

Review Article

Physiological Importance of Hydrogen Sulfide: Emerging Potent Neuroprotector and Neuromodulator

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Hydrogen sulfide (H₂S) is an emerging neuromodulator that is considered to be a gasotransmitter similar to nitrogen oxide (NO) and carbon monoxide (CO). H₂S exerts universal cytoprotective effects and acts as a defense mechanism in organisms ranging from bacteria to mammals. It is produced by the enzymes cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), 3-mercaptopyruvate sulfurtransferase (MST), and D-amino acid oxidase (DAO), which are also involved in tissue-specific biochemical pathways for H₂S production in the human body. H₂S exerts a wide range of pathological and physiological functions in the human body, from endocrine system and cellular longevity to hepatic protection and kidney function. Previous studies have shown that H₂S plays important roles in peripheral nerve regeneration and degeneration and has significant value during Schwann cell dedifferentiation and proliferation but it is also associated with axonal degradation and the remyelination of Schwann cells. To date, physiological and toxic levels of H₂S in the human body remain unclear and most of the mechanisms of action underlying the effects of H₂S have yet to be fully elucidated. The primary purpose of this review was to provide an overview of the role of H₂S in the human body and to describe its beneficial effects.

1. Introduction

Hydrogen sulfide (H₂S) is a poisonous gas that is a toxicant in most organs in the human body. It acts as a gaseous signaling molecule and chemical reagent involved in many physiological processes, including the pathogenesis of various diseases such as neurodegenerative disease, heart failure, and diabetes [1, 2]. As a result, the beneficial roles of this compound were neglected for many years due to its toxic nature. However, in recent years, the benefits of gasotransmitters such as nitric oxide (NO) and carbon monoxide (CO) have acted as a fillip to investigating the benefits of H₂S [3]. Furthermore, a reevaluation of the endogenous levels of H₂S confirmed its existence and advantages in mammalian tissues [4].

H₂S is a sulfur analog of water and, due to its weak intermolecular force, exists in a gaseous form that is colorless but has an offensive odor [5]. At a pH of 7.4 in the mammalian body, one-fifth of the total H₂S subsists in an undissociated form, with the remaining content existing as hydrosulfide anions (HS⁻) and sulfide (S²⁻). The high lipid solubility of H₂S allows it to easily penetrate the plasma membrane of cells in its undissociated form [6] but it remains unclear whether this undissociated form is physiologically pertinent [7]. Various studies performed on rat, human, and bovine brain tissues have determined that H₂S is present at levels of up to 50–160 μmol/L in tissues and that sodium hydrogen sulfide (NaHS) is one of the physiological donors of H₂S [8].

Although it is known that H₂S protects nerves from oxidative stress, saves photoreceptor cells in the retina from light-induced degeneration, regulates endoplasmic reticulum stress, and defends the kidneys from ischemic reperfusion injury [9], the role of H₂S in the central nervous system (CNS) has attracted a lot of attention over the past few decades. The neuromodulation and neuroprotection of nerve cells are a common feature of H₂S [9] and its enzymes exert effects in a variety of diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Down's syndrome, cerebral ischemia, and Huntington's disease [10, 11]. Additionally, following injury in the peripheral nervous system (PNS), peripheral nerves undergo Wallerian degeneration and macrophages are recruited into the distal nerve pump [12]. The regeneration of these injured peripheral nerves is associated with the demyelination, dedifferentiation, and proliferation of Schwann cells, which takes place serially. Recently, the possible involvement of H₂S in demyelinating disorders and nerve degenerative disorders has also been suggested [13, 14].

Thus, the present review focuses on the physiological roles of H₂S in different systems and organs, including the CNS, and in peripheral nerve degeneration and regeneration. A consensus regarding findings in these areas will aid in the determination of appropriate avenues for H₂S in research investigating neural regeneration and the treatment of neurodegenerative diseases and may lead to potential therapeutic strategies that employ H₂S.

2. Biosynthesis of H₂S

Two pyridoxal-5'-phosphate- (PLP-) dependent enzymes present in mammalian tissues, cystathionine β -synthase (CBS; EC 4.2.1.22) and cystathionine γ -lyase (CSE; EC 4.4.1.1), are primarily responsible for the biosynthesis of H₂S from L-cysteine (L-Cys) [15, 16]. H₂S can be produced by other pathways as well. Cysteine first reacts with ketoacids to form 3-mercaptopyruvate via the catalytic action of cysteine aminotransferase (CAT; EC 2.6.1.3) and then 3-mercaptopyruvate is desulfurated by 3-mercaptopyruvate sulfurtransferase (MST; EC 2.8.1.2) to form H₂S [17]. H₂S is mostly synthesized by cystathionase in the liver, kidneys, enterocytes, and vascular smooth muscle cells, by CBS in the brain, and by MST in cardiac tissues [18]. Recently, it was reported that dihydrolipoic acid (DHLA) and thioredoxin are the endogenous reducing substances that cause MST to release H₂S [16] and that CBS is the catalytic agent responsible for the condensations of cysteine and homocysteine, which produces H₂S and cystathionine via a β -replacement reaction [19, 20]. The distributions of CBS and CSE in mammalian tissue are different. A cardiovascular study determined that CSE plays a major role in producing H₂S under normal physiological conditions [21] while another study found that the MST pathway mainly contributes to its production in the brain and that this pathway is regulated by intracellular calcium (Ca²⁺) in a concentration-dependent manner [16, 22, 23].

A recent study used Western blot and immunohistochemistry analyses to investigate DAO expression and methylene blue assays to assess H₂S biosynthesis and revealed that

H₂S is also produced from D-cysteine via the enzyme D-amino acid oxidase (DAO) [24]. The H₂S production pathway that uses D-cysteine primarily operates in the cerebellum and kidney and, thus, was termed the DAO/MST pathway [25, 26]. Although DAO is confined to peroxisomes and MST is located in the mitochondria, these factors exchange numerous enzymes and metabolites [16]; these findings provide strong support for calling this pathway the DAO/MST pathway. Interestingly, the production of H₂S via DAO is subdued by indole-2-carboxylic acid but this effect was not seen with MST [26]. A nonenzymatic pathway for the production of H₂S also exists and involves the reduction of elemental sulfur to H₂S by reducing equivalents procured via the oxidation of glucose [27]. Either hyperglycemia or the escalation of oxidative stress conditions can nurture the production of H₂S via this nonenzymatic route in mammalian erythrocytes [8]. The endogenous production and metabolism of H₂S and its aforementioned biosynthetic and transformation pathways are illustrated in Figure 1.

It is believed that two possible mechanisms can explain the release of H₂S. First, after its production, H₂S may be liberated by the enzymes involved in its synthesis and, second, H₂S may be stored and released in response to physiological needs in mammalian tissue [28]. H₂S is released from acid-labile sulfur (sulfur atom in iron-sulfur complex) under acidic conditions, while under alkaline conditions bound sulfane-sulfur comes into play; the favorable pH range for its release under these conditions is approximately 5.4 and 8.4, respectively [29]. The discovery of the DAO/MST pathway suggests that additional H₂S biosynthetic pathways may be revealed in the future.

3. Interrelationships with Other Gasotransmitters

Although H₂S, NO, and CO have similar molecular targets and cellular actions, these compounds also have a tendency to compete with each other. For example, the gasotransmitters CO and NO have particular relationships with CBS [8]. After the initial demonstration of the physiological roles of H₂S in 1996 [31], it took 5 more years to determine that NO can bind to CBS and can impede enzymatic activity and that CBS has a high affinity for CO [32]. However, the exact mechanisms underlying these relationships remain unknown. NO also modulates the endogenous production of H₂S in smooth muscle cells and vessels [33]. Previously, it was thought that the signaling pathways and functional mechanisms associated with H₂S and NO were autonomous, but their combined effects on angiogenesis and vasorelaxation have complicated this issue for researchers. If endothelial NO synthase (eNOS) is blocked, then it fully rescinds the angiogenic effects of H₂S whereas the silencing of H₂S significantly attenuates the angiogenic effects of NO [34]. Additionally, both H₂S and NO activate protein kinase G, as well as its cellular signaling, and 1-H-[1,2,4]oxadiazolo[4-3,-a]quinoxalin-1-one (ODQ), which is a soluble guanylyl cyclase inhibitor that decreases both H₂S- and NO-induced angiogenesis [35].

Under severe conditions such as heart inflammation and heart failure events, H₂S and NO cooperate and communicate

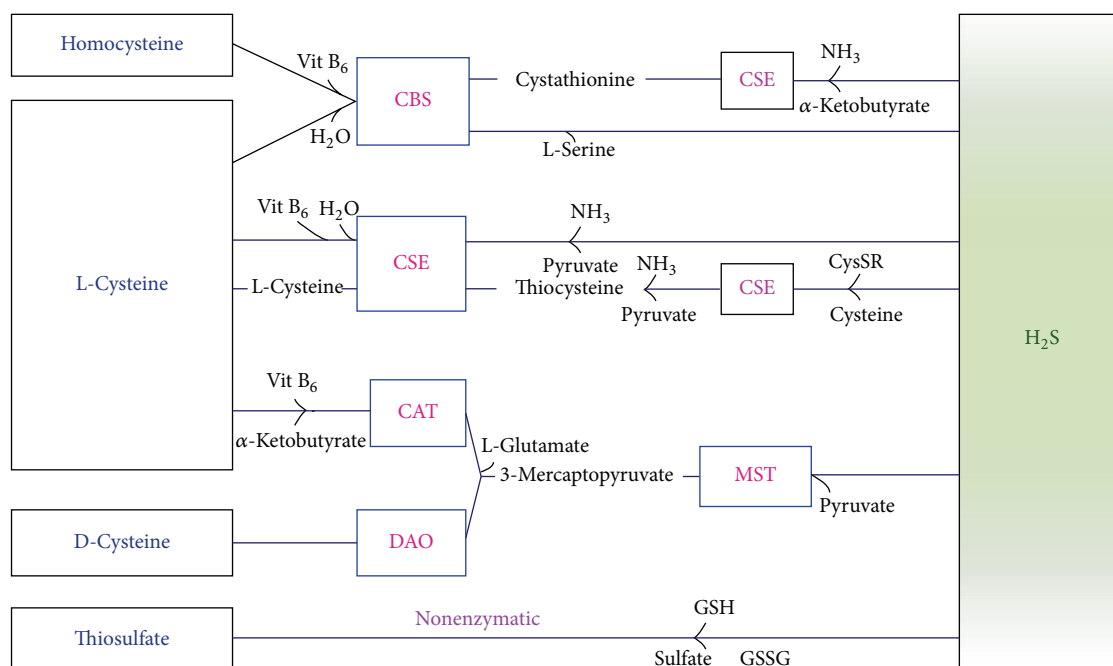


FIGURE 1: Biosynthetic pathways and the transformation of H₂S in the mammalian body. H₂S is synthesized in the mammalian body via both enzymatic and nonenzymatic pathways but the nonenzymatic pathway accounts for only a small portion of its production. CBS and CSE both use PLP and vitamin B₆ as cofactors. In the presence of cysteine and more so in the presence of homocysteine, CBS catalyzes the production of H₂S, and the condensations of homocysteine and serine are the most recognized reactions catalyzed by CBS. CSE uses L-cysteine as the substrate to form two gases, H₂S and NH₃, as well as pyruvate. MST and CAT produce H₂S and pyruvate from 3-mercaptopyruvate, which is formed from L- or D-cysteine, and α-ketoglutarate, which is produced by CAT. Thiosulfate nonenzymatically produces H₂S and all essential components of this nonenzymatic path are present in vivo. Thiosulfate can be converted into sulfite in the liver, kidney, or brain tissues via thiosulfate reductase or by thiosulfate sulfurtransferase in the liver. H₂S is also released from thiosulfate and persulfides [8, 30].

with each other to stimulate thiol-sensitive compounds that produce unambiguous positive outcomes for inotropic and lusitropic heart abnormalities [36]. Ex vivo aortic explants of wild-type and CSE-knockout (CSE-KO) mice were used to explore the possible interaction between H₂S and NO and revealed that CSE-KO mice exhibit a significant decrease in vascular neogenesis [37]. The authors also proposed that the interaction of these gasotransmitters stimulates endothelial cell proliferation. The administration of H₂S to rats with clinical symptoms of hypoxic pulmonary hypertension has also been shown to increase plasma CO concentrations [38]. CO and H₂S act on the same target but have opposite patterns of outcome. For example, coevoked channel activation is completely suppressed by potassium cyanide (KCN; 1 mM) but there are no consequences during H₂S-induced channel activation [39]. Thus, the precise nature of the relationship between these gasotransmitters in various physiological pathways remains unclear and requires further investigation. However, even if H₂S, NO, and CO compete with each other, their interactions are likely to result in beneficial effects on mammalian physiology.

4. Effect of H₂S on the CNS

H₂S has a proven neuromodulatory role in the protection of neurons from oxidative stress, as evidenced by its inhibition of hypochlorous acid-mediated oxidative damage [40] and

ONOO⁻-mediated protein nitration and cytotoxicity [41] in neuroblastoma cells. Recent studies have also established that H₂S plays an important role in the upregulation of the GABA β-receptor at both pre- and postsynaptic sites [42]. Astrocytes and microglial cells play important roles in the regulation of brain pH levels, neurotransmitter levels, and neuronal excitability [43] while microglia are also associated with the progression of neuronal diseases such as AD [44] and PD [45]. H₂S evokes Ca²⁺ waves in astrocytes that trigger a Ca²⁺ influx via its channels in the plasma membrane [7] and also reversibly increases Ca²⁺ levels in microglia in a dose-dependent manner [46].

In addition to regulating Ca²⁺ homeostasis, H₂S may also be involved in long-term potentiation (LTP) and the modulation of various neurotransmitters [5]. H₂S facilitates hippocampal LTP via the activation of N-methyl-D-aspartate (NMDA) receptors as well as the phosphorylation of these receptors by protein kinase A (PKA) [47] and regulates intracellular Ca²⁺ level in astrocytes and hippocampal slices [10]. H₂S also safeguards neurons by controlling endoplasmic stress via the balancing of membrane potentials and the activation of K_{ATP} and cystic fibrosis transmembrane conductance regulator chloride (CFTR Cl⁻) channels [9]. Most neurons in the nucleus solitarius, which are believed to play a role in the cardiovascular system, are depolarized by H₂S [48]. Additionally, a donor of H₂S, NaHS, is linked to

the inhibition of apoptosis, decreases of edema in the brain, and the amelioration of cognitive dysfunction, which could attenuate early brain injury development due to subarachnoid hemorrhage via several mechanisms [49]. The major roles and possible therapeutic targets of H₂S are illustrated in Figure 2.

Thus, it can be concluded that H₂S exerts protective and modulatory effects on nerve cells, either cooperatively or independently. Although the physical and chemical properties of H₂S remain elusive, its roles in these processes have become more clearly defined and most of its mechanisms of action are understood.

4.1. H₂S and PD. PD is primarily characterized by cognitive deficiencies resulting from changes in the nucleus basalis of Meynert and the cerebral cortex and the continuous loss of dopaminergic neurons in the mesencephalon [50]. H₂S inhibits oxygen consumption and 6-OHDA-evoked nicotinamide adenine dinucleotide phosphate (NADPH) oxidation and activates microglial cells in the midbrain which, in turn, lead to the accumulation of proinflammatory factors in the subcortical part of the forebrain [51]. This is the primary mechanism by which H₂S decreases the chances of further neuronal injury and degeneration [52]. The neuroprotective role of H₂S has also been demonstrated in experimental rat models of neurotoxin-induced PD [50]. The advantageous effects of H₂S are due to its activation or suppression of different protein kinases, such as PKC, PI3K/Akt, p38, JNK, and the ERK-MAPKs [53], which decrease oxidative stress and inflammation and exert antiapoptotic actions.

Although L-Dopa is the most commonly used drug for the treatment of PD due to its ability to maintain dopamine levels, it cannot block or reverse the progression of PD. Additionally, long-term L-Dopa therapy may lead to neurodegeneration [54] and dyskinesia [55] in and of itself. H₂S stimulates glutamate transporter functioning and leads to direct sulfa hydration via the ERK/MAPK pathway, which attenuates the production of reactive oxygen species and decreases oxidative stress [56, 57]. Thus, it can be concluded that L-Dopa and H₂S may be more effective for the treatment of PD when used in combination. A mouse model of PD constructed using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) plus probenecid injections results in the destruction of dopaminergic neurons but the administration of H₂S increases the survival rate of neurons and is protective against MPTP-induced toxicity [58]. Thus, H₂S not only protects peripheral tissues but also effectively treats neurological damage related to PD. Recently, it was shown that drinking coffee and inhaling cigarettes can inhibit monoamine oxidase (MAO) [59], which suggests that there is a lower risk of PD in coffee drinkers and smokers. Cakmak found that coffee contains *Prevotella*-derived H₂S and that H₂S is a well-documented constituent of cigarette smoke.

4.2. H₂S and AD. AD, which is one of the most familiar types of dementia, is caused by activated microglia and increases in neuritic plaques carrying the β -amyloid protein [60]. This neurodegenerative disease has been exhaustively researched because it affects the cortex and hippocampus and

leads to severe cognitive dysfunction [61]. The etiology of AD is multifactorial and presumably includes a number of distinctive etiopathogenic mechanisms [62]. CBS is thought to be the main source of H₂S in the brain. In 1996, it was first shown that S-adenosylmethionine, which is a CBS activator, is significantly reduced in subjects with AD [63]. Moreover, the severity of AD is related to altered levels of H₂S [64] because the pathological state of AD in the human body has been associated with lower levels of endogenous H₂S and the accumulation of homocysteine in the brain [65, 66]. Several series of in vitro and in vivo experiments demonstrated the role of H₂S in the promotion of cell growth and preservation of mitochondrial function [67] as well as in the retardation of oxidative stress factors such as amyloid beta peptides (A β), malondialdehyde (MDA), hypochlorite (HOCl), and 4-hydroxy-2-nonenal (4-HNE) [68, 69]. In adult male Wistar rats without serious signs of H₂S toxicity, spa water with excessive amounts of H₂S has the ability to improve cognitive processes by decreasing A β deposits and targeting the APP, PST, and ON/4R-tau isoforms [70]. Additionally, NaHS, which is a donor of H₂S, retards protein oxidation and lipid peroxidation in the neuroblastoma cells of AD patients [71].

Cerebral atrophy, seizures, and intellectual disabilities can be caused by the autooxidation of homocysteine [72, 73] and hyperhomocysteinemia has been identified in brains of AD patients [74]. H₂S protects against and reduces homocysteine-induced toxicity and oxidative stress through its antioxidant properties in the adrenal medulla (PC12 cells) and vascular smooth muscle cells of rats [75, 76]. Synaptic dysfunction and vascular inflammation are also believed to play crucial roles in the pathogenesis of AD [77]. Recent analyses of the expressions of mRNA and synaptic proteins in C57BL/6J wild-type male mice clearly demonstrated that plasma homocysteine-induced alterations in learning and memory processes were associated with synaptic remodeling in the hippocampus [78]. Thus, H₂S can influence synaptic remodeling. Vascular dementia (VD) is another common neurodegenerative disorder that, much like AD, is caused by cerebral ischemia. H₂S modulates oscillatory coupling in the hippocampus and may represent a possible molecular mechanism underlying the changes in VD patients [79].

Although neurodegenerative pathologies like AD and PD do not initially involve inflammation, various experimental findings suggest that the inflammatory responses of macrophages, microglia, and astrocytes contribute to the progressions of both diseases [14]. The relevance of the CBS, CSE, MST, and CAT enzymes in the development of AD and PD is still unexplained and direct evidence supporting the potential advantages of H₂S as a therapeutic strategy for these diseases is unavailable.

4.3. Other CNS Diseases. Various experimental studies have correlated the effects of H₂S in different pathological states of the human body. Ischemic stroke increases tissue levels of H₂S in the cerebral cortex [80] while H₂S has been shown to protect the embryonic brain against ischemia-reperfusion injury [81]. A rat model of febrile seizure is associated with elevated plasma levels of H₂S, and Down's syndrome is known to cause the overaccumulation of H₂S

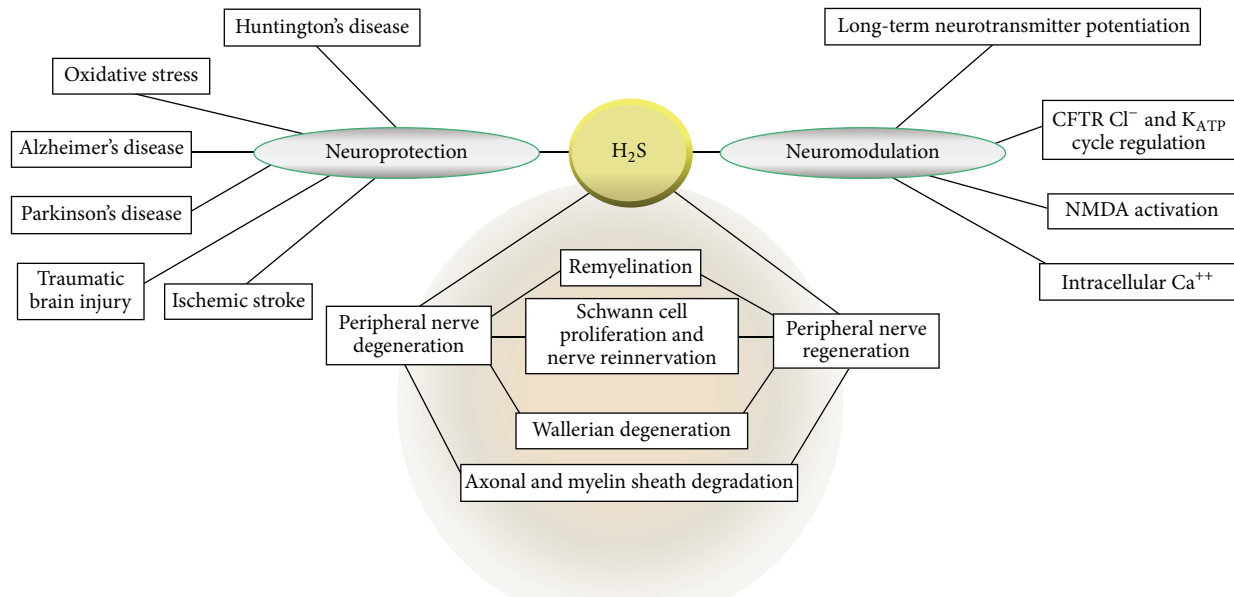


FIGURE 2: Therapeutic targets and possible physiological functions of H₂S. Enough experimental evidence has been collected to prove the prominent role of H₂S in normal pathophysiology. Therefore, many therapeutic targets exist for H₂S in mammalian body; its roles in neuroprotection, neuromodulation, and antiproliferation, as well as its functions during peripheral nerve degeneration and regeneration, are widely appreciated.

in the brain [42]. Similarly, there are increased total plasma homocysteine levels in patients with Huntington's disease and CBS deficiencies lead to homocystinuria [50]. Additionally, H₂S reverses learning and memory problems caused by damage to the hippocampus [82, 83].

5. H₂S and the PNS

Even if the most important roles that glial cells play involve the physical and metabolic support of neurons via the maintenance of the extracellular environment, these support cells are often referred to as “glial culprits” because the CNS lacks the ability to regenerate itself, even after injury [84]. On the other hand, Schwann cells in the PNS are best known for their roles in supporting nerve regeneration, conducting nerve impulses along axons, and modulating neuromuscular synaptic activity and nerve development [85]. The possible roles of H₂S in peripheral nerve degeneration and regeneration are discussed below and supported with experimental evidence.

5.1. H₂S in Peripheral Nerve Degeneration. Based on the degrees of damage in the nerve and surrounding connective tissue, peripheral nerve damage may be classified as neurapraxia, axonotmesis, and neurotmesis, with the latter being a severe type of peripheral nerve injury [86]. As stated above, nerve regeneration after injury is possible in the PNS and involves major events such as Wallerian degeneration, axonal degeneration, remyelination, axonal regeneration, and nerve reinnervation. H₂S plays vital roles throughout this process. Axonal regeneration and remyelination begin in the distal part of injured peripheral nerves and involve axonal

degeneration and the degradation of the myelin sheath of Schwann cells, which is termed Wallerian degeneration [87].

The effects of H₂S on peripheral nerve degeneration and regeneration may be best explained by recent *ex vivo* experiments using the sciatic nerves of mice. In these experiments, Park et al. [12] utilized N-ethylmaleimide (NEM), which is an inhibitor of all cysteine peptidases, to inhibit the production of H₂S during Wallerian degeneration and found that NEM inhibits not only CSE but also the basal expression of MST. Based on analyses of several markers of Schwann cell dedifferentiation and proliferation, these authors concluded that H₂S signaling has great value after peripheral nerve injury regarding myelin fragmentation, axonal degradation, and Schwann cell dedifferentiation and proliferation. Additionally, these findings demonstrated that H₂S production influences transcriptional regulation in Schwann cells during Wallerian degeneration. A similar study inhibited these processes via NEM or through several Schwann cell dedifferentiation or immaturity markers including lysosomal associated membrane protein 1 (LAMP1), neurotrophin receptor p75 (p75^{NTR}), the protein coded by JUN gene (c-jun), and phospho-ERK 1/2 (p-ERK1/2) [15]. Jung and Jeong found that these types of inhibition decreased myelin ovoid fragmentation, axonal degeneration, and Schwann cell dedifferentiation, demyelination, and proliferation through neurotrophin receptors, the MAPK pathway, lysosomal protein degradation, and transcriptional regulation.

The use of these markers in current research has garnered much attention. For example, the LAMP1 marker is related to the degeneration of peripheral nerves, including the nonuniform morphology of myelinated axons, in aged individuals [88]. The function of p75^{NTR} is associated not only

with cell death and survival but also with the maintenance of axonal elongation and the release of neurotransmitters between sympathetic neurons and cardiac myocytes [89]. Furthermore, the reexpression of p75^{NTR} has been identified in various pathological scenarios, including neurodegenerative disorders [90]. Due to its roles as a protein and a component of a transcription factor, the inactivation of c-jun in mice resulted in delays and/or the failure to properly complete the regeneration procedure and an enhancement of neuronal death [91]. Although the molecular pathways are not yet fully understood, the absence of c-jun causes the complete downregulation of neurotrophic genes such as artemin (Artn), brain-derived neurotrophic factor 1 (BDNF-1), glial cell-derived neurotrophic factor (GDNF), leukemia inhibitory factor (LIF), and nerve growth factor (NGF). These findings suggest that neurotrophins may be a potential target for the treatment of various neuropathies. Studies of the molecular mechanisms involved in those processes explained above have revealed the capability of Schwann cells to regenerate axons and to rescue motor neurons following nerve injury [92].

However, many issues relevant to this process remain unexplained, including the relationships between neurotrophic factors and H₂S, H₂S production, and remyelination that is associated with the extracellular matrix (ECM) protein, as well as intracellular regulators, hormones, and transcriptional regulators that involve H₂S [15]. Other than H₂S, the ubiquitin proteasome system (UPS) is another factor that is essential for the regenerative functions of peripheral nerves after injury [93, 94].

5.2. H₂S in Peripheral Nerve Regeneration. Other issues associated with the role of H₂S in peripheral nerve regeneration involve the responses of Schwann cells in H₂S production. Schwann cells are believed to be an important factor in the regeneration process because peripheral axons have no function as H₂S producers during Wallerian degeneration [12]. Nerve injury leads to the dedifferentiation of Schwann cells from myelinated cells to immature undeveloped cells [15] and, as discussed in Section 5.1, decreases in H₂S production attenuate changes in markers of dedifferentiation. Thus, it is important that reductions in H₂S production nurture both the regeneration of axons and the remyelination during the last stage of Wallerian degeneration. Immature undeveloped Schwann cells undergo multiplication and reach the target, injured organ, which is when the possible beneficial effects of H₂S come into play. Remyelination is another important process involved in nerve regeneration whereby Schwann cells are able to flourish due to myelination and the inhibition of H₂S production (via transcriptional regulation through krox20 and c-jun), which is fundamental to this stage of regeneration [15].

Despite the above findings, very few studies have attempted to analyze the roles that H₂S plays in peripheral nerve degeneration and regeneration. Although our research group is currently conducting studies to identify the core effects of H₂S, the existing literature strongly supports the importance of H₂S in nerve degeneration and regeneration.

6. Other Functions of H₂S

The exciting evolution of H₂S in the field of neuroscience has revealed its importance not only in the PNS but also in various physiological and pathological conditions. For example, endogenous levels of H₂S have been shown to influence exogenous H₂S during cell apoptosis [95]. Additionally, the antiproliferative and proapoptotic effects of H₂S have a significant influence on various disorders such as vascular graft occlusion, atherosclerosis, and neointimal hyperplasia [96]. H₂S also regulates glutathione levels by enhancing the hustle of the cysteine/glutamate antiporter at the cellular level, which directly neutralizes free radicals and reactive oxygen compounds and balances the levels of vitamins C and E in their reduced form [97]. The acute inhalation of H₂S protects lungs from injuries induced by ventilators and relaxes pulmonary vascular tissue but epidemiological data suggest that the long-term exposure to even low levels of H₂S can cause bronchial hyperresponsiveness [8].

Relative to other parts of the body, the gastrointestinal tract (GIT) contains the largest amount of H₂S, where it subsidizes the homeostatic control of GIT mucosal defenses and repairs damage [31]. However, the signaling pathways of H₂S in the GIT remain unclear. Other beneficial effects of H₂S on translation and transcription include the control of endoplasmic reticulum stress and activating the unfolding protein response. During these processes, CSE increases H₂S production and ultimately restores endoplasmic reticulum homeostasis via the sulfa hydration reaction [98]. Additionally, type 1 diabetes is believed to involve the overproduction of H₂S [18], and H₂S may be helpful for patients with erectile dysfunction due to its involvement in the relaxation of the smooth muscle that causes the erection of the penis [99]. Recently, six fatal cases of H₂S poisoning were reported during an attempt to unblock a wastewater cistern in which the primary reason for death was H₂S aspiration and because it is a mediator and regulator of various physiological conditions, H₂S can have serious toxic effects [100].

The roles of H₂S in insulin resistance syndrome and regional ischemic damage, as well as its dose-dependent relationship with methylglyoxal (MG) in vascular smooth muscle cells, also require explanation [3]. Because it is an antioxidant bulwark, H₂S has the capacity to sense chromaffin cells and chemoreceptors [101] but it has yet to be determined how H₂S increases local blood perfusion and/or ventilation [102]. Further justification is needed for the production of H₂S via MST under physiological conditions because this process requires full alkaline conditions [103].

7. Therapeutic Prospect and Potential of H₂S

Almost two decades of research on H₂S unfastened series of positive outcomes and its potential is expanding every day. Molecular mechanisms of H₂S are being uncovered and various types of molecular and sulfa hydration targets are on the phase of identification which may lead us to reveal its biological activities [10]. Several *in vivo* and *in vitro* studies on AD and PD model have already proved their therapeutic effectiveness for treatment [40, 68, 104, 105].

Surprisingly, inhaled H₂S has found to have protective effect against neuropathic pain and brain edema which has also made researchers think seriously in this topic because we can develop our opinion and research arena on hydrogen sulfide donor compounds against neuropathic pain and brain edema [106, 107]. Even though H₂S has to deal with its own double face (toxic and protective) attitude which has pushed it into several controversies, it is recently found that various ion channels in multiple systems and organs advocate the protective role of H₂S [108]. Because of the overall effect, H₂S-releasing drugs are now under clinical trial after their verified effectiveness in animal model. This trend of clinical trial on finding H₂S donors or H₂S-releasing drugs can be a very big breakthrough for the treatment of several diseases which are almost incurable till date [109]. H₂S-releasing derivatives of mesalamine [110] and diclofenac [111] have already been shown to decrease inflammatory disease and gastric hemorrhagic lesions compared to original drugs and some possibility for the treatment of injured brain after subarachnoid hemorrhage (SAH) via H₂S is also a great progress [112] because another study demonstrated that it reduces the level of reactive oxygen species and lipid peroxides malondialdehyde following SAH [113]. Recent studies on the effect of H₂S on brain synaptic remodeling and its role in GABA-mediated and glutamate neurotransmission have even increased its prospective potential in physiological standpoint [114]. Even with the difference between community and industry based results, the effect of environmental exposure to H₂S on CNS has exposed its novel and diverse role [115]. Neuroprotective role of H₂S after traumatic brain injury has also proven its potentiality and efficacy for other CNS related diseases [116]. Thus, it can be summarized that future prospect of H₂S in development of new therapeutic strategy is wide and bright.

8. Concluding Remarks

An adequate amount of evidence has been gathered in support of H₂S as a gasotransmitter and modulator in mammalian tissue, particularly in the nervous system. H₂S is principally produced in the liver, kidney, enterocytes, and vascular smooth muscle cells via cystathionase and partially produced in cardiac tissue by MST. It is catabolized in mitochondria by thiosulfate reductase, and thiosulfate in the urine may be used as a marker of H₂S biosynthesis. H₂S is capable of both suppressing and promoting inflammation but it remains unclear how these proinflammatory and anti-inflammatory activities can be enhanced or attenuated. The role of H₂S in the Schwann cell response to peripheral nerve injury has been well established by experimental evidence, and the importance of H₂S signaling during Wallerian degeneration, where it broadly affects Schwann cell dedifferentiation and proliferation, has been repeatedly demonstrated.

The bidirectional relationship between H₂S and NO is another area of particular research interest and therapeutic potential. Experimental studies using inhibitors or donors of endogenous H₂S have produced clear evidence of its effects but clinical studies that can define its role in the

treatment of diseases are necessary. Pharmaceutical companies should accelerate their attempts to formulate, design, and produce H₂S-releasing drugs with sustained/controlled release functions as they are likely to be highly innovative for the treatment of neurodegenerative diseases. Thus, therapeutic prospects of H₂S signaling for patients with neurodegenerative disease and demyelination disorders are imminent. However, the uncontrollable release, unidentified byproducts, and unclear mechanisms of release and action represent major issues related to the research and clinical use of H₂S. Although it is currently a time of great interest and excitement regarding the potential of H₂S in medicine and biology, many hypotheses regarding H₂S have yet to be supported and many issues remain unanswered. Even though various novel molecular targets have been identified and research is hastily expanding, biomedical research into this gasotransmitter is still in its initial stages.

Competing Interests

The authors reported no potential conflict of interests.

Authors' Contributions

Sandesh Panthi and Hyung-Joo Chung contributed equally to this work.

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