by which H_2S contributes to healing. A number of authors [46,47] note that H_2S donors increase blood flow to the stomach. Potential contributions of H_2S vascular actions to its beneficial effect on ulcer healing need further study.

The role of H_2S in apoptosis

In the studies of Guo *et al*. [51], it was shown that the preconditioning of the cell culture of SMM with a donor of H_2S – sodium hydrogen sulfide dose-dependently prevented apoptosis of stomach cells caused by ischemia-reperfusion. Such an effect was also observed in endogenous hyperproduction of H_2S.

Today, it is shown that H_2S constrains the processes of apoptosis of cells through a variety of mechanisms. According to some studies, H_2S is capable of inhibiting the expression of proapoptotic factors – caspase-3, Fas, FasL, and TNFα [52]. H_2S donors may activate casein kinase 2, which activates the repressor of apoptosis by its phosphorylation. It is indicative that H_2S can suppress the activity of calciurine, which causes damage to mitochondria and defoliates apoptotic regulatory protein.

The effect of H_2S on apoptosis is also realized at mitochondria level. H_2S suppresses the formation of ROS in mitochondria, stabilizes mitochondrial membrane and therefore prevents the development of apoptosis in cells [53].

According to the results of our research [54], the independent administration of NaHS to experimental rats practically did not affect the parameters of the cell cycle of stomach mucous membrane of the rats. These results do not fully coincide with those described in the literature with regard to anti-apoptotic and pro-apoptotic properties of H_2S, including the gastric mucosa [55,56]. However, it should be noted that the ability of donor H_2S, S-propargyl-cysteine to stimulate apoptosis, manifested itself in the model of gastric cancer cells culture, and was accompanied by increase in antiapoptotic genes expression (p53 and Bax) in the tumor and its cells [55]. Instead, the anti-apoptotic effect of H_2S was documented by other authors [55,56], which showed that the preconditioning of the cell culture of SMM with a H_2S-NaHS donor dose alertly prevented apoptosis of the stomach cells caused by ischemia-reperfusion. Such an effect was also observed in endogenous overproduction of H_2S. Mechanisms of its action include the ability to reduce the induction of c-Jun NH2-terminal kinase (JNK)-mithogen-activated protein kinase (MAPK) -fused retinopathy and the activation of NF-κB by ischemia-reperfusion. H_2S also induced S-sulfhydration of Keap1, and subsequent disassociation of Keap1/Nrf2 and activation of Nrf2. H_2S was found to exhibit a protective effect through the removal of free oxygen radicals, impedment of p38 and JNK-dependent cell apoptosis and the NF-κB-dependent inflammation process. The authors consider that this "apoptosis-neutral" position of H_2S depends on the experimental conditions and may be explained by the fact that NaHS was administered to rats without a simulated pathology, with its dose being rather low (5% of LD_{50}), hence, increasing its level in the body but not exceeding the threshold toxicity. In addition, in favor of the safety of H_2S in the stomach of intact animals, it does not only affect the processes of DNA fragmentation, but also the stability of other parameters of the cell cycle. It should be noted that the literature describes the effects of H_2S on the processes of apoptosis in the stomach and other organs usually manifested in conditions of pathology. Confirmation of this hypothesis was obtained by administering diclofenac sodium together with H_2S. Under these conditions, the anti-apoptotic effect of the donor sulfide (NaHS) was detected.

The most vivid example of the modulating effect of H_2S on the GIT state under conditions of xenobiotic-induced toxicity is so-called NSAIDs-gastropathy. Nonsteroidal anti-inflammatory drugs, especially under their prolonged

use, inhibit the synthesis of H_2S, and the administration of its donor reduces the severity of NSAIDs-induced stomach lesions in rats [50]. Combined use of NSAIDs and H_2S has led to decrease in the number of cells with fragmented DNA and normalization of regenerative properties of gastric mucosa [49]. In addition, H_2S-releasing NSAIDs exhibit significantly less peptic ulceration and a high degree of analgesic and anti-inflammatory activity, which is the basis for the combination of naproxen, aspirin, diclofenac, etc. [54].

CONCLUSIONS

Based on the analysis of literature data, it can be assumed that H_2S, a molecule produced in the GIT, plays an important role in regulating secretory and motor-evacuation functions, and stimulates microcirculation and reparative properties of the digestive tract. The data obtained convincingly indicate expediency of further advanced studies of the impact of H_2S deficiency and its excess on pathological processes in the GIT, which may be an effective approach to reducing gastrotoxicity, including that induced by medicinal products.

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REFERENCES

1. Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. *J Neurosci.* 1996;16(3):1066-71.
2. Łowicka E. Bełtowski J. Hydrogen sulfide (H_2S) – the third gas of interest for pharmacologists. *Pharmacol Rep.* 2007;59:4-24.
3. Zaichko NV, Melnik AV, Yoltukhivskyy MM, Olhovskiy AS, Palamarchuk IV. Hydrogen sulfide: metabolism, biological and medical role. *Ukr Biochem J.* 2014;86(5):5-25.
4. Huang Xu, Wen-Xie. Synthesis of H_2S in the Gastrointestinal Tract. *J Gastroenterol Hepatol Res.* 2015;4(2):1459-64.
5. Sha L, Linden DR, Farrugia G, Szurszewski JH. Effect of endogenous hydrogen sulfide on the transwall gradient of the mouse colon circular smooth muscle. *J Physiol.* 2014;592 (5):1077-89.
6. Módis K, Coletta C, Erdélyi K, Papapetropoulos A, Szabo C. Intramitochondrial hydrogen sulfide production by 3-mercaptopyruvate sulfurtransferase maintains mitochondrial electron flow and supports cellular bioenergetics. *FASEB J.* 2013;27(2):601-11.
7. Pouokam E, Steidle J, Diener M. Regulation of colonic ion transport by gasotransmitters. *Biol Pharm Bull.* 2011;34(6):789-93.
8. Kimura H. Hydrogen sulfide and polysulfides as signaling molecules. *Proc Jpn Acad Ser B. Phys Biol Sci.* 2015;91(4):131-59.
9. Cheng P, Wang F, Chen K, Guo C. Hydrogen sulfide ameliorates ischemia/reperfusion–induced hepatitis by inhibiting apoptosis and autophagy pathways. *Mediators Inflamm.* 2014(2):935251
10. Voloshchuk NI, Taran IV. Expression of gastrotoxic activity of sodium diclofenac with deficiency and excess hydrogen sulfide in the experiment. *Farmakologiya ta likars'ka toksikologiya*. 2014;4-5(40):17-24.
11. Myasoedova OA. Korzhov VI. The role of hydrogen sulfide in the implementation of the physiological functions of the body. *Zhurn NAMN Ukraïni.* 2011;17(3):191-200.
12. Tan BH, Wong PT, Bian JS. Hydrogen sulfide: a novel signaling molecule in the central nervous system. *Neurochem Int.* 2010;56:3-10.
13. Kimura H. Hydrogen sulfide: its production and functions. *Exp Physiol.* 2011;96(9):833-5.
14. Huang X, Meng XM, Liu DH, Wu YS, Guo X, Lu HL, et al. Different regulatory effects of hydrogen sulfide and nitric oxide on gastric motility in mice. *Eur J Pharmacol.* 2013;720(1-3):276-85.
15. Lu W, Li J, Gong L. H_2S modulates duodenal motility in male rats via activating TRPV1 and K(ATP) channels. *Br J Pharmacol.* 2014;171(6):1534-50.
16. 1Kasparek MS, Linden DR, Farrugia G, Sarr MG. Hydrogen sulfide modulates contractile function in rat jejunum. *J Surg Res.* 2012;175(2):234-42.
17. Medani M, Collins D, Docherty NG, Baird AW, O'Connell PR, Winter DC. Emerging role of hydrogen sulfide in colonic physiology and pathophysiology. *Inflamm Bowel Dis.* 2011;17(7):1620-5.
18. Mimoun S, Andriamihaja M, Chaumontet C, Atanasiu C, Benamouzig R, Blouin JM, et al. Detoxification of H(2)S by differentiated colonic epithelial cells: implication of the sulfide oxidizing unit and of the cell respiratory capacity. *Antioxid Redox Signal.* 2012;17(1):1-10.
19. Mard SA, Askari H, Neisi N, Veisi A. Antisecretory effect of hydrogen sulfide on gastric acid secretion and the involvement of nitric oxide. *Biomed Res Int.* 2014;2014:480921.
20. Ise F, Takasuka H, Hayashi S, Takahashi K, Koyama M, Aihara E, et al. Stimulation of duodenal HCO_3^- secretion by hydrogen sulphide in rats: relation to prostaglandins, nitric oxide and sensory neurones. *Acta Physiol* (Oxf). 2011;201(1):117-26.
21. Berg A, Redeen S, Erics A, Sjostrand SE. Nitric oxide – an endogenous inhibitor of gastric acid secretion in isolated human gastric glands. *BMC Gastroenterol.* 2004;4(1):16.
22. Mard SA, Askari H, Neisi N, Veisi A. Antisecretory Effect of Hydrogen Sulfide on Gastric Acid Secretion and the Involvement of Nitric Oxide. *Biomed Res Int.* 2014;480921.
23. Zhao P, Huang X, Wang ZY, Qiu ZX, Han YF, Lu HL, et al. Dual effect of exogenous hydrogen sulfide on the spontaneous contraction of gastric smooth muscle in guinea-pig. *Eur J Pharmacol.* 2009;616(1-3):223-8.
24. Wallace JL, Vong L, McKnight W Dicay M, Martin GR. Endogenous and exogenous hydrogen sulfide promotes resolution of colitis in rats. *Gastroenterol.* 2009;137(2):569-78.
25. Chen ZF, Zhao B, Tang XY, Li W, Zhu LL, Tang CS, et al. Hydrogen sulfide regulates vascular endoplasmic reticulum stress in apolipoprotein E knockout mice. *Chin Med J* (Engl). 2011;124(21):3460-7.
26. Kubo S, Doe I, Kurokawa Y, Kawabata A. Hydrogen sulfide causes relaxation in mouse bronchial smooth muscle. *J Pharmacol Sci.* 2007;104(4):392-6.
27. Han YF, Huang X, Guo X, Wu YS, Liu DH, Lu HL, et al. Evidence that endogenous hydrogen sulfide exerts an excitatory effect on gastric motility in mice. *Eur J Pharmacol.* 2011;673(1-3):85-95.
28. Gil V, Parsons S, Gallego D, Huizinga J, Jimenez M. Effects of hydrogen sulphide on motility patterns in the rat colon. *Br J Pharmacol.* 2013;169(1):34-50.
29. Ondrias K, Stasko A, Cacanyiova S, Sulova Z, Krizanova O, Kristek F, et al. H(2)S and HS(-) donor NaHS releases nitric oxide from nitrosothiols, metal nitrosyl complex, brain homogenate and murine L1210 leukaemia cells. *Pflugers Arch.* 2008;457:271-9.
30. Miyamoto R, Koike S., Takano Y, Shibuya N, Kimura Y, Hanaoka K, et al. Polysulfides (H_2Sn) produced from the interaction of hydrogen sulfide (H_2S) and nitric oxide (NO) activate TRPA1 channels. *Sci Rep.* 2017;7:45995.
31. Huang X, Xu Wen-Xie. Synthesis of H_2S in the gastrointestinal tract. *J Gastroenterol* Hepatol *Res.* 2015;4(2)1459-64.

32. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. *EMBO J*. 2010;20(21):6008-16.
33. Medeiros JV, Bezerra Lucetti VH, Lima-Jnior RC, Lima-Júnior RC, Barbosa AL, Tavares BM, et al. Role of KATP channels and TRPV1 receptors in hydrogen sulfide-enhanced gastric emptying of liquid in awake mice. *Eur J Pharmacol*. 2012;693(1-3):57-63.
34. Nagao M, Duenes JA, Sarr MG. Role of hydrogen sulfide as a gasotransmitter in modulating contractile activity of circular muscle of rat jejunum. *J Gastrointest Surg*. 2012;16(2):334-43.
35. Linden DR. Hydrogen sulfide signaling in the gastrointestinal tract. *Antioxid Redox Signal*. 2014;20(5):818-30.
36. Yamane S, Kanno T, Nakamura H, Fujino H, Murayama T. Hydrogen sulfide-mediated regulation of contractility in the mouse ileum with electrical stimulation: Roles of l-cysteine, cystathionine-synthase, and K+-channels. *Eur J Pharmacol*. 2014;740:112-20.
37. Parajuli SP, Choi S, Lee J, Kim YD, Park CG, Kim MY, et al. The inhibitory effects of hydrogen sulfide on pacemaker activity of interstitial cells of cajal from mouse small intestine. *Korean J Physiol Pharmacol*. 2010;14(2):83-9.
38. Linden DR, Sha L, Mazzone A, Stoltz GJ, Bernard CE, Furne JK, et al. Production of the gaseous signal molecule hydrogen sulfide in mouse tissues. *J Neurochem*. 2008;106(4):1577-85.
39. Distrutti E, Sediari L, Mencarelli A, Renga B, Orlandi S, Antonelli E, et al. Evidence that hydrogen sulfide exerts antinociceptive effects in the gastrointestinal tract by activating KATP channels. *J Pharmacol Exp Ther*. 2006;316(1):325-35.
40. Gil V, Gallego D, Jimnez M. Effects of inhibitors of hydrogen sulphide synthesis on rat colonic motility. *Br J Pharmacol*. 2011;164(2):485-98.
41. Ma L, Wallace JL. Endothelial nitric oxide synthase modulates gastric ulcer healing in rats. *Am J Physiol*. 2000;279:341-6.
42. Zhu YZ, Wang ZJ, Ho P, Loke YY, Zhu YC, Huang SH, et al. Hydrogen sulfide and its possible roles in myocardial ischemia in experimental rats. *J Appl Physiol*. 2007;102(1):261-8.
43. Fiorucci S, Distrutti E, Cirino G, Wallace JL. The emerging roles of hydrogen sulfide in the gastrointestinal tract and liver. *Gastroenterol*. 2006;131:259-71.
44. Zanardo RC, Brancaleone V, Distrutti E, Fiorucci S, Cirino G, Wallace JL. Hydrogen sulfide is an endogenous modulator of leukocyte–mediated inflammation. *FASEB J*. 2006;20:2118-20.
45. Fiorucci S, Antonelli E, Distrutti E, Rizzo G, Mencarelli A, Orlandi S, et al. Inhibition of hydrogen sulfide generation contributes to gastric injury caused by anti–inflammatory nonsteroidal drugs. *Gastroenterol*. 2005;129:1210-24.
46. Wallace JL, Dicay M, McKnight W, Martin GR. Hydrogen sulfide enhances ulcer healing in rats. *FASEB J*. 2007;21(14):4070-6.
47. Peura DA. Prevention of nonsteroidal anti–inflammatory drug-associated gastrointestinal symptoms and ulcer complications. *Am J Med*. 2004;117 (5):63-71.
48. Qu K, Chen CP, Halliwell B, Moore PK, Wong PT. Hydrogen sulfide is a mediator of cerebral ischemic damage. *Stroke*. 2006;37:889-93.
49. Voloshchuk NI, Taran IV, Mel'nik AV. Vascular mechanism in the diclophenac induced gastrotoxicity: the association with the level of hydrogen sulfide. *Curierul Med*. 2015;58(1):7-11.
50. Wallace JL, Ianaro A, de Nucci G. Gaseous mediators in gastrointestinal mucosal defense and injury. *Digest Dis Sci*. 2017; 62(9):2223-30.
51. Guo C, Liang F, Shah Masood W, Yan X. Hydrogen sulfide protected gastric epithelial cell from ischemia/reperfusion injury by Keap1 s-sulfhydration, MAPK dependent anti-apoptosis and NF-κB dependent anti-inflammation pathway. *Eur J Pharmacol*. 2014;15(725):70-8.
52. Elrod JW. Hydrogen sulfide attenuates myocardial ischemia – reperfusion injury by preservation of mitochondrial function Proc. *Natl Acad Sci* (USA). 2007;104:15560-5.
53. Kimura H. Hydrogen sulfide: from brain to gut. *Antioxid Redox Signal*. 2010;12(9):1111-23.
54. Voloshchuk N, Taran I, Toziuk O, Chereshniuk I, Denysiuk O. Influence of H_2S donor on changes in the cell cycle and the apoptosis process induced by diclofenac in the rat gastric mucosa. *Georgian Med News*. 2018;(282):140-5.
55. Ma K, Liu Y, Zhu Q, Liu CH, Duan JL, Tan BK, et al. H_2S donor, S-propargyl-cysteine, increases CSE in SGC-7901 and cancer-induced mice: evidence for a novel anti-cancer effect of endogenous H_2S? *PLoS One*. 2011;6 (6):20525.
56. Yonezawa D, Sekiguchi F, Miyamoto M, Taniguchi E, Honjo M, Masuko T, et al. A protective role of hydrogen sulfide against oxidative stress in rat gastric mucosal epithelium. *Toxicology*. 2007;20(1-2):11-8.