

A review on hydrogen sulfide: Is it pro-nociceptive or anti-nociceptive?

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ABSTRACT

Pain is sensed by the activation of painful nociceptors in the periphery or by pain mediators, such as bradykinin, serotonin, histamine, and prostaglandin, released from the damaged tissue, afferent transmission to the medulla spinalis, and by transmission stages to the high centers over the dorsal horn. Pain, which was seen as only a warning sign in the past, is now accepted as a phenomenon in itself that needs to be treated and the search for new, stronger active substances with fewer side effects in the treatment of pain is in demand. Hydrogen sulfide (H₂S) is a modulator of T-type Ca²⁺ channels, especially in Cav3.2, which are known to play a critical role in the processing of pain. H₂S can also show an anti-nociceptive effect by opening K⁺ channels and blocking nociceptors. Exciting preclinical data has demonstrated that H₂S-derived Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesic agents can be used to treat various types of pain. H₂S increases the resistance of gastric mucosa against injury occurred by drugs used for pain relief and accelerates its repair, so it provides an advantage to derivatized drugs. In addition, H₂S donors have also been shown to induce analgesia through μ-opioid receptors. Based on the studies, it is thought that the combination of H₂S with opioid receptor agonists may provide an additive or even synergistic analgesic effect. It is estimated that the modification of H₂S, with currently used analgesic drugs to prevent various side effects and increase analgesic effects, is a promising and wise approach.

Keywords: Hydrogen sulfide, Pain, Analgesic effect

INTRODUCTION

Gasotransmitters are molecules that regulate physiological and pathophysiological effects in mammalian tissues. Nitric oxide (NO) was the first molecule to emerge as an endogenous gas with biological activities, followed by carbon monoxide (CO), and H₂S (Cunha et al.; 2008; Shefa et al., 2017). In recent years, the number of studies aiming to understand the physiological effects and mechanism of action of H₂S has increased rapidly.

Previously, H₂S was defined as a colorless, poisonous gas with a rotten smell. However, it was later discovered that it was produced by enzymatic and non-enzymatic reactions in mammalian tissue and was responsible for many different biological activities (Li, Liu, Wang, Zhang, & Wang, 2020). H₂S is a molecule that is slightly larger than water and is similar to the water molecule. However, H₂S is less polar than water because the sulfur atom is less electronegative than the oxygen atom. Therefore, intramolecular forces are weaker and the melting and boiling point is lower than water (Caliendo, Cirino, Santagada, & Wallace, 2010). It also has acidic properties and has a high solubility in water. H₂S is found in two forms; mostly in neutral molecular form (H₂S) and mono ionized form (HS⁻) in physiological conditions (pH 7.4) (Zheng et al., 2017).

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H₂S biosynthesis

Cysteine is the main source of H₂S in mammals and it is synthesized by the desulfurization of L-cysteine primarily with cystathionine β-synthetase (CBS) and cystathionine lyase (CSE) (Wang, 2002; Predmore, Lefer, & Gojon, 2012; Donatti et al.; 2014). CBS enzyme is expressed in the liver, kidneys, brain (mostly Bergmann glial cells and astrocytes), ileum, uterus, placenta, and pancreatic islets. The expression of the CSE enzyme occurs in the liver, kidneys, thoracic aorta, ileum, portal vein, uterus, brain, pancreatic islets, and placenta (Kimura, 2011). 3-mercaptopyruvate sulfide transferase (3-MST) is another enzyme that is naturally responsible for the production of H₂S in the body (Huang & Moore, 2015, Kimura, 2011). 3-MST has been localized in the liver, kidneys, heart, lung, thymus, testicles, thoracic aorta, and brain (Kimura, 2011), and it is mostly located in the mitochondrial region, whereas CSE and CBS are mostly found in the cytosol. CBS and CSE enzymes produce H₂S using many different substrates. 3-MST catalyzes sulfur transfer reactions only from 3-mercaptopyruvate (3-MP) to various donors (Predmore et al., 2012). H₂S can also be obtained from glycolysis or direct reduction of glutathione and elemental sulfur (Kolluru, Shen, & Kevil, 2013).

Physiological roles and therapeutic targets of H₂S

The amount of available data on the physiological role of endogenous H₂S is increasing day by day. Many studies showed that H₂S performs physiological effects in a wide concentration range of 10 μM to 300 μM. The first described physiological effect of H₂S is the ability to relax smooth muscles (Cunha et al., 2008, Donatti et al., 2014). Endogenous H₂S has numerous physiological and pathophysiological roles in the cardiovascular, neuronal, gastrointestinal, urinary, and endocrine systems. H₂S has anti-inflammatory, antitumor, ion channel regulator, cardiovascular protective, and antioxidant effects (Fukami, Sekiguchi, & Kawabata, 2017). In addition, it has important roles in tissue repair and healing, apoptosis, cell cycle, mitochondrial function, energy metabolism, obesity, and aging (Rose, Moore, & Zhu, 2017). H₂S regulates insulin secretion from pancreatic beta cells, by activating the K⁺-ATP channel and suppressing L-type Ca²⁺ channel functions (Tang, Wu, & Wang, 2010). However, some studies suggest that H₂S inhibits insulin release, acts as part of a homeostatic mechanism that reduces glucose-induced cellular stress in pancreatic beta cells through its antioxidant properties, and it has been thought that this mechanism protects pancreatic beta cells from excessive-high glucose level-induced apoptotic cell death (Okamoto et al., 2014). Moreover, H₂S stimulates N-methyl-D-aspartic acid (NMDA) receptors, regulates the release of excitatory neurotransmitter and it is involved in the regulation of synaptic plasticity for NMDA receptor-mediated learning and memory (Tang et al., 2010).

H₂S has many therapeutic targets, including Alzheimer's, Parkinson's diseases, acute myocardial infarction, stroke, atherosclerosis, hypertension, erectile dysfunction, metabolic syndrome, diabetes, thrombosis, cancer, heart failure, organ transplantation, Huntington's disease, and peripheral arterial diseases (Predmore et al., 2012; Kimura, 2019). This study aims to draw attention to the role of H₂S in the process of pain formation and treatment.

H₂S and pain

Pain is the body's alarm system that creates reflexes to avoid the harmful agent and may lead to the treatment of damaged tissue. The Association for the Study of Pain (IASP) has described pain as 'an unpleasant feeling experience that occurs due to tissue damage that has occurred or will occur'. This definition emphasizes that pain occurs as a result of complex processes controlled by many different variables. Pain has continued to be one of the most investigated health problems for centuries (Orr, Shank & Black, 2017). Existing drugs do not provide adequate management of pain. Therefore, the search for novel therapeutic agents in the treatment of pain is still ongoing.

Various endogenous mediators such as serotonin, bradykinin, substance P, histamine, NO, and CGRP are known to play a role in the modulation of pain. Recent studies suggest that H₂S may play a role in the modulation as well and may be a new hope for pain management. H₂S has dual or even more complex roles in pain processing. It exhibits a pro-nociceptive effect, yet on the other hand, it produces an anti-nociceptive effect with different mechanisms.

The Goals of H₂S in the process of pain

The targets of H₂S in the anti-nociceptive effects

H₂S and K⁺-ATP channels

Studies have shown that potassium channels mediate the receptors (alfa2-adrenoceptor, opioid, GABA_B, muscarinic M₂, adenosine A₁, serotonin 5-HT_{1A}, cannabinoid, etc.) which play a role in pain modulation and the effects of other anti-nociceptive drugs (nonsteroidal anti-inflammatory and tricyclic anti-depressants, etc.). Many specific K⁺ channel subtypes are involved in the generation of the anti-nociceptive effect, but the most studied type is the K⁺-ATP channel. The opening of K⁺ channels in the peripheral and central nervous system is an important mechanism that mediates the anti-nociceptive effect of many drugs and natural products (Ocaña, Cendán, Cobos, Entrena, & Baeyens 2004; Tsantoulas & McMahon, 2014).

H₂S is thought to have a dual effect in inflammatory hypernociception: 1. It stimulates neutrophil migration and thus produces pro-nociceptive effect, 2. It modulates the K⁺-channels and shows the anti-nociceptive effect by directly blocking the nociceptor sensitivity (Cunha et al., 2008). In other words, H₂S acts as a negative regulator of visceral nociception by activating the K⁺-ATP channels and weakens the pain, while it also induces cytokine release (TNF-α) and produces a peripheral pro-nociceptive effect in relation to neutrophil migration (Tang et al., 2010).

Regarding the anti-nociceptive effect of H₂S, it is claimed that the anti-nociceptive effect induced by sodium hydrosulfide (NaHS), the H₂S donor, is reversed by the K⁺-ATP channel blocker glibenclamide. Also, it is reported that the K⁺-ATP channel opener, pinacidil, potentiates the NaHS-induced anti-nociceptive effect (Distrutti, 2006). These data indicate that K⁺ channels mediate the anti-nociceptive effect of H₂S (Distrutti, 2006; Lucarini et al.; 2018).

H₂S and NO

NO plays complex and different roles in the regulation of pain. Experiments with NO donors have revealed contradictory results because these molecules show both pro-nociceptive and anti-nociceptive effects (Schmidtko, Tegeder, & Geisslinger, 2009; Miculescu & Gordh, 2009). In the literature, NO is described as an important neurotransmitter that plays a role in the nociceptive process. Moreover, experimental data indicates that NO inhibits pain in the peripheral and central nervous systems. The analgesic effect of NO involves the activation of an intracellular signaling pathway including cyclic guanosine monophosphate (GMP) formation, protein kinase G (PKG) activation, and consequently the opening of K⁺ channels. Opening these channels increases the K⁺ current, which causes hyperpolarization of nociceptive neurons. It has also been shown that nitric oxide mediates the analgesic effect of drugs like opioids and NSAIDs (Cury, Picolo, Gutierrez, & Ferreira, 2011; Gomes, Cunha, & Cunha, 2020).

The H₂S donor NaHS-induced anti-nociceptive effect is reversed with NO synthase inhibitors. This data suggests that NO mediates the anti-nociceptive effect of H₂S (Distrutti, 2006; Xu et al., 2019).

H₂S and opioid receptors

Opioids have an inhibitory effect on pain by decreasing the Ca²⁺ influx from the voltage-dependent calcium channels in the neuron membrane, inhibition of adenyl cyclase (AC), and opening of K⁺ channels in the neuron membrane via the Gi protein (Distrutti et al., 2011; Przewłocki & Przewłocka, 2001).

Since H₂S has an effect on potassium channels, the role of opioid receptors in the analgesic effect of H₂S was evaluated with the visceral pain model induced with colorectal distension and a significant reduction in visceral sensitivity and pain was observed (Distrutti et al., 2011). In addition, the contribution of opioid receptors to analgesia was investigated by applying selective μ , κ , and δ opioid receptor antagonists to rats. Of these, CTAP, a selective antagonist of the μ receptor, was found to strongly inhibit H₂S induced analgesia, and hence, H₂S has been shown to induce analgesia via μ opioid receptors. (Distrutti et al.; 2011).

The targets of H₂S in the pro-nociceptive effects

H₂S and Ca²⁺ channels

Ca²⁺ channels play a critical role in the processing of somatic or visceral nociceptive information and pain control (Tang et al., 2010). H₂S is a modulator of T-type Ca²⁺ channels and distinguishes between the different subtypes of these channels (Elies, Scragg, Boyle, Gamper, & Peers, 2016; Fukami et al., 2017). It selectively regulates Cav3.2, but Cav3.1 and Cav3.3 are not affected. In nociceptor neurons, H₂S increases the function of Cav3.2 T-type calcium channels and TRPA1 channels and causes neuronal stimulation followed by pain or hyperalgesia/allodynia (Fukami et al., 2017).

In cystitis models induced on mice, it has been observed that H₂S facilitates the stimulation of sensory neurons through activation of Cav3.2 T-type Ca²⁺ channels in the later stages of the disease and leads to bladder pain. Pretreatment with

DL-propargylglycine, an inhibitor of the CSE enzyme involved in the synthesis of H₂S, eliminates nociceptive changes. This study suggests that targeting CSE or Cav3.2 T-type Ca²⁺ channels for the treatment of pain in patients with interstitial cystitis may be useful in developing a new therapeutic strategy (Matsunami et al., 2011).

H₂S increases the activity of Cav3.2 T-type calcium channels, leading to somatic pain and visceral nociception in the pancreas, colon, and bladder. It is suggested that H₂S mediates colonic nociception by activating Cav3.2 predominantly (Tsubota & Kawabata, 2019). Specifically, the role of Cav3.2 T-type Ca²⁺ channels in H₂S-mediated pain signals was investigated using the genetic deletion method and conclusive evidence is provided that Cav3.2 has an important role in HS-induced somatic and colonic pain (Matsui et al., 2019).

In another recent study, it was hypothesized that H₂S donor NaHS is effective in the treatment or prevention of migraine pain by decreasing in membrane currents through purinergic receptor P2X3 and suppression of ATP-induced calcium signals in trigeminal ganglion neurons (Koroleva et al., 2020).

H₂S and TRP channels

The transient receptor potential ankyrin-1 (TRPA1) is a member of the TRP channel family (Huang & Moore, 2015; Fukami et al., 2017). It is thought to be associated with the H₂S-induced pro-nociceptive process by working with Cav3.2. The transient receptor potential vanilloid 1 (TRPV1) also shows similar effects. It has been suggested that activation of TRPV1 and TRPA1 receptors with H₂S during neuroinflammation may lead to migraine pain by contributing to nociceptive stimulation in primary afferents (Koroleva, 2017). In a study using streptozotocin (STZ) induced diabetic rats, it was suggested that H₂S contributes to the formation of hyperalgesia and this is mediated by TRPV1, TRPA1, and TRPC channels (Roa-Coria et al., 2019). In summary, H₂S-induced hyperalgesia and pro-nociception are associated with the sensitization of both T-type Ca²⁺ channels and TRPA1 and TRPV1 channels (Tang et al., 2010).

However, in a recent study, it was emphasized that activation of primary sensory neurons with TRPA1 may have an analgesic effect, and somatostatin release, which has an inhibitory effect on pain, may be the source of this effect. This study presents new and original data on the analgesic effect of dimethyltrisulphite (DMTS), an organic trisulfite releasing H₂S, is realized by the activation of TRPA1-mediated somatostatin release and sst4 receptors (Pozsgai, Báta, & Pintér, 2019).

Also, it has been shown that polysulfide, an endogenous sulfur compound produced by the oxidation of hydrogen sulfide, has dual roles in the regulation of inflammatory pain through TRPA1 activation. It causes pain due to inflammation in the early stage but then relieves pain due to oxidative stress (Oguma, Takahashi, Okabe, & Ohta, 2021).

New approaches in the treatment of pain and H₂S

Recent studies have shown that H₂S modulates the inflammatory process. H₂S donors reduce edema, prevent leukocytes from adhering to endothelium and inhibit pro-inflammatory

cytokine synthesis. It also increases the resistance of the gastric mucosa to injury and accelerates its repair. Considering this information, it is thought that when anti-inflammatory drugs are modified to release H₂S, the efficiency will increase and the toxicity will decrease. Indeed, some NSAIDs have been modified to release H₂S, and preclinical data are promising (Wallace, 2007; Verma, Akhtar, & Singh, 2017).

NSAIDs are used to fight inflammation. However, they cause side effects by lowering the protective prostaglandin level. When H₂S is accompanied by NSAIDs, side effects will decrease and a better anti-inflammatory effect will be obtained (Verma et al; 2017).

A novel H₂S-releasing naproxen derivative, ATB-346 [2-(6-methoxynaphthalen-2-yl)-propionic acid 4-thiocarbamoyl phenyl ester] was developed. It inhibits COX activity and releases H₂S. The low dose of ATB-346 administered once a day was more effective than standard doses of naproxen or celecoxib and it significantly reduced pain in patients with osteoarthritis. It has been found to be safer for gastro-intestinal system (GI) compared to other NSAIDs (Wallace, 2007; De Cicco et al., 2016). In another recent study, sulindac was compared with NOSH-sulindac (AVT-18A) a nitric oxide and hydrogen sulfide donor, for its gastrointestinal safety, anti-inflammatory, and analgesic effects. The results show that NOSH-sulindac is safe for the GI and has a similar level of analgesic and anti-inflammatory effects to sulindac (Kashfi, Chattopadhyay, & Kodela, 2015).

NO and H₂S donor NOSH-aspirin dose-dependently reduced acetic acid-induced writhing responses and carrageenan-induced hyperalgesia and at the same dose, it was found more effective than aspirin. The potent effects of NOSH-aspirin have been associated with the reduction of the production of pro-nociceptive cytokines, such as IL-1b, and the direct activation of K⁺-ATP channels. Also, NOSH-aspirin is capable of reducing the neuronal sensitivity caused by PGE₂ by upregulation of K⁺-ATP channels. The anti-nociceptive effects of NOSH-aspirin on PGE₂-induced hyperalgesia were reversed with glibenclamide (Fonseca, Cunha, Kashfi, & Cunha, 2015).

An experimental study has shown that H₂S can increase the anti-nociceptive effect of dipyrone centrally and peripherally. It was also emphasized that the combination with H₂S donors can reduce the analgesic dose and thus side effects in this study (Erol et al., 2020). Furthermore, EV-34, a new H₂S-releasing ibuprofen derivative molecule, may be advantageous in patients with cardiovascular risk due to the cardioprotective effect of H₂S (Gyöngyösi et al., 2021). One of the most serious side effects of opioid drugs is that they cause addiction. In a study with morphine-dependent mice, it was stated that the use of opioids with H₂S prevented opioid dependence by inhibiting the cAMP pathway (Yang, Wu, Wood, Whiteman, & Bian, 2014). In another study, it was emphasized that H₂S synthase inhibitors such as CSE inhibitor propargylglycine and CBS inhibitor hydroxylamine may be beneficial in preventing morphine tolerance (Cetin et al., 2021).

In addition to NSAIDs, it has been suggested that the combination of H₂S with opioid receptor agonists such as trimebutin

can provide an additive and even synergistic analgesic effect. GIC-1001 (trimebutine 3-thiocarbonyl benzene-sulphate) is seen as a potential drug candidate because it strengthens the analgesic effects of trimebutine with H₂S release *in vivo*. This component shows the spasmolytic and peripheral opioid agonist effects of trimebutine as well as the anti-nociceptive effect of H₂S. Orally administered trimebutine only slightly reduced pain response in colorectal distention, however, GIC-1001 at the same doses significantly reduced nociceptive responses in mice (Cenac et al., 2015).

H₂S doses and administration methods may affect the pain response. It is hypothesized that systemic administration of enzymatic H₂S synthesis inhibitors and slow H₂S-releasing agents/low-dose H₂S-donors may be effective in reducing nociceptive and neuropathic pain (Guo, Li, & Yang, 2020). There are many studies showing that microglia activation mediates the pathogenesis of neuropathic pain. H₂S weakens the activation of microglia and central nervous system inflammation. For this reason, to investigate the effects of H₂S inhalation on neuropathic pain, a chronic constriction injury model of the sciatic nerve was established in mice. The results of this study show that inhaled H₂S inhibits the development of neuropathic pain in mice, possibly by suppressing microglial activation and attenuating the release of inflammatory cytokines. (Kida, Marutani, Nguyen, & Ichinose, 2015).

Oxaliplatin and paclitaxel, which are anti-cancer drugs, induce neuropathic pain in animal models. And it was observed that thiosulfocyanates (allyl-isothiocyanate and synthetic phenyl- and carboxyphenyl isothiocyanate) suppressed pain *via* H₂S release in neuropathic pain induced by anticancer drugs. The anti-neuropathic effect is largely thought to be mediated by the activation of Kv7 channels (Mannelli et al., 2017). GYY4137 is a novel, water-soluble, H₂S-releasing molecule, and it is thought to be an innovative approach in the treatment of resistant pain like neuropathic pain which is induced by chemotherapeutic drugs (Rose et al., 2017; Mannelli et al., 2017). Additionally, a recent study indicated that GYY4137 inhibits paclitaxel-induced neuropathic pain, possibly by blocking the reduction in paclitaxel-induced H₂S formation in tissues (Qabazard et al., 2020). Finally, another study suggested that H₂S could perhaps alleviate neuropathic pain using the NO / cGMP / PKG pathway and μ -opioid receptors (Li et al., 2020).

In another study, the effects of H₂S on bone cancer pain were investigated and a negative correlation was observed between H₂S level and pain scores. H₂S inhalation significantly reduced bone cancer pain by reducing thermal hyperalgesia and mechanical allodynia. This study suggests that H₂S may suppress the development of neuropathic pain in rats, by the deactivation of microglia and inhibition of inflammation in the spinal cord, in which the proliferator-activated receptor gamma/p38/Jun N-terminal kinase (PPAR γ /p38/JNK) pathway is involved (Zhuang et al., 2018).

Also, it has been shown that 4-methylbenzenecarbothioamide (4-MBC), an H₂S releasing thiobenzamide, reduced nociceptive response induced by formaldehyde and induced a long lasting inhibitory effect on carrageenan mechanical allodynia. The an-

ti-inflammatory and anti-nociceptive activities of 4-MBC may be induced by reducing neutrophils recruitment and cytokine and chemokine production (Melo et al., 2019).

More recent studies have investigated the effects of slow-release hydrogen-treated sulfur donors in neuropathic pain and osteoarthritis. Slow-release H₂S donors, allyl isothiocyanate (A-ITC), and phenyl isothiocyanate (P-ITC) have been shown to alleviate mechanical allodynia, grip strength deficits, and depressive-like behaviors accompanying osteoarthritis (Batalá, Cabarga, & Pol, 2020). It has also been suggested that A-ITC and P-ITC administration are effective in the treatment of neuropathic pain possibly by inhibiting inflammation and activating endogenous antioxidant responses (Cabarga et al., 2020).

RESULTS AND RECOMMENDATIONS

H₂S is a gas neurotransmitter that has attracted more attention in recent years. It is known that H₂S regulates physiological and pathophysiological events in many tissues. It has been reported in various studies that it also plays a role in pain modulation, but this role is complicated. H₂S plays dual or more complex roles in pain processes and it can exhibit pro-nociceptive or anti-nociceptive effects depending on the type of pain model and the different targets such as ion channels and receptors. However, recent studies provide exciting evidence that H₂S-derived analgesic agents can be used in the treatment of various types of pain. It is a well-known fact that existing analgesic drugs have various side effects, such as gastrointestinal damage and opioid addiction. Many studies have shown that the addition of H₂S to analgesic drugs reduces these side effects. However, due to the fact that the supraphysiological levels of H₂S have highly toxic effects, extreme care should be taken when developing H₂S-based therapeutic agents. Considering the information obtained, it is thought that H₂S may be the pioneer of a new therapeutic class in the future with its broad biological activity and predicted effects in current experimental studies.

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