

Review on the Safety and Benefits of Hydrogen Sulfide Ingestion

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Abstract

Introduction. Hydrogen sulfide (H₂S) is a gaseous signaling molecule with diverse roles in both physiological and pathological processes across various biological systems. It is endogenously synthesized in mammalian cells and plays significant roles in inflammation, oxidative stress, and vascular function. Recent studies have highlighted its involvement in cardiovascular health and its potential as a therapeutic target in diseases such as cancer and neurodegenerative disorders.

Methods. The review encompasses a comprehensive analysis of H₂S's dual nature in toxicity and therapeutic potential, including its role in cellular processes and its applications in cardiovascular, neurological, and inflammatory diseases. Additionally, the safety profile of H₂S, particularly its toxicity at higher concentrations and the development of countermeasures, was examined. The impact of occupational and environmental exposure to H₂S was also assessed.

Results. H₂S exhibits a dualistic nature where low concentrations have protective, anti-apoptotic effects, whereas higher concentrations are cytotoxic, leading to increased oxidative stress and mitochondrial dysfunction. Therapeutically, H₂S shows promise in treating cardiovascular diseases, neurodegenerative conditions, and certain cancers. However, the potential risks associated with its toxicity require careful management. Current research focuses on the development of H₂S-releasing compounds and novel delivery systems to optimize its therapeutic benefits while minimizing risks.

Conclusion. Hydrogen sulfide represents a molecule with considerable therapeutic potential across a spectrum of diseases, particularly in cardiovascular and neurodegenerative disorders. Despite its promising applications, the dual nature of H₂S as both a therapeutic agent and a toxic substance demands careful management and continued research to fully harness its benefits while mitigating associated risks.

Keywords. Hydrogen Sulfide - Gasotransmitter - Toxicity - Cardiovascular Health - Neuroprotection - Oxidative Stress - Inflammation - Therapeutic Potential - Mitochondrial Dysfunction - H₂S-releasing Compounds

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Introduction

Hydrogen sulfide (H_2S) is a gaseous signaling molecule with a wide range of physiological and pathological roles across different biological systems. Once primarily recognized for its toxicity and foul odor, H_2S has gained attention for its critical functions as a gasotransmitter, influencing processes such as inflammation, oxidative stress, apoptosis, and vascular function (Kaziród et al., 2022; Zhu et al., 2022). It is synthesized endogenously in mammalian cells by enzymes like cystathionine β -synthase (CBS), cystathionine γ -lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST), and has been shown to have protective effects in cardiovascular health, particularly against conditions such as arrhythmias, atherosclerosis, and myocardial infarction (Ding et al., 2022). H_2S 's therapeutic potential extends beyond cardiovascular diseases, with studies investigating its role in cancer, where it modulates tumorigenesis and serves as a potential target for therapy (Bian, 2022). Additionally, in plants, H_2S acts as a crucial signaling molecule regulating growth, development, and stress responses (Khattak et al., 2022). The development of H_2S -releasing drugs and the use of H_2S -responsive nanomaterials further underscore its potential in treating various pathological conditions, including its application in precision gas therapy for cancer (Gönbe, Aydinoğlu, and Öğülenler, 2022). However, H_2S exposure in industrial and agricultural settings presents significant health risks, particularly in occupations such as coal mining, oil extraction, and livestock operations, where workers are at risk of toxic exposure (van Goor et al., 2016; Fabian-Wheeler et al., 2017). The dangers of H_2S exposure are also evident in confined spaces, municipal services, and during natural disasters, highlighting the importance of stringent safety measures and risk management (Drimal et al., 2010; Sams et al., 2013). Despite its toxic potential, the ingestion and endogenous production of H_2S play a critical role in various physiological processes, including gastrointestinal health, modulation of ER stress in myocardial diseases, and pain management through ion channel modulation. Its interactions with gut microbiota and protective roles in muscle pathophysiology, such as in Duchenne muscular dystrophy, provide a foundation for exploring H_2S as a preventive and therapeutic agent in numerous conditions (Santana Maldonado, Weir, and Rumbelha, 2023; Zhao et al., 2023; Buret et al., 2022). Overall, H_2S is a multifaceted molecule with significant implications for health, disease, and safety across a wide range of biological and environmental contexts (Zhang et al., 2021).

This study aims to provide a comprehensive analysis of hydrogen sulfide (H_2S), examining its dual nature as both a toxic substance and a therapeutic agent. The research focuses on the role of H_2S in key cellular processes and its potential applications in treating cardiovascular, neurological, and inflammatory diseases. Additionally, the study addresses the safety concerns associated with H_2S , particularly its toxicity at higher concentrations, and explores the development of strategies to counteract these toxic effects. The impact of H_2S exposure in occupational and environmental settings is also evaluated, offering a thorough understanding of its risks and benefits across various contexts.

Safety Analysis

Toxicological profile

H_2S exhibits a dual nature in toxicity. At lower concentrations (0.01 to 0.03 ppm), H_2S has pro-survival and anti-apoptotic effects, while at higher levels (around 100 ppm), it becomes anti-proliferative and pro-apoptotic (Seydi et al., 2022). H_2S toxicity increases with concentration, potentially leading to pulmonary edema when inhaled. Poisoning primarily occurs through inhalation, causing irritation to mucous membranes, particularly the eyes, where prolonged exposure at low levels (around 20 ppm) can lead to irritative conjunctivitis. At extremely high concentrations (above 1000 ppm), H_2S can cause apnea by inhibiting the brain's breathing center (Sawaya et al., 2024). In rats, exposure to very high concentrations of H_2S (800 ppm) led to unconsciousness, while exposure to 400 ppm for 4 hours caused central nervous system depression and pulmonary edema. Neurological impairments were observed in rats exposed to 80–200 ppm over periods ranging from 5 days to 11 weeks. Additionally, damage to the nasal olfactory epithelium occurred at lower concentrations, with adverse effects observed at 80 ppm following acute

exposure and at 30 ppm during intermediate-duration exposure (Toxicological Profile For Hydrogen Sulfide And Carbonyl Sulfide, 2016).

H₂S can induce cytotoxicity by increasing reactive oxygen species (ROS) levels, causing mitochondrial dysfunction, lysosomal membrane damage, and altering glutathione (GSH) levels in brain neurons, potentially linked to neurodegenerative diseases (Munasinghe et al., 2018). In term of mitochondrial function, at high levels, H₂S inhibits cytochrome c oxidase (Complex IV) in the mitochondrial electron transport chain, a critical enzyme for aerobic respiration and ATP production. By binding competitively to Complex IV, H₂S prevents oxygen from binding, causing a disruption in the electron transport chain and halting ATP production. Thus, lead to a loss of cellular energy and, if sustained, may result in cell death (Szabo et al., 2014). A previous study showed that, exposure to H₂S led to a depletion of GSH and reduce intracellular ferric iron (Fe³⁺) to ferrous iron (Fe²⁺), which producing highly reactive hydroxyl radicals (•OH). These radicals are potent ROS that can cause extensive damage to cellular components, leading to oxidative stress, cell injury, and ultimately contributing to the toxic effects of H₂S (Truong et al., 2006).

In cases of acute accidental poisoning, H₂S can lead to fatalities, with toxicology revealing lethal levels of thiosulfate as a metabolite of H₂S (Goto et al., 2020). Moreover, H₂S exacerbates copper (Cu) cytotoxicity by promoting ROS generation, mitochondrial dysfunction, and intracellular Cu accumulation, leading to increased toxicity (Jin et al., 2015). Countermeasures for H₂S toxicity focus on binding free H₂S, mitochondrial protection, and mitigating end organ damage to develop effective antidotes (Ng et al., 2019).

Acute and chronic health effects of H₂S ingestion

Acute ingestion of H₂S can lead to severe toxicity, causing rapid coma and cardiac dysfunction, potentially resulting in death due to electromechanical dissociation of the heart (Buret et al., 2022). Long-term neurological deficits may also arise from H₂S's direct neurotoxic effects on neurons, compounded by prolonged apnea and circulatory failure (Feng et al., 2022). Conversely, chronic exposure to low H₂S levels has been associated with various chronic organ pathologies, while H₂S has shown protective effects in chronic organ degenerations (Jin et al., 2015). Moreover, H₂S at physiological concentrations plays critical roles as a gasotransmitter, impacting multiple signaling pathways in renal physiology and disease, including diabetic nephropathy and hypertensive nephropathy (Rumbeiha et al., 2016). Understanding the dual nature of H₂S in acute and chronic settings is crucial for developing effective therapeutic strategies and mitigating potential health risks.

Reported cases of toxicity

Instances include a sewer worker's fatal exposure resulting in acute respiratory distress syndrome and death (Goolam et al., 2023), two fatalities in water treatment plants due to accidental H₂S poisoning (Munasinghe et al., 2018), and a fisherman's survival after exposure to high H₂S concentrations from a fish garbage room (Oktavia, 2021). H₂S, a by-product of various industrial processes, poses risks in settings like sewage processing and the petroleum industry (Sheikh et al., 2017). Additionally, chemical suicides involving H₂S underscore its ease of production and potential for harm (Ng et al., 2019). These cases emphasize the need for awareness, safety regulations, and effective countermeasures against H₂S toxicity, as there are currently no FDA-approved antidotes for H₂S exposure.

Beneficial Effects

A naturally occurring compound within the body, H₂S plays a critical role as a signaling molecule in various physiological processes. Its therapeutic applications are diverse, impacting areas such as cardiovascular health, neuroprotection, and inflammation management. These multifaceted benefits indicate that H₂S could be a valuable component in developing treatments for a variety of ailments, making it a focus of ongoing medical research and pharmaceutical development.

Therapeutic uses of H₂S

H₂S has emerged as a significant gasotransmitter, akin to nitric oxide and carbon monoxide, with a broad spectrum of physiological and therapeutic effects across various medical conditions (Gönbe, Aydinoğlu, and Öğülen, 2022). One of its key roles is in promoting angiogenesis through the upregulation of vascular endothelial growth factor (VEGF), which underscores its potential in treating diseases associated with impaired angiogenesis, such as diabetic wound healing and ischemic conditions (Zhang et al., 2023). H₂S improves wound healing in type 2 diabetic by enhancing angiogenesis. It accelerates wound closure, enhance capillary density, and preserve the function of endothelial progenitor cells (EPCs), which are crucial for angiogenesis. The beneficial effects of H₂S were linked to the upregulation of key angiogenesis-related factors, including Angiopoietin-1 (Ang-1), VEGF, PDGF, HIF-1 α , and eNOS at both transcriptional and protein levels. H₂S also promoted granulation tissue formation and increased the number of small blood vessels in ischemic muscles, suggesting that it aids in the healing of diabetic wounds by modulating key growth factors and signaling pathways involved in blood vessel formation (Liu et al., 2014; Wang and Li, 2019).

The therapeutic application of H₂S, particularly in critical illnesses, is driven by its regulatory effects on vascular tone, inflammation, oxidative stress, and apoptosis. Clinical trials are currently exploring its benefits in conditions like myocardial infarction, pre-eclampsia, and COVID-19 pneumonia (Merz et al., 2022). In the context of cardiovascular disease, H₂S supplementation has shown promise in models of myocardial ischemia-reperfusion injury and chemotherapy-induced cardiotoxicity, which highlights the need for the development of H₂S -releasing compounds to enhance its bioavailability and therapeutic efficacy (Hu and Lukesh III, 2023).

Innovative delivery methods, such as biocompatible porous solids like metal-organic frameworks (MOFs), offer a novel approach for the safe and effective delivery of H₂S, demonstrating potential in mitigating ischemia-reperfusion injury (Chen et al., 2021). The cardioprotective effects of H₂S are further evidenced by its ability to attenuate myocardial cellular oxidative damage and hypertrophic signaling, as seen with the novel H₂S prodrug SG-1002 (Islam et al., 2023). According to Shen et al (2015), H₂S has some mechanisms as cardioprotective, including antioxidative action by activating the Nrf2 pathway and ROS, preserving mitochondrial function, reducing cardiomyocyte apoptosis, and inhibiting inflammation. H₂S also promotes angiogenesis by increasing VEGF expression and activating the PI3K/Akt pathway, regulates ion channels to stabilize heart function, and enhances nitric oxide (NO) production through eNOS activation. Additionally, H₂S influences gene expression via microRNAs and inhibits phosphodiesterase-5 (PDE-5) to further reduce oxidative stress, collectively contributing to its cardioprotective effects.

In cancer therapy, particularly for triple-negative breast cancer (TNBC), H₂S donors and their derivatives have shown significant promise in inhibiting tumor growth and metastasis by modulating key cellular processes such as apoptosis and cell cycle regulation (Li et al., 2020). However, the dual role of H₂S in both promoting and inhibiting angiogenesis, depending on its concentration and context, presents a complex yet promising therapeutic avenue (Evgen'ev and Frenkel, 2020). H₂S donors like GYY4137, DATS, and NaHS have demonstrated potential in regulating cell proliferation, viability, migration, and invasion in various cancers, including colon, breast, gastric, and ovarian cancers. They achieve this by interacting with signaling pathways such as PI3K/AKT, MAPK, Wnt/ β -catenin, EGFR/ERK/MMP-2, PTEN/AKT, and TGF- β 1, and by downregulating migration-associated proteins like MMPs and EMT-inducing factors (Ngowi et al., 2021). H₂S also plays a complex role in apoptosis, influencing cell death through multiple pathways depending on its concentration and cellular context. At non-toxic levels, H₂S can induce mitochondria-dependent apoptosis, while also having the ability to inhibit apoptosis by suppressing the mitochondrial K⁺atp/MAPK-mediated pro-apoptotic pathway under certain conditions. Additionally, H₂S impacts exogenous apoptosis via TNF receptor pathways by inhibiting TNF- α -induced apoptosis through the sulfurylation of NF- κ B, and it can either promote or protect against cell death in ER stress-related apoptosis, depending on the context (Gao et al., 2024). The development of H₂S donors with controlled release profiles and the exploration of existing drugs coupled with H₂S-donating groups

offer a multifaceted approach to harnessing the therapeutic potential of H₂S (Szabo and Papapetropoulos, 2017).

Beyond its applications in cardiovascular and cancer therapies, H₂S shows broad therapeutic potential across a range of pathophysiological conditions. It plays a crucial role in cardiovascular health by influencing vasodilation, angiogenesis, inflammation, and cellular redox homeostasis, which are essential for the prevention and treatment of cardiovascular diseases (Hu and Lukesh III, 2023). H₂S also has significant neuroprotective potential, as it reduces oxidative stress, lipid peroxidation, and neuroinflammation, and inhibits cell death processes in both the central and peripheral nervous systems, offering therapeutic possibilities for neurotrauma and neurodegenerative diseases (Rodkin et al., 2023).

Moreover, H₂S provides protection against neurotoxicity by modulating key regulators of antioxidant and inflammatory responses and by directly detoxifying neurotoxicants, suggesting its utility in combating neurological diseases (Aschner et al., 2022). H₂S is proposed to protect the brain by modulating key antioxidant and inflammatory pathways through S-sulfhydration of regulators like Sirt1, nuclear factor erythroid 2–related factor 2 (Nrf2), and NF-Kb (Aschner et al., 2022). H₂S directly interacts with ROS and reactive nitrogen species (RNS), modulating redox signaling and affecting cellular functions such as autophagy, apoptosis, and inflammation, which underscores its therapeutic potential for a range of diseases (Liu et al., 2022). In terms of imbalance ROS and RNS, H₂S acts as a direct scavenger of harmful ROS and RNS, such as hydrogen peroxide (H₂O₂), superoxide (O₂⁻), and peroxynitrite (ONOO⁻), thereby preventing cellular damage, including DNA damage, protein misfolding, and organelle injury. Additionally, H₂S upregulates the antioxidant defense system through the activation of the Nrf2 pathway, which increases the expression of antioxidant enzymes like heme oxygenase-1 (HO-1) and glutathione peroxidase (GPx) (Xiao et al., 2018).

In the cardiovascular system, H₂S and its synthesizing enzymes protect against pathologies like arrhythmias, atherosclerosis, and myocardial infarction by modulating molecular signaling cascades and redox regulation (Kolluru et al., 2023). It also acts as a neuroprotectant by modulating mitochondrial activity and reducing oxidative damage in neurodegenerative diseases (Zhou and Wang, 2023). The vasorelaxant properties of H₂S-donating molecules further highlight its cardiovascular protective effects (Marini et al., 2023).

Additionally, in skeletal muscle, H₂S mitigates immobilization-induced muscle atrophy through its anti-inflammatory and antioxidant properties (Xu et al., 2022). Beyond its role in oxidative stress and inflammation, H₂S also influences metabolic disturbances in obesity and diabetes through the persulfidation of proteins, enzymes, and transcription factors (Comas and Moreno-Navarrete, 2021). Finally, H₂S contributes to cellular redox homeostasis by quenching reactive species, modulating antioxidant enzyme expression, and influencing sirtuin signaling pathways, all of which are crucial for health and disease management (Corsello, Komaravelli, and Casola, 2018).

Clinical trials and biomedical research

Clinical trials and preclinical studies have explored its therapeutic potential across a range of conditions, from neurotrauma and mental disorders to cardiovascular diseases and cancer, highlighting its complex biological functions and signaling mechanisms (Rodkin et al., 2023; Hu and Lukesh III, 2023; Wen et al., 2022; Khan et al., 2022). In the realm of neurology, H₂S has been identified as a promising neuroprotective agent, offering protection against various forms of neurotrauma and potentially mitigating the progression of neurodegenerative diseases like Alzheimer's and Parkinson's (Liu, Hessler, and Henary, 2023). Its neuroprotective effects are also considered against a wide spectrum of neurotoxicants, suggesting a broader application in preventing neurological damage (Wang and Tang, 2022). Cardiovascular research has revealed H₂S's involvement in key processes such as vasodilation, angiogenesis, and redox homeostasis, positioning H₂S donors as potential therapeutic agents for myocardial ischemia-reperfusion injury and cardiotoxicity induced by cancer chemotherapy (Piragine et al., 2023). Moreover, H₂S and its synthesizing enzymes have been shown to protect against various cardiovascular pathologies, underscoring its significance in cardiovascular health and disease (Aschner et al., 2022). Cancer research

has focused on the dual role of H₂S in tumorigenesis, with studies exploring the use of H₂S donors and inhibitors to suppress cancer progression (Munteanu et al., 2022). Additionally, the development of H₂S donor conjugate drugs, combining H₂S with existing clinical drugs, represents an innovative approach to enhance therapeutic efficacy and safety (Kolluru et al, 2023). Despite these promising findings, the translation of H₂S research into clinical practice remains in its infancy. Few H₂S -releasing compounds have advanced to clinical studies, indicating the need for further research to fully understand its therapeutic potential and limitations. Nonetheless, the ongoing exploration of H₂S in biomedical research continues to uncover its vast potential across a spectrum of diseases, suggesting a promising future for H₂S-based therapies.

Discussion

H₂S therapy embodies the delicate balance of risk versus benefit due to its dual biological nature. While it offers considerable potential health benefits, significant risks arise, especially at higher concentrations. This dualism demands careful management for H₂S's safe and effective clinical application.

H₂S plays a pivotal role in cardiovascular health by inducing vasodilation, improving blood flow, and reducing blood pressure. It also protects against ischemia-reperfusion injury, crucial in conditions like heart attacks and strokes. In neurology, its antioxidant properties help mitigate oxidative stress and neuroinflammation, central to neurodegenerative diseases such as Alzheimer's and Parkinson's, by protecting neurons from damage and cell death. Additionally, H₂S modulates inflammation, which is fundamental in many chronic diseases, thus providing potential therapeutic benefits in inflammatory disorders.

At lower concentrations, H₂S acts as a pro-survival and anti-apoptotic agent, preventing unnecessary cell death and maintaining tissue health. However, at higher levels, it becomes cytotoxic, exacerbating conditions like neurodegenerative diseases by increasing reactive oxygen species (ROS), causing mitochondrial dysfunction, and altering crucial cellular mechanisms. Its acute toxicity is well-documented, with high concentrations leading to rapid coma, cardiac dysfunction, and often fatal outcomes. Furthermore, H₂S can enhance the toxicity of metals like copper, increasing oxidative stress and cellular damage.

To harness the therapeutic potential of H₂S while minimizing risks, several strategies are crucial. Developing methods for controlled release and precise dosing is essential, potentially through innovative delivery systems like biocompatible porous solids or metal-organic frameworks. Leveraging H₂S therapy in specific contexts, such as localized treatment of ischemic injury or targeted neuroprotection, can enhance therapeutic outcomes. Establishing robust monitoring systems to track H₂S levels and implementing strict safety protocols are vital for mitigating the risks of accidental high exposures.

Ongoing research into the molecular mechanisms of H₂S action and its interactions with other cellular components is critical. This research can lead to better strategies for mitigating its cytotoxic effects while enhancing its therapeutic benefits. The future of H₂S therapy lies in the ability to finely tune its administration, exploiting its beneficial properties while safeguarding against its inherent risks.

As research progresses, the clinical applications of H₂S could expand significantly, provided that the balance between its beneficial and hazardous effects is carefully managed. The growing understanding of H₂S as a signaling molecule and a modulator of various biological processes lays a solid foundation for innovative treatments across a spectrum of diseases. Further investigation is needed into how H₂S interacts within the body and with other signaling molecules, which could provide insights into more comprehensive treatment approaches.

Increasing the number and scope of clinical trials is fundamental to transitioning H₂S from a research compound to a therapeutic agent. Collaborations across disciplines, such as chemistry, pharmacology, biotechnology, and nanotechnology, could enhance the development and application of H₂S -based therapies. With continued investigation and collaboration across scientific fields, H₂S could become a pivotal element in treating a broad range of diseases, further highlighting its importance as a biomedical agent.

Conclusion

H₂S exhibits a dual nature in terms of toxicity and therapeutic potential. At low concentrations, H₂S demonstrates pro-survival and anti-apoptotic effects, whereas at high levels, it becomes anti-proliferative and pro-apoptotic. It can induce cytotoxicity in brain neurons by increasing ROS, causing mitochondrial dysfunction, and altering glutathione levels, which are linked to neurodegenerative diseases. Acute exposure to high concentrations of H₂S can lead to severe toxicity, rapid coma, cardiac dysfunction, and potentially death through electromechanical dissociation of the heart. Chronic exposure to low levels, however, is associated with various organ pathologies, though it also shows protective effects in chronic organ degenerations. Additionally, H₂S plays a crucial role in cardiovascular and renal physiology and disease, influencing processes like vasodilation and angiogenesis, and has potential therapeutic applications in treating conditions ranging from myocardial infarction to neurodegenerative diseases. Effective countermeasures against H₂S toxicity are focused on binding free H₂S, protecting mitochondria, and mitigating end-organ damage, but currently, there are no FDA-approved antidotes for H₂S exposure. Instances of fatal and non-fatal exposures underscore the need for heightened awareness and safety regulations in industries where H₂S is prevalent.

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