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Mechanisms and therapeutic potential of hydrogen sulfide in traumatic central nervous system injuries

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Abstract

Traumatic central nervous system injuries encompass brain and spinal cord injuries. Recent studies have identified hydrogen sulfide (H_2S) as a potent endogenous gasotransmitter with multifaceted roles in neuroprotection and central nervous system repair. In this systematic review, we explore the mechanisms and therapeutic potential of H_2S in traumatic central nervous system injuries, emphasizing its anti-inflammatory, antioxidant, and anti-apoptotic properties. H_2S suppresses inflammation by modulating the nuclear factor-kappa B pathway, shifting microglial polarization to a reparative phenotype. Further, it mitigates oxidative stress by activating the nuclear factor erythroid 2-related factor 2 and mechanistic target of the rapamycin pathway, and inhibiting glutamate-mediated damage. Additionally, H_2S regulates cell death by inhibiting apoptosis, ferroptosis, pyroptosis, and autophagy while promoting axonal growth and microvascular integrity. Emerging H_2S delivery strategies, including slow-releasing donors such as GYY4137 and advanced hydrogel-based systems, address challenges in achieving sustained and targeted therapeutic effects. Although preclinical evidence has demonstrated the promise of H_2S-based therapies, further research is required to optimize delivery methods, investigate concentration-dependent effects, and validate clinical efficacy. This review provides a comprehensive foundation for advancing H_2S as a therapeutic agent in traumatic central nervous system injuries.

Key Words: central nervous system injury; gasotransmitter; hydrogen sulfide; inflammation; neuroprotection; oxidative stress; programmed cell death; spinal cord injury; therapeutic delivery; traumatic brain injury

Introduction

Traumatic central nervous system (CNS) injuries, such as traumatic brain injury (TBI) and spinal cord injury (SCI), represent a critical medical challenge, owing to the limited regenerative capacity of neural tissues and the devastating consequences on patients' quality of life.[1] Traumatic CNS injuries are the leading cause of long-term disability and mortality worldwide, imposing significant societal and economic burdens.[2,3] By 2021, there will be more than 15 million SCI patients and 38 million TBI patients worldwide, leading to an approximate total of 10 million years lived with disability.[1,4] Despite advances in acute care and rehabilitation, effective therapeutic strategies for CNS repair and functional recovery remain elusive.[5] The pathophysiology of traumatic CNS injuries is complex and involves primary mechanical damage, followed by secondary processes such as neuroinflammation, oxidative stress, excitotoxicity, and programmed cell death.[6,7] These secondary mechanisms exacerbate the initial injury and hinder recovery by creating an inhibitory microenvironment that impedes neuronal survival and axonal regeneration.[8] The complexity of traumatic CNS injuries poses a significant challenge to the exploration of their mechanisms and treatment.

Hydrogen sulfide (H_2S) has a long-standing therapeutic history dating back to ancient civilization, as evidenced by the global tradition of bathing in sulfur-containing hot springs for medicinal purposes.[9-11] It has long been believed that bathing in sulfur-rich hot springs provides therapeutic benefits for certain diseases.[12-14] While systematic scientific research on H_2S only emerged in the late 20th century, its biomedical significance has undergone remarkable reinterpretation in recent decades. Historical records from the past century have documented occasional poisoning incidents associated with sulfur spring bathing, including severe cases with fatal outcomes,[15,16] which initially reinforced the perception of H_2S as a hazardous gas.[17,18] Nevertheless, contemporary studies have revolutionized our understanding by revealing H_2S as an essential endogenous signaling molecule with multifaceted regulatory functions.[19,20] Cutting-edge research has further highlighted its neuroprotective capabilities against CNS injuries through three key mechanisms: oxidative stress modulation, inflammatory response suppression, and programmed cell death

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regulation.[21-25] This paradigm shift demonstrates the scientific community's persistent exploration of the therapeutic potential H_2S, successfully reconciling its dual nature as both a historical remedy and a modern pharmacological target.[26]

To advance the understanding of the systematic effects of H_2S in traumatic CNS injuries, we reviewed three pivotal aspects: the dynamic biological characteristics of endogenous H_2S, its context-dependent neuroprotective mechanisms, and cutting-edge strategies for targeted H_2S delivery. Special emphasis was placed on the evaluation of clinical translation challenges, including H_2S donors and delivery systems. By synthesizing mechanistic insights with technological innovations in H_2S modulation, this work seeks to establish a translational roadmap for the development of H_2S-based therapies in traumatic brain and SCI management.

Methods

Herein, we conducted a systematic literature search in PubMed using the following search strategy: (((Hydrogen Sulfide[Title/Abstract]) OR (H_2S[Title/Abstract])) AND ((spinal cord injury[Title/Abstract]) OR (spinal cord[Title/Abstract]) OR (traumatic brain injury[Title/Abstract]) OR (central nerve[Title/Abstract])))) AND ((“1000/1/1”[Date - Publication]: “2024/12/5”[Date - Publication])). The search yielded a total of 109 articles. Studies were selected based on the following predefined criteria: Inclusion criteria: Original research articles investigating H_2S in traumatic CNS injuries (TBI or SCI); studies reporting mechanistic insights into H_2S neuroprotection; articles describing H_2S delivery methods or therapeutic outcomes in animal models or clinical settings; English-language publications with full-text availability. Exclusion criteria: reviews, meta-analyses, commentaries, or conference abstracts; studies focusing on non-traumatic CNS pathologies; articles lacking experimental validation of H_2S mechanisms/therapeutic effects; duplicate publications; and studies with insufficient methodological detail. The screening process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[27] and involved the following steps: All articles retrieved from the search were reviewed for relevance based on their titles and abstracts. A total of 38 articles with irrelevant titles or abstracts were excluded, leaving 71 articles for further analysis. An additional 1 article was identified through a citation search, increasing the total to 72 articles. Of the remaining 72 articles, 17 were reviews and were therefore excluded. In addition, three articles were excluded after full-text review because they were found to be irrelevant to the study focus. This process resulted in the final set of 52 articles included in the analysis.

A total of 52 articles were subjected to a thorough full-text review and analysis. Each article was carefully examined to extract relevant data on the role of H_2S in the CNS with a specific focus on SCI and TBI. Key information, including study design, intervention methods, dosages, outcomes, and conclusions, were systematically recorded and synthesized for further analysis. A detailed flowchart of the screening process is shown in **Figure 1**.

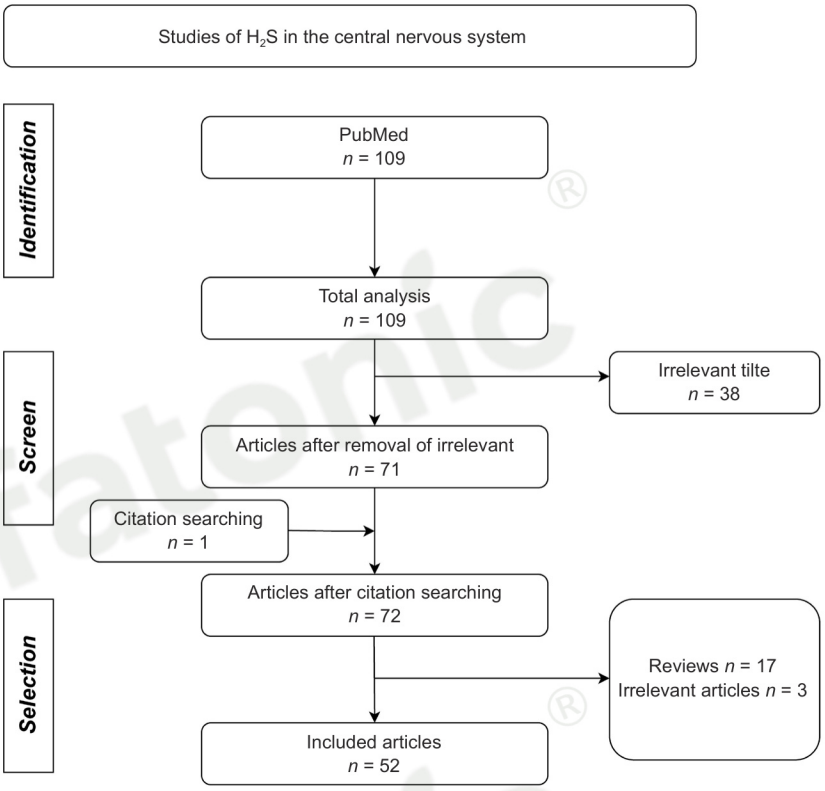


Figure 1 | **Flow chart of article screening.**
Initially, 109 articles were identified through a systematic search of the PubMed database. After 38 irrelevant articles were removed based on title and abstract screening, 71 articles were retained. Additional articles were identified by citation tracking. Subsequently, 17 review articles and 3 studies irrelevant to the full-text review were excluded, resulting in the final inclusion of 52 articles for analysis. Created with Adobe Illustrator 29.2.1. H_2S: Hydrogen sulfide.

Biological Characteristics of Hydrogen Sulfide

H_2S is one of the three major gasotransmitters, alongside nitric oxide and carbon monoxide.[28] These small gaseous molecules share several key characteristics that define them as gasotransmitters, including that they are endogenously produced, freely permeable across membranes, and exert specific biological effects via signaling pathways.[29,30] Unlike traditional neurotransmitters and hormones, gasotransmitters do not require membrane receptors for their action; instead, they diffuse freely and interact with intracellular targets.[19]

H_2S primarily exists in the cell cytosol and mitochondria.[30] Its physiological concentration in the plasma remains controversial, owing to inconsistencies in measurement methods.[31] However, it is known to be endogenously synthesized in mammalian tissues via enzymatic and non-enzymatic pathways (**Figure 2**). The primary enzymatic pathway involves three key enzymes. Cystathionine γ-lyase is predominantly expressed in the cardiovascular system, liver, and kidneys, and uses L-cysteine as a substrate to produce H_2S.[23,32,33] Cystathionine β-synthase is highly expressed in the CNS, particularly in astrocytes, and catalyzes the conversion of L-cysteine and L-homocysteine to H_2S.[34] 3-Mercaptopyruvate sulfurtransferase was further found in both mitochondria and cytosol, and works in conjunction with cysteine aminotransferase to generate H_2S.[35] In addition to these enzymatic sources, non-enzymatic pathways, such as the reduction of thiosulfate and conversion of other sulfur-containing substances, contribute to H_2S production under certain physiological or pathological conditions.[36,37]

Among the various gasotransmitters, H_2S has the same redox activity as nitric oxide and carbon monoxide, which enables it to modulate cellular oxidative states and participate in sulfhydration—a post-translational modification of proteins critical for cellular signaling.[20,38] H_2S combines the roles of modulating inflammation, oxidative stress, and cellular metabolism.[23-25] The broader spectrum of its effects is attributed to its diverse interactions with molecular targets, such as ion channels, enzymes, and transcription factors.[39-41]

In the CNS, H_2S acts as a neuromodulator and cytoprotective agent. The regulation of H_2S levels in the CNS is tightly controlled by enzymatic activity and cellular redox states.[26,34,42] Dysregulation of H_2S has further been implicated in various neurological conditions, including Alzheimer's disease, Parkinson's disease, and traumatic CNS injuries.[42-44] The endogenous production and diverse nervous system roles of H_2S underscore its therapeutic potential for neuroprotection and CNS repair.

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Mechanisms of Hydrogen Sulfide in Traumatic Central Nervous System Injury

The multifaceted actions of H_2S in reducing inflammation, oxidative stress, and cell death, while promoting regeneration and remodeling the injury microenvironment, highlight its therapeutic potential in traumatic CNS injury (**Figure 3**). These mechanisms provide a strong foundation for the development of H_2S-based therapies, offering new hope for functional recovery following traumatic CNS injury. The studies related to H_2S in traumatic CNS injury are summarized in **Table 1**.[44-69]

Anti-inflammatory mechanisms

Inflammation is a hallmark of secondary injury following a traumatic CNS injury. In the early stages of injury, an inflammatory storm leads to additional neuronal death, while persistent chronic inflammation impedes tissue regeneration and repair of tissues.[70] H_2S exhibits significant anti-inflammatory effects through various mechanisms. In traumatic CNS injury, H_2S effectively suppresses the nuclear factor-kappa B (NF-κB) pathway, which regulates the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α.[57,58,64,67,68,71] H_2S also inhibits the expression of IL-18 and cyclooxygenase-2, upstream activators of NF-κB.[64,65,69] In murine TBI models, H_2S administration reduced pro-inflammatory cytokines (IL-1β, tumor necrosis factor-α), suppresses nuclear translocation of NF-κB p65 subunit to inhibit NF-κB pathway activation, and ultimately correlates with functional recovery in motor tasks, anxious behavior, and memory restoration.[58,65] Additionally, H_2S reduces microglial and macrophage activation, thus mitigating inflammation at the injury site.[64,69,72] For example, in SCI models, H_2S preconditioning shifted microglial polarization toward the anti-inflammatory phenotype, thereby preventing spinal neuron loss and ameliorating motor dysfunction.[64,69] This polarization facilitates tissue repair by releasing anti-inflammatory mediators such as IL-10 and transforming growth factor-β, thus creating a favorable environment for neural regeneration.[73] Astrocytes have been implicated in persistent chronic inflammation and impede nerve tissue.[74] ATB-346 (an H_2S-releasing derivative of naproxen) has been demonstrated to reduce the excessive infiltration of astrocytes around injured areas 10 days post-injury.[65]

Antioxidant mechanisms

Oxidative stress is a key contributor to neuronal damage in patients with TBI or SCI. In traumatic CNS injury, H_2S mediates potent antioxidant protection through multi-mechanistic pathways, including scavenging of reactive oxygen species, attenuating lipid peroxidation, and mitigating oxidative damage to critical cellular structures.[44,60,61,75] These coordinated actions collectively sustain neuronal and glial functional integrity. The therapeutic efficacy of H_2S in traumatic CNS injury involves the coordinated regulation of oxidative stress pathways through two key mechanisms: first, it suppresses glutamate excitotoxicity by targeting the p53/glutaminase 2 pathway.[56] Second, it enhances the endogenous antioxidant capacity via nuclear

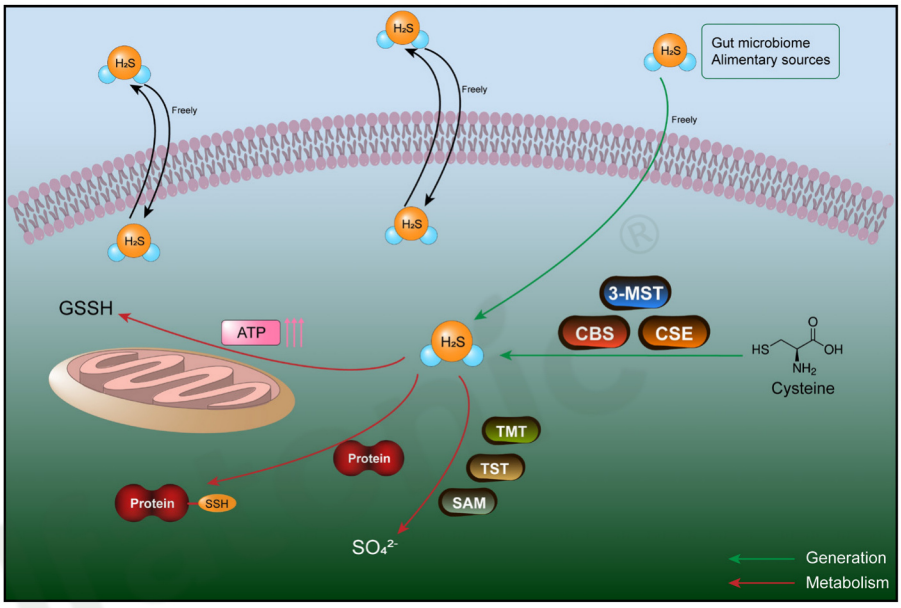


Figure 2 | Metabolism of hydrogen sulfide.
H_2S is produced enzymatically by CSE, CBS, and 3-MST from cysteine/homocysteine. Key metabolic fates include mitochondrial ATP synthesis via GSSH formation, protein S-sulfhydration to modulate enzymatic activity and redox signaling, and catabolism of sulfate. Created with Adobe Illustrator 29.2.1. 3-MST: 3-Mercaptopyruvate sulfurtransferase; ATP: adenosine triphosphate; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; GSSH: glutathione persulfid; H_2S: hydrogen sulfide; SAM: S-adenosylmethionine e; TMT: S-methyltransferase; TST: thiosulfate sulfurtransferase.

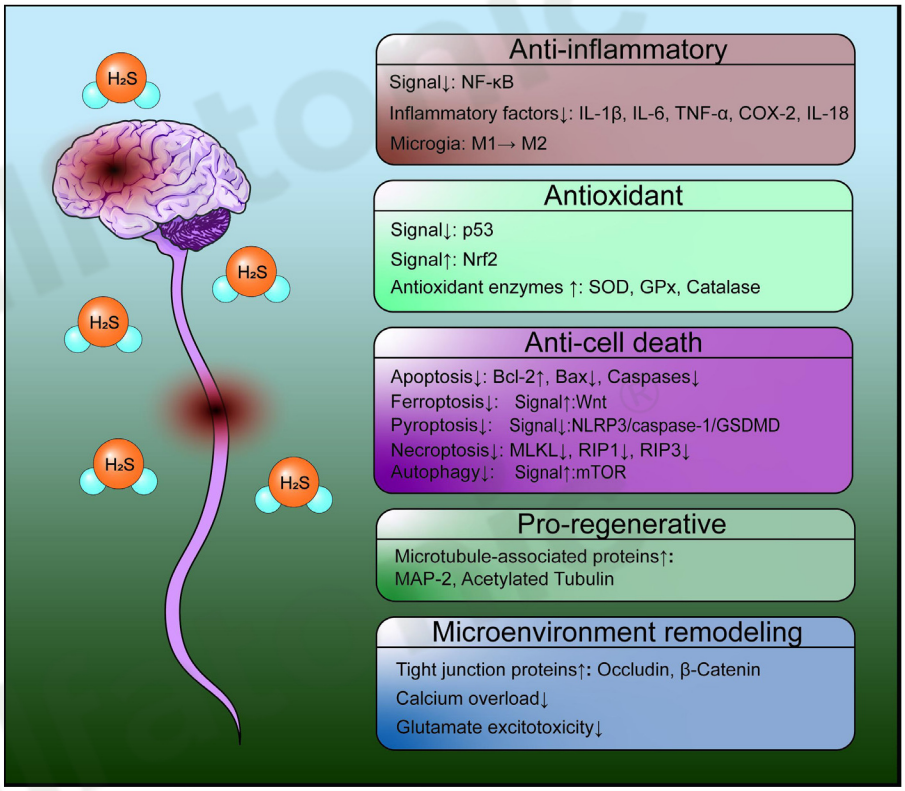


Figure 3 | Therapeutic mechanism of hydrogen sulfide in traumatic brain and spinal cord injuries.
Hydrogen sulfide mitigates secondary injury and promotes functional recovery following CNS trauma through anti-inflammatory, antioxidant, and anti-cell death pathways, while enhancing neural regeneration and extracellular microenvironment remodeling. Created with Adobe Illustrator 29.2.1. CNS: Central nervous system; COX-2: cyclooxygenase-2; GPx: glutathione peroxidase; GSDMD: gasdermin D; H_2S: hydrogen sulfide; IL: interleukin; MAP-2: microtubule-associated-protein 2; MLKL: mixed lineage kinase domain-like protein; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor-kappa B; NLRP3: NOD-like receptor pyrin domain containing 3; Nrf2: nuclear factor erythroid 2-related factor 2; RIP: receptor-interacting serine/threonine-protein kinase; SOD: superoxide dismutase; TNF: tumor necrosis factor-α.

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Table 1 | Experimental investigations of H2S in traumatic CNS injury models

Drug	Study	Year	Animal	Model	Route of administration	Dosage	Time*	Main finding
Sodium hydrosulfide	Zhang et al.[45]	2013	Mouse	TBI	Intraperitoneal	45 μmol/kg	Once before	H_2S levels fluctuate dynamically post-TBI, with NaHS treatment reducing lesion volume and promoting recovery.
	Kesherwani et al.[46]	2013	Rat	SCI	Intraperitoneal	50 μM	1 h	NaHS reduces oxidative stress and inflammation in acute spinal cord injury.
	Jiang et al.[47]	2013	Rat	TBI	Intraperitoneal	3 mg/kg	5 min	H_2S protects against TBI by activating mitoKATP channels, improving blood–brain barrier integrity, and reducing oxidative stress.
	Zhang et al.[48]	2014	Mouse	TBI	Intraperitoneal	1 μmol/kg	15, 30 min, 1, 2, 4 h	H_2S provides neuroprotection post-TBI by reducing apoptosis, suppressing autophagy, and improving functional outcomes.
	Li et al.[49]	2015	Rat	SCI	Intraperitoneal	30 μmol/kg	30 min before	H_2S protects against spinal cord ischemia-reperfusion injury by promoting autophagy and reducing damage.
	Karimi et al.[50]	2017	Rat	TBI	Intraperitoneal	3 and 5 mg/kg	5 min before	NaHS prevents memory deficits induced by TBI, supporting its neuroprotective potential.
	Yang et al.[51]	2017	Rat	SCI	Intraperitoneal	28 μmol/kg	12 h and every day	H_2S attenuates bone loss post-SCI by mitigating oxidative stress and activating Wnt/β-catenin signal.
	Xie et al.[52]	2017	Rat	TBI	Intraperitoneal	5.6 mg/kg	1 h before	H_2S reduces autophagic neuronal cell death in SCIR injury by mitigating oxidative stress via the AKT-mTOR pathway.
	Liu et al.[53]	2018	Rat	SCI	Intraperitoneal	30 umol/kg	30 min before	H_2S reduces neuronal apoptosis in SCIR injury by modulating the Caspase-7/microRNA-30c axis.
	Wang et al.[54]	2018	Rat	SCI	Intraperitoneal	5.6 mg/kg	30 min and every day	H_2S improves functional recovery and BSCB integrity post-SCI by inhibiting ER stress-dependent autophagy.
	Xu et al.[55]	2018	Mouse	TBI	Intraperitoneal	1 μmol/kg	30 min before	NaHS restores mitochondrial function, inhibits autophagy, and activates the PI3K/Akt/mTOR pathway to promote recovery post-TBI.
	Sun et al.[56]	2021	Rat	TBI	Intraperitoneal	1 mmol/kg	Once before	H_2S protects against glutamate-induced oxidative stress in TBI via the p53/GLS-2 pathway, improving motor and cognitive outcomes.
	Xu et al.[57]	2021	Rat	SCI	Intraperitoneal	5.6 mg/kg	Every day after	H_2S promotes functional recovery post-SCI by activating Nrf2 nuclear translocation and reducing inflammation and oxidative stress.
	Chen et al.[58]	2022	Mouse	TBI	Local drug delivery	–	–	H_2S-releasing hydrogel reduces neuronal pyroptosis and inflammation post-TBI, mitigating brain edema and neurodegeneration.
	Huerta de la Cruz et al.[59]	2022	Rat	TBI	Intraperitoneal	3.1 and 5.6 mg/kg	Every day	NaHS treatment alleviates hemodynamic disturbances and excessive sympathetic activity post-TBI without affecting motor-sensory function.
	Chen et al.[60]	2023	Mouse	TBI	Intraperitoneal	1 μmol/kg	Every day	NaHS reduces ferroptosis and improves cognitive deficits post-TBI by activating the Wnt signaling pathway and mitigating oxidative stress.
	López-Preza et al.[61]	2023	Rat	TBI	Intraperitoneal	3.1 mg/kg	Every day	NaHS prevents vascular dysfunction post-severe TBI by reducing ROS and restoring eNOS and H_2S-synthesizing enzyme expression.
	Nasir et al.[44]	2025	Mouse	TBI	Intraperitoneal	3.1 mg/kg	Every day	NaHS improves cognitive and motor deficits post-TBI by restoring synaptic plasticity, dendritic structures, and neurotransmitter balance.
Sodium sulfide	Bredthauer et al.[62]	2018	Pig	SCI	Intravenous	0.2 mg/kg + 1, 2 mg/kg/h	2 h before 8 h after	Intravenous H_2S fails to prevent neuronal damage or restore function in a porcine SCI model.
	Rodkin et al.[63]	2024	Mouse	TBI	Intraperitoneal	0.1 mg/kg	Every day	H_2S reduces inducible nitric oxide synthase and amyloid-beta precursor protein expression in neuronal and glial cells post-TBI.
ATB-346	Campolo et al.[64]	2013	Mouse	SCI	Oral	30 μmol/kg	1, 10 h and every day	ATB-346 accelerates spinal cord injury recovery by reducing inflammation, nitrosative stress, glial activation, and apoptosis.
	Campolo et al.[65]	2014	Mouse	TBI	Oral	30 μmol/kg	1 and 6 h	ATB-346 improves motor function and reduces cortical damage post-TBI by inhibiting inflammation and promoting neurotrophic factors.
Hydrogen sulfide	Kakinohana et al.[66]	2019	Mouse	SCI	Inhalation	80 ppm	23 h after SCI, for 5 h	Inhaled H_2S prevents delayed paraplegia by reducing inflammation, apoptosis, and neurodegeneration post-SCI.
Ferric tetrasulfide	Wang et al.[67]	2022	Rat	SCI	Local drug delivery	–	–	Sustained H_2S release enhances corticospinal tract regeneration and promotes axonal alignment and growth.
JK	Albashari et al.[68]	2024	Rat	SCI	Local drug delivery	–	–	H_2S-releasing hydrogel promotes axonal regeneration and reduces inflammation post-SCI, enhancing neural repair and functional recovery.
GYY4137	Xie et al.[69]	2024	Rat	SCI	Intraperitoneal	50 mg/kg	30 min before	Slow-releasing H_2S donor reduces neuronal death post-SCI by inhibiting pyroptosis, apoptosis, and necroptosis.

*: Unless otherwise indicated as "before," all drug administrations were performed after injury induction. BSCB: Blood-spinal cord barrier; CNS: central nervous system; eNOS: endothelial nitric oxide synthase; ER: endoplasmic reticulum; GLS-2: glutaminase 2; H_2S: hydrogen sulfide; JK: lithium 2 (phenylphosphonothioylamino)-3-phenylpropanoate; NaHS: sodium hydrosulphide; Nrf2: nuclear factor erythroid 2-related factor 2; PI3K/Akt/mTOR: phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin; ROS: reactive oxygen species; SCI: spinal cord injury; SCIR: spinal cord ischemia-reperfusion; TBI: traumatic brain injury.

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factor erythroid 2-related factor 2-driven enzyme expression.[75] These combined actions restore post-TBI levels of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and malondialdehyde, while concurrently normalizing catalase levels, thereby reversing critical oxidative stress biomarkers.[47,57,75] The antioxidative properties of H_2S confer multi-dimensional neuroprotection across CNS injury models. In the rat TBI model, H_2S attenuates blood-brain barrier hyperpermeability, mitigates cerebral edema progression, and reduces lesion volume expansion.[47] Further, in an SCI model, H_2S suppresses oxidative stress-induced spinal cavitation while enhancing functional recovery, as evidenced by elevated Basso, Beattie, and Bresnahan locomotor scores.[57] These coordinated effects collectively validate H_2S as a potent modulator of secondary injury cascades. In addition, the systemic antioxidant effects of H_2S extend beyond the primary injury site. H_2S also reduces SCI-induced bone loss, a common comorbidity of chronic SCI, by alleviating oxidative stress.[51] It is also worth noting that experimental evidence reveals a concentration-dependent dual role of H_2S in primary spinal cord neuron cultures: 50 μM sodium sulfide enhances neurite outgrowth, whereas concentrations exceeding 100 μM induce nuclear factor erythroid 2-related factor 2-mediated oxidative stress response and peroxiredoxins, resulting in > 60% neuronal mortality compared to controls.[76] This biphasic action highlights the importance of optimizing H_2S delivery to maximize neuroprotection, while avoiding paradoxical harm.

Anti-cell death mechanisms

Programmed cell death pathways, including apoptosis, ferroptosis, pyroptosis, necroptosis, and autophagy, exacerbate neuronal loss following traumatic CNS injury. H_2S inhibits these processes via various pathways.[69] Ferroptosis, an iron-dependent cell death mechanism, is potently inhibited by H_2S in both TBI and SCI. First, H_2S targets the Caspase-7/microRNA-30c axis to suppress apoptosis initiation, and second, through modulation of the mitochondrial apoptotic machinery. This involves elevating anti-apoptotic B-cell lymphoma-2 expression while suppressing the pro-apoptotic X protein associated with B-cell lymphoma-2, thereby attenuating cytochrome c release and downstream caspase activation cascades.[48,53,56,64,66,69,77,78] In weight-drop TBI models, H_2S was found to attenuate neuronal and glial apoptosis, thereby effectively mitigating TBI-induced motor dysfunction, spatial memory deficits, and cerebral edema.[48,56,77] Parallel therapeutic effects have been observed in spinal cord ischemia-reperfusion injury models, in which H_2S upregulates Caspase-7, while downregulating microRNA-30c, resulting in reduced neuronal apoptosis and smaller ischemic lesion areas in spinal cord tissue.[53,69] Regarding ferroptosis, H_2S counteracts TBI-induced suppression of the Wnt/β-catenin signaling pathway, thereby upregulating glutathione peroxidase 4 expression to enhance mitochondrial antioxidant defense. This molecular restoration attenuates lipid peroxidation and neuronal ferroptosis, correlating with improved motor coordination and cognitive function in TBI models.[60] H_2S exerts multi-target neuroprotection by suppressing the NOD-like receptor pyrin domain containing 3/caspase-1/gasdermin D pyroptosis axis.[58,69] In models of TBI, this modulation attenuates cerebral edema, reduces neurodegenerative pathology, and mitigates neuroinflammation, concurrently improving motor dysfunction, anxiety-like behaviors, and memory deficits, while decreasing tissue lesion volumes.[58] Similarly, in SCI models, H_2S preserves spinal neuron viability and prevents post-ischemia-reperfusion motor impairment through pyroptosis pathway inhibitions.[69] The activation of vital proteins for necroptosis, including mixed kinase domain-like protein, receptor-interacting protein 1, and receptor-interacting protein 3 were also inhibited by H_2S.[69] This inhibition attenuates neuronal necroptotic death and promotes functional recovery after post-SCI.[69]

In neurons affected by traumatic CNS injury, the increased expression of autophagy markers, including vacuolar protein sorting 34, sequestosome 1, microtubule-associated protein 1 light chain 3-II, and Beclin-1, was significantly inhibited by H_2S.[48,55] Further, by activating phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin signaling pathway, H_2S restores mitochondrial function, inhibits autophagy, and promotes functional recovery after TBI.[55] Concurrently, H_2S can also reduce oxidative stress in SCI, thereby significantly inhibiting autophagic cell death through protein kinase B/mechanistic target of the rapamycin pathway.[52] In neurons, increases in the autophagy markers vacuolar protein sorting 34, sequestosome 1, microtubule-associated protein 1 light chain 3-II, and Beclin-1 were all abrogated by H_2S.[48,55] Interestingly, H_2S has also been shown to inhibit autophagy and protect the spinal cord by promoting expression of microRNA-30c.[49] This underscores the complexity of traumatic CNS injury and highlights the need for further investigations into the underlying mechanisms and therapeutic potential of H_2S in this context.

Pro-regenerative mechanisms

H_2S exerts a range of pro-regenerative effects in the injured CNS by directly enhancing neuroplasticity, axonal growth, and cellular repair mechanisms. A key component of neuronal regenerative capacity is their ability to modulate cytoskeletal dynamics. H_2S promotes the expression of microtubule-associated proteins such as microtubule-associated protein 2 and acetylated tubulin in SCI models, which are critical for axonal stability and elongation.[68]

This structural support is further complemented by the H_2S-mediated upregulation of synaptic proteins, reinforcing synaptic integrity and functional connectivity in post-injury recovery. Synaptic remodeling also plays a significant role in CNS regeneration, while H_2S has been demonstrated to influence synaptic plasticity-related proteins and neurotransmitter receptors in TBI models.[44] H_2S further promotes axonal repair and regeneration in both TBI and SCI. In TBI models, sodium hydrosulphide (NaHS) administration restores N-methyl-d-aspartate receptor subunit expression and reverses dendritic spine loss, leading to improvements in cognitive function and motor coordination.[44]

Microenvironment remodeling

H_2S also plays a crucial role in actively remodeling the injury microenvironment to support neural repair and regeneration. Following traumatic CNS injury, the extracellular matrix undergoes significant changes that can either promote or inhibit recovery. One of the key aspects of microenvironmental remodeling is the regulation of the blood-brain barrier and blood-spinal cord barrier. H_2S donors such as NaHS have further been reported to preserve the integrity of these barriers by stabilizing tight junction proteins such as occludin and β-catenin, thereby reducing vascular permeability and preventing excessive immune cell infiltration in TBI models.55 This limits secondary damage and maintains homeostasis within the injured CNS, ultimately attenuating neuronal degeneration and apoptosis. Furthermore, by modulating intracellular calcium signaling in astrocytes, H_2S supports synaptic homeostasis and mitigates calcium-mediated excitotoxicity.[72] This demonstrates significant potential for SCI management, particularly given that calcium overload and excitotoxicity constitute the critical pathological mechanisms driving acute-phase secondary damage.[79] Furthermore, the ability of H_2S to regulate extracellular glutamate levels and reduce excitotoxicity provides additional neuroprotection, and helps to shape a regenerative microenvironment in TBI models.56 Moreover, biomaterial-based approaches utilizing H_2S-releasing hydrogels have shown promising effects in guiding tissue regeneration. Anisotropic ferrofluid hydrogels loaded with Fe_3S_4 nanoparticles not only release H_2S in a controlled manner but also promote directional axonal growth and maintain proper neuronal alignment in SCI models.[67] These findings highlight the potential of H_2S in designing advanced biomaterials that facilitate CNS repair by optimizing the structural and biochemical properties of the injury microenvironment.

Hydrogen Sulfide Delivery Strategies and Emerging Technologies

Challenges in hydrogen sulfide delivery

The therapeutic potential of H_2S in TBI and SCI has driven significant advancements in its delivery methods and technologies. The major obstacles to effective H_2S delivery include systemic toxicity, rapid metabolism, and target specificity. Excess H_2S concentrations can lead to adverse effects, including cellular toxicity and oxidative stress. Endogenous H_2S is rapidly metabolized, necessitating sustained release systems for prolonged therapeutic effects. Achieving localized delivery to injured CNS tissues without influencing the other systems remains a critical challenge. Given the numerous challenges associated with the gaseous and highly reactive nature of H_2S, innovative strategies are critical for achieving controlled and targeted delivery, maximizing its therapeutic efficacy while minimizing potential toxicity.

Hydrogen sulfide donors for controlled release

H_2S donors are defined as compounds designed to release H_2S at controlled rates, addressing issues of rapid metabolism and toxicity. Several classes

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of H_2S donors have thus far been developed and applied in traumatic CNS injury in animal experiments (**Table 1**).

Sodium sulfide and NaHS are both commonly used inorganic salts that release H_2S upon dissolution. These are often applied in experiments performed to explore pathological and physiological mechanisms. Although effective in experimental settings, their rapid-release profiles limit their clinical applicability. These donors may be more suitable if a rapid response is required. In the prevention of spinal cord ischemia-reperfusion injury, intranasal administration of glutathione trisulfide and panthionine trisulfide increased sulfane sulfur levels in the olfactory bulb, forebrain, and whole spinal cord within 30 minutes, which can prevent delayed paraplegia after transient spinal cord ischemia in mice.[71]

Several drugs with sustained-release properties have been developed, including GYY4137, AP39, and AP123. These drugs are more suitable for precise implantable drug delivery and have greater potential for long-term treatment. GYY4137 is a synthetic donor that releases H_2S slowly over time, providing sustained therapeutic effects with reduced toxicity. Studies have demonstrated its efficacy in reducing inflammation, oxidative stress, and apoptosis in SCI models.[69,78] AP39 and AP123 are mitochondria-targeted donors that selectively deliver H_2S to mitochondria, enhancing cellular bioenergetics and protecting against oxidative damage.[80,81] Prodrugs, such as SG1002, are metabolized *in vivo* to release H_2S, thereby offering a promising approach for systemic administration with controlled release characteristics, but have not yet been applied in traumatic CNS injuries.[82]

Hydrogen sulfide delivery systems

Delivery systems for H_2S encompass both traditional methods and new technologies. Although conventional approaches that provide a foundational drug delivery strategy are typically systemic, advanced systems have evolved to deliver drugs locally, thereby addressing challenges such as targeted specificity and controlled release. Together, these approaches enable the effective administration of H_2S in traumatic CNS injuries.

Intraperitoneal and intravenous injection are common routes of systemic delivery of H_2S donors, offering rapid distribution but limited targeting specificity. Oral administration is also a common mode of systemic administration, while oral drugs are usually not administered directly to common inorganic salts, except ATB-346, a novel H_2S-releasing derivative of naproxen.[64,65] Inhalation is a convenient method for administering drugs during surgery. Inhalation of 50 mg/kg glutathione trisulfide reached the spinal cord tissue after 30 minutes, which had a preventive effect on spinal cord ischemia-reperfusion injury.[71]

Local drug delivery generally involves loading a drug onto a hydrogel.[58,67,68] Hydrogels capable of releasing H_2S locally and sustainably offer a promising platform for traumatic CNS injuries. Injectable hydrogels also facilitate local drug delivery.[68] Hydrogel filling of the injured area can form an integrated implant-tissue interface to restore tissue continuity and reduce cavity formation.[58] By improving the properties of hydrogels, it is possible to make them respond to environmental factors, such as pH or temperature, leading to improved therapeutic outcomes. The H_2S donors loaded in the hydrogel include ferric tetrasulfide, lithium 2-[phenylphosphonothioylamino]-3-phenylpropanoate (JK) and NaHS. Ferric tetrasulfide is commonly used in ferromagnetic fluids and releases H_2S under weakly acidic conditions. A paramagnetic ferrofluid is formed by the uniform dispersion of magnetic substances in a liquid, in which particles are arranged in the magnetic field and remain stable over time.83 Anisotropic hydrogels with linear channels promote linear axon extension.[84] A previously developed magnetic-induced anisotropic hydrogel can form magnetic-field-induced micropores and channels in line with the long axis of the nerve, facilitating nerve extension after regeneration and establishing effective connections between neurons.[67] JK is a novel H_2S donor based on phosphonamidothioate, which exhibits high water solubility and slow and controlled production of H_2S. The JK-class H_2S donors tended to evolve H_2S more rapidly at the lower pH.[85]

Future Directions and Perspectives

Despite significant advancements in the current understanding of the therapeutic potential of H_2S in traumatic CNS injury, further efforts are required to overcome existing challenges and transform them to clinical applications. Future research should focus on mechanism investigation, development of advanced H_2S donors, and clinical translation.[86]

While the neuroprotective roles of H_2S in traumatic CNS injuries have been well-documented,[87] deeper investigations into its underlying mechanisms are essential. Particular attention should be paid to its synergistic interactions with other gasotransmitters, such as nitric oxide and carbon monoxide, to uncover potential pathways that may enhance neuroprotection and repair.[26] These studies provide a foundation for the development of combination therapies targeting multiple signaling pathways.

Overall, creating more efficient, stable, and highly targeted H_2S donors is a priority. Systemic administration must address the risk of systemic toxicity, while local delivery methods remain the most effective and direct approaches. Integrating tissue engineering technologies such as hydrogel-based delivery systems could further improve outcomes by ensuring localized and sustained release. However, the concentration-dependent effects of H_2S must be carefully managed, as excessive local accumulation can lead to toxic effects. Long-term evaluation of implantable delivery methods is therefore necessary to monitor their efficacy and potential adverse effects over time. Advancements in biomaterials science, nanotechnology, and molecular biology will be critical for developing innovative delivery platforms. Multidisciplinary collaboration can drive the design of smart delivery systems capable of responding to injury-specific stimuli such as pH changes or oxidative stress, thereby enhancing therapeutic precision. The combination of these systems with gene therapy offers a promising avenue for the development of personalized treatment strategies.

Nanomaterial-based delivery systems have improved H_2S therapy for traumatic CNS injuries by addressing the critical limitations of conventional H_2S donors. These systems leverage high payload capacities to stabilize gaseous H_2S or its donors, ensuring sustained intracellular delivery and overcoming rapid systemic clearance.[88] Targeted delivery is further achieved through surface modifications, like functionalization with choline analogs such as 2-methacryloyloxyethyl phosphorylcholine, which exploits interactions with endothelial nicotinic acetylcholine receptors or choline transporters to enhance blood-brain barrier penetration.[89,90] For example, nanomotors engineered with 2-methacryloyloxyethyl phosphorylcholine demonstrated a 74.5% blood-brain barrier penetration rate in murine models, nearly doubling the efficiency of non-motor systems (42.1%), while achieving 20.5% mitochondrial targeting efficiency in damaged neurons through chemotactic interactions between 3-mercaptopyruvate sulfurtransferase and L-cysteine.[89] Such designs can enable the spatiotemporally controlled release of H_2S, particularly in response to pathological cues like oxidative stress or enzymatic activity, as seen in Parkinson's disease models where mitochondrial-targeted H_2S nanomotors promoted growth and differentiation of neuron.[90] With the resolution of critical biological challenges including biocompatibility, biodegradation kinetics, biodistribution control, and long-term biosafety, H_2S-releasing nanomaterials have emerged as a transformative class of therapeutic donors for traumatic CNS injury repair, offering good spatiotemporal precision for gasotransmitter delivery.[88]

Advancing H_2S-based therapies towards achieving clinical application will require rigorous preclinical safety assessments and dose optimization studies. Exploring the synergistic effects of H_2S with other therapeutic agents in specific subtypes of traumatic CNS injuries, such as mild TBI or SCI, will also be crucial. These efforts must be supported by well-designed clinical trials to validate safety, efficacy, and optimal administration protocols.

Limitations

Although this review comprehensively summarizes the current understanding of H_2S in traumatic CNS injuries, several limitations in the review design should be considered. First, only English-language publications were included, which may have led to language bias. Second, most of the included studies were based on preclinical models, which limits the direct applicability of the findings to clinical situation. Third, because of the differences in H_2S donors, dosages, administration routes, injury models, and outcome assessments, heterogeneity among studies impeded direct comparisons. These limitations underscore the need for more standardized and translational research to validate and extend the therapeutic potential of H_2S in traumatic CNS injuries.

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Conclusion

Overall, this review highlights the multifaceted mechanisms by which H_2S exerts neuroprotective and regenerative effects in traumatic CNS injuries, including anti-inflammatory, antioxidant, and anti-apoptotic pathways. As the first comprehensive review focusing on the role of H_2S in TBI and SCI, it encompasses the latest research advancements in this field. Given its diverse physiological roles, H_2S holds promise as a versatile therapeutic agent for traumatic CNS injuries, warranting further exploration in clinical settings. Overall, we wish to highlight that despite advancements in H_2S delivery systems and a growing understanding of its mechanisms have laid a strong foundation for future translational research, clinical application remains premature. Further basic research will be necessary to validate the therapeutic effects and address the challenges related to delivery precision, safety, and clinical validation. Addressing these gaps through innovative delivery technologies, mechanistic studies, and rigorous clinical trials is essential to unlock the full therapeutic potential of H_2S.

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