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REVIEW ARTICLE

Hydrogen Sulfide (H_2S) Signaling as a Protective Mechanism against Endogenous and Exogenous Neurotoxicants

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Abstract: In view of the significant role of H_2S in brain functioning, it is proposed that H2S may also possess protective effects against adverse effects of neurotoxicants. Therefore, the objective of the present review is to discuss the neuroprotective effects of H_2S against toxicity of a wide spectrum of endogenous and exogenous agents involved in the pathogenesis of neurological diseases as etiological factors or key players in disease pathogenesis. Generally, the existing data demonstrate that H_2S possesses neuroprotective effects upon exposure to endogenous (amyloid β, glucose, and advanced-glycation end-products, homocysteine, lipopolysaccharide, and ammonia) and exogenous (alcohol, formaldehyde, acrylonitrile, metals, 6-hydroxydopamine, as well as 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) and its metabolite 1-methyl-4-phenyl pyridine ion (MPP)) neurotoxicants. On the one hand, neuroprotective effects are mediated by S-sulfhydration of key regulators of antioxidant (Sirt1, Nrf2) and inflammatory response (NF-κB), resulting in the modulation of the downstream signaling, such as SIRT1/TORC1/CREB/BDNF-TrkB, Nrf2/ARE/HO-1, or other pathways. On the other hand, H2S appears to possess a direct detoxicative effect by binding endogenous (ROS, AGEs, Aβ) and exogenous (MeHg) neurotoxicants, thus reducing their toxicity. Moreover, the alteration of H_2S metabolism through the inhibition of H2S-synthetizing enzymes in the brain (CBS, 3-MST) may be considered a significant mechanism of neurotoxicity. Taken together, the existing data indicate that the modulation of cerebral H_2S metabolism may be used as a neuroprotective strategy to counteract neurotoxicity of a wide spectrum of endogenous and exogenous neurotoxicants associated with neurodegeneration (Alzheimer's and Parkinson's disease), fetal alcohol syndrome, hepatic encephalopathy, environmental neurotoxicant exposure, *etc.* In this particular case, modulation of H2S-synthetizing enzymes or the use of H_2S-releasing drugs should be considered as the potential tools, although the particular efficiency and safety of such interventions are to be addressed in further studies.

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1. INTRODUCTION

Hydrogen sulfide (H_2S) is a colorless, water-soluble, and flammable gas with the odor of rotten eggs. The certain physical and chemical similarity of H_2S with water (H_2O) mediates its high solubility in water and, consequently, body fluids [1, 2]. Environmental sources of H_2S include anaerobic decomposition of sulfate by bacteria, degradation of S-containing mammalian proteins, geothermal activity, and anthropogenic industrial activities. These industries include the oil and gas industry, animal feeding operations, geothermal power plants, *etc.* [3]. H_2S was considered a toxic agent

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for more than 300 years. The most characteristic features of acute H_2S toxicity include central neurotoxicity, pulmonary edema, conjunctivitis, and olfactory paralysis. At the same time, chronic H_2S exposure at both high and low doses was also found to be neurotoxic [4].

In contrast to exogenous H_2S exposure, the findings of the last two decades demonstrated that endogenous H_2S may be involved in the physiological regulation of the organism's functions. In 1996, Abe and Kimura revealed a high rate of H_2S production in the brain, as well as the neuromodulator effect of the molecule [5]. Since then, the increasing body of data on the physiological functions of H_2S has been accumulated. H_2S has been considered as the third gasotransmitter, after nitric oxide (NO) and carbon monoxide (CO) [6], involved in a variety of processes in cardiovascular [7], immune [8], endocrine, and reproductive systems [9]. Being toxic at high and neuroprotective at low concentrations, H_2S may pose a hormetic effect [10], as clearly demonstrated for NO [11].

The role of endogenous H_2S in the nervous system is mediated by its involvement in synaptic transmission, long-term potentiation, redox homeostasis, mitochondrial bioenergetics, secondary messenger signaling, proteostasis, autophagy, inflammatory response, and cellular senescence [12].

Recent studies demonstrated neuroprotective effects of H_2S in a number of neurological and neurodegenerative models of diseases, including Parkinson's [13] and Alzheimer's disease [14], traumatic [15], hemorrhagic [16], and ischemia/reperfusion injury [17]. In this review, we discuss the neuroprotective effects of H2S against toxicity of a wide spectrum of endogenous and exogenous agents involved in the pathogenesis of neurological diseases as etiological factors or key players in disease pathogenesis.

2. A BRIEF REVIEW OF H_2S BIOCHEMISTRY AND NEURONAL FUNCTIONS

Endogenous H_2S is synthetized predominantly from L-cysteine by cystathionine-β-synthetase (CBS) and cystathionine γ-lyase (CSE) involved in the homocysteine metabolism trans-sulfuration pathway (Fig. **1**). CBS catalyzes interaction between L-homocysteine and L-serine with the formation of L-cystathionine and H_2O. L-serine may be replaced by L-cysteine to yield H_2S instead of H_2O as a reaction product. However, the reactivity of CBS toward L-cysteine is lower as compared to L-serine [18]. CBS also catalyzes the formation of lanthionine and homolanthionine with the release of H_2S upon reaction between two cysteine and homocysteine molecules, respectively [18]. Another closely related enzyme, CSE, catalyzes the decomposition of L-cystathionine with the formation of L-cysteine, α-ketobutyrate, and NH3. It is also involved in the biosynthesis of H_2S through α and β-elimination of L-cysteine [19]. Another pathway of H_2S synthesis involves the activity of two enzymes, cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST). CAT was shown to catalyze the transformation of L-cysteine to 3-mercaptopyruvate, whereas the latter undergoes a 3-MST-catalyzed reaction together with α-ketoglutarate with the formation of L-glutamate, pyruvate, and H_2S [20]. In addition, a closely related pathway for H_2S synthesis from D-cysteine was revealed. Specifically, D-cysteine is oxidized to 3-MP by D-amino acid oxidase (DAO) with the subsequent 3-MST-catalyzed formation of H_2S [21]. While considering the relevance for the nervous system, it has been demonstrated that CSE provides a minor contribution to cerebral H2S production as compared to CBS and 3-MST due to its low abundance in the brain [22]. It has been also demonstrated that 3-MST is mainly localized in neurons, whereas CBS is more characteristic for astrocytes [23].

H_2S-mediated S-sulfhydration or S-sulfuration of the proteins is considered as the mechanism of post-translational protein modification, which contributes to a significant extent to intracellular H_2S signaling [24]. Recent studies demonstrated that intact cysteine (Cys-SH) residues are unlikely to be S-sulfurated by H_2S, although protein –SH group oxidation by reactive oxygen (*e.g.*, $O_2^{-\bullet}$) or reactive nitrogen ($NO^{\bullet}$) species increases protein susceptibility to S-sulfhydration. In addition, proteins containing disulfide bonds are also considered the potential targets for S-sulfhydration (Fig. **2**) [25].

Recent studies revealed a wide spectrum of proteins subjected to S-sulfhydration, including enzymes and receptors, transcription factors, and ion channels [26]. Post-translational modification of these proteins by H_2S may underlie its impact on neurological diseases through the modulation of neuroinflammation (NF-κB), neuronal oxidative stress (Keap1, p66Shc), AGEs toxicity (*e.g.*, RAGE), mitochondrial energy metabolism (*e.g.*, ATP5A1, IRF1), endoplasmic reticulum stress (PTP1B), *etc.* Specific proteins involved in neurodegeneration, like parkin, are also affected by S-sulfhydration, thus at least partially contributing to Parkinson's disease pathogenesis [25].

In addition to S-sulfhydration, H_2S is known to regulate redox homeostasis [10] that is tightly associated with vitagene network signaling, possessing a neuroprotective effect [27].

Although the above-referenced studies characterized the outcome of the target proteins with H_2S for each particular metabolic pathway, their involvement in the response to neurotoxic exposures is also unclear.

3. ENDOGENOUS NEUROTOXICANTS

3.1. Amyloid β

Amyloid β (Aβ) is a physiological product of amyloid precursor protein (APP) proteolysis by β- and γ-secretases [28]. Within a physiological range, Aβ is involved in a number of functions, including the regulation of synaptic transmission, brain recovery, maintenance of blood-brain barrier integrity, *etc*. [29]. However, an imbalance between Aβ cleavage and production, with a shift to a latter, results in Aβ accumulation and subsequent neurotoxicity [30]. The latter is mediated by oxidative stress, neuroinflammation, and apoptosis, leading to neuronal damage and a significant decline in brain functions [31].

The last decade of extensive studies demonstrated that H_2S may modulate Aβ neurotoxicity by addressing both Aβ production and cleavage, as well as particular mechanisms of Aβ toxicity. Specifically, H_2S was shown to down-regulate BACE1 expression and Aβ1-42 secretion through the activation of the PI3-K/Akt signaling pathway [32]. A similar

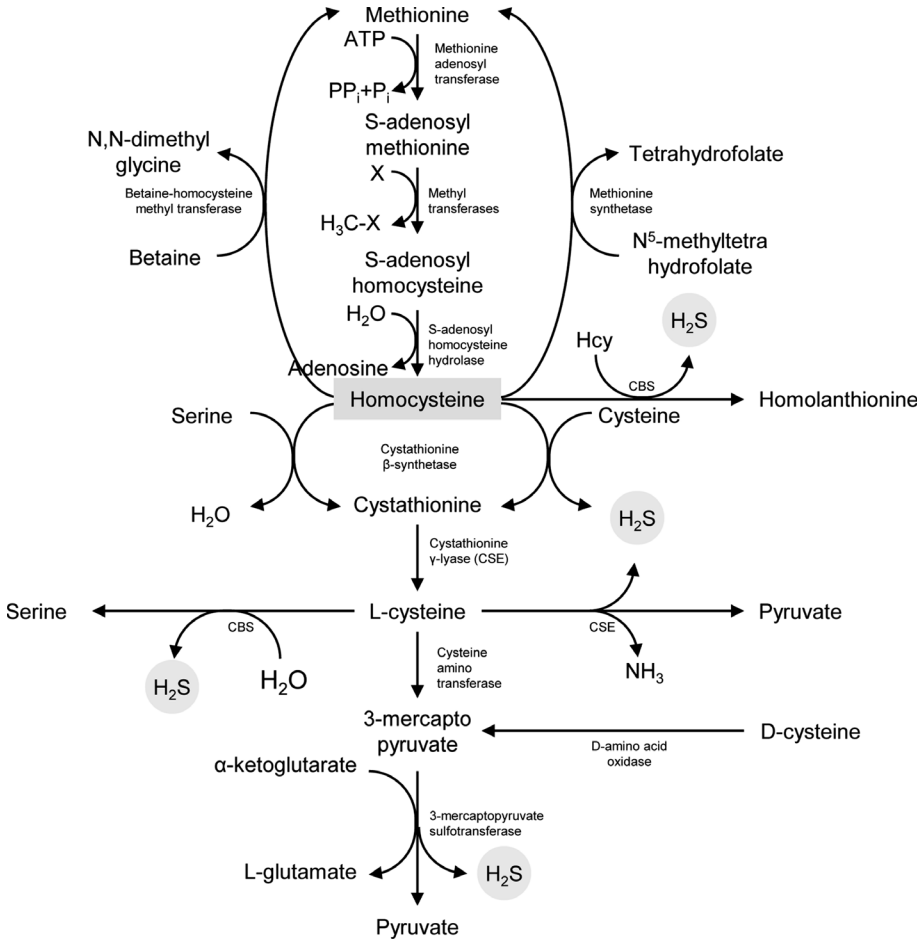

Fig. (1). Mechanisms of endogenous H_2S synthesis.

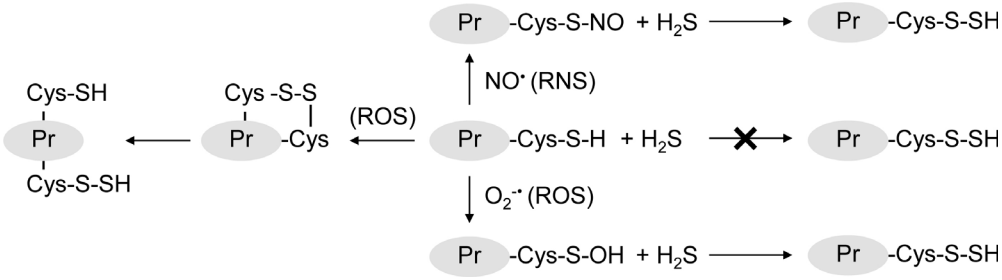

Fig. (2). Mechanisms of H_2S-induced protein S-sulfhydration.

mechanism was shown to be involved in H_2S-induced γ-secretase (PS1) down-regulation [33]. In addition, down-regulation of cAMP production and cAMP-responsive element-binding protein (CREB) phosphorylation may underlie the inhibitory effect of H_2S on γ-secretase and subsequent Aβ42 production [34].

In turn, the increase in ADAM17 activity in response to H_2S treatment was shown to result in increased levels of non-amyloidogenic C83 fragment and a concomitant decrease in the production of amyloidogenic C99 fragment [35]. It has been demonstrated that H_2S may up-regulate disintegrin and metalloprotease 10 (ADAM10), also resulting in a shift to a non-amyloidogenic APP processing product [36]. Finally, in an *in vitro* study, it has been demonstrated that H_2S prevents β-sheet formation protein fibrillation through the organization of trisulfide bridges, resulting in the formation of small spherical aggregates possessing lower cytotoxicity as compared to protein fibrils [37]. Therefore, endogenous H_2S may be considered a significant amyloidogenesis modulator inhibiting the formation and up-regulating its proteolytic cleavage, resulting in decreased Aβ deposition.

At the same time, certain studies demonstrated bimodal dose-dependent effects of H_2S on amyloid processing. Specifically, 30 μM NaHS significantly reduced Aβ levels along with a reduction of presenilin 1, presenilin enhancer 2, and γ-secretase expression, whereas treatment of APP/PS1 neurons with 50 μM NaHS possessed significant opposite effects [38], thus demonstrating the potential difference in mechanisms involved in physiological and toxicological effects of H_2S.

In parallel with a decrease in Aβ production, H_2S was shown to interfere with the mechanisms of Aβ neurotoxicity.

H2S-induced up-regulation of Nrf2 signalling led to an increase in HO-1 and GST expression, which is in agreement with the reported role of H2S as an endogenous antioxidant. These changes in redox homeostasis were associated with reduction of Aβ1–40 and Aβ1–42 levels, neuronal damage, as well as APP and BACE1 levels, altogether resulting in the improvement of cognitive function [39]. Moreover, H_2S was shown to be a component of the neuroprotective signaling pathway, being mediated by BDNF expression, and resulting in the up-regulation of Nrf2 expression, reduced Ab accumulation, and TNFa levels in the prefrontal cortex and hippocampus [40].

Improvement of mitochondrial function, including ATP synthesis and oxidative mitochondrial DNA damage by increasing mitochondrial H_2S levels, was shown to be protective against Aβ-induced memory loss [41]. Correspondingly, H_2S-releasing aspirin prevented Aβ-induced mitochondrial membrane potential loss [42]. Taken together with the observed Bcl2 up-regulation and inhibition of Bax expression and caspase 3 levels [43], these findings are indicative of the reduction of Aβ-associated mitochondria-dependent apoptosis.

In addition to oxidative stress and mitochondrial dysfunction, H_2S was shown to ameliorate Aβ-induced neuroinflammation in rat hippocampus through the inhibition of NF-κB activation by reducing IKB-α degradation [44] with a subsequent decrease in hippocampal TNF-α, IL-1β and IL-6 levels and COX-2 activity [45]. In Aβ-exposed microglia, H_2S attenuated proinflammatory effects and mitochondrial dysfunction through the down-regulation of JNK and p38-MAPK pathway [46, 47]. Concomitantly, a key role of p38 MAPK and p65 NF-κB modulation in H2S-induced the prevention of hippocampal astrogliosis and microgliosis, as well as IL-1β and TNF-α overexpression was demonstrated in Aβ1-40-exposed rats [48].

Direct interaction between H_2S and target proteins through the induction of persulfidation may underlie certain neuronal effects [49]. Specifically, in parallel with the inhibition of ATP-induced Aβ1–42 production, H_2S inhibited STAT3 phosphorylation and subsequent Cathepsin S activation, as well as induced Cathepsin S sulfhydration at Cys25, thus resulting in the inhibition of NF-κB signaling and the resulting neuroinflammation [50].

H2S also plays a significant role in the regulation of tau protein phosphorylation, another key player in Alzheimer's disease [51]. Particularly, H_2S ameliorated tau phosphorylation in severe transgenic 3×Tg Alzheimer's disease mice model [52] as well as Zucker diabetic fatty rats [53]. Specifically, H2S was shown to ameliorate Tau phosphorylation at Thr181, Ser396, and Ser202 residues in 3xTg-AD mice [43].

A recent study demonstrated that H_2S is capable of GSK3β sulfhydration with subsequent inhibition of Tau hyperphosphorylation. Moreover, binding Tau to H_2S-producing enzyme cystathionine γ-lyase up-regulates activity of the latter, whereas this process is down-regulated in Alzheimer's disease [54]. Certain studies also investigated the impact of H_2S on the PI3K/Akt pathway, being involved in the regulation of GSK3β phosphorylation. On the one hand, H_2S-dependent sulfhydration of AKT was shown to affect Akt-mediated GSK3β phosphorylation and inactivation, thus promoting Tau phosphorylation [55]. In contrast, another study revealed that the prevention of mitochondrial translocation of phosphatase and tensin homologs deleted on chromosome 10 (PTEN) by H_2S may result in PI3K/Akt pathway activation upon Ab exposure [56].

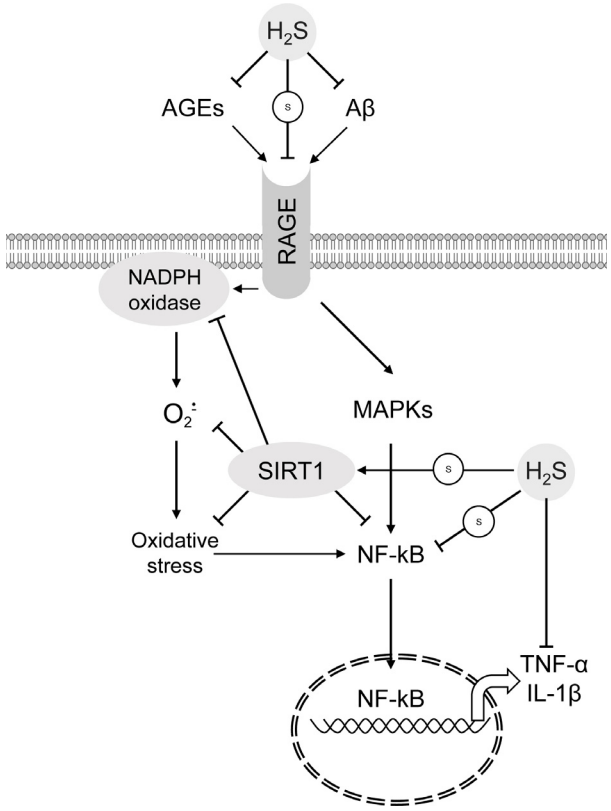

Fig. (3). The impact of endogenous H_2S on amyloidogenesis and tau phosphorylation.

3.2. Glucose and Advanced Glycation End-products

The brain requires an adequate supply of glucose, being the primary energy source for neuronal processes [57]. However, persistent increase in glucose levels is known to be neurotoxic due to the formation of ROS, reactive carbonyls, and non-enzymatic protein glycation with the formation of advanced glycation end-products [58]. Recent findings demonstrate that H_2S may be involved in the systemic regulation of carbohydrate metabolism [59], although certain studies demonstrated that H_2S may be directly involved in the modulation of neurotoxic effects of glucose and AGEs.

A recent study demonstrated that H_2S possesses significant neuroprotection under hyperglycemic conditions through the up-regulation of autophagy and SIRT1 expression, thus reducing SH-SY5Y cell senescence [60]. Concomitantly, H_2S-induced SIRT1 up-regulation was found to underlie a reduction in proinflammatory cytokine expression in HT-22 neuronal cells through the modulation of mTOR/NF-κB signaling [61]. These findings demonstrate that H_2S-dependent SIRT1 modulation may be considered a regulator

of oxidative stress and neuroinflammation upon hyperglycemic conditions. In addition, H_2S was shown to ameliorate proamyloidogenic effects, including increased Aβ1-42 levels and BACE-1 mRNA and protein expression in primary neuronal culture exposed to high glucose concentrations [62], thus also contributing to the earlier discussed role of H2S in amyloidogenesis.

In vivo studies using rodent diabetes models also revealed neuroprotective effects of H2S. In particular, in diabetic rats, treatment with H_2S donor GYY4137 significantly reduced microglial activation and proinflammatory cytokine expression in parallel with increased astrocyte count in the spinal cord, as well as improved sensory functions [63]. Improvement of memory function by H_2S was also shown to be associated with the reduction of neuroinflammation and improvement of cholinergic neurotransmission through the down-regulation of acetylcholinesterase activity after intracerebroventricular injection of streptozotocin [64], disrupting local glucose uptake and being a model of Alzheimer's disease [65].

AGEs accumulation in brain tissues was shown to possess significant neurotoxic effects, contributing to a broad spectrum of neurodegenerative diseases [66], especially Alzheimer's disease [67]. Recent studies demonstrated that H_2S metabolism may be considered both a target and modulator of AGEs neurotoxicity. Specifically, exposure of RSC96 Schwann neural cells to methylglyoxal and glucose resulted in significant inhibition of H_2S production through down-regulation of cystathionine-β-synthase (CBS) expression and activity in association with ROS and RNS overproduction, loss of mitochondrial membrane potential, and reduced cell viability. It is notable that improvement of CBS activity through calcitriol supplementation ameliorated these changes, thus being indicative of the potential role of H_2S in neuroprotective effects of vitamin D [68]. It has been also demonstrated that H_2S-mediated neuroprotection against methylglyoxal neurotoxicity and up-regulation of Keap1/Nrf2 signaling is dependent on the formation of cysteine persulfides [69]. Moreover, polysulfides occurring from H_2S oxidation were shown to scavenge methylglyoxal, thus decreasing intracellular AGEs accumulation and protein glycation and reducing cytotoxicity to differentiated SH-SY5Y cells [70]. In addition, H_2S was shown to ameliorate neurotoxic effects of D-galactose through the reduction of AGEs formation and oxidative stress in neuroblastoma SH-SY5Y cells [71].

Moreover, H_2S may also interfere with RAGE signaling, which is known to contribute significantly to neurotoxic effects of AGEs in Alzheimer's disease [72]. Specifically, H_2S was shown to reduce RAGE expression, as well as RAGE dimerization through S-sulfhydration at C259/C301 residues, thus reducing RAGE-dependent toxic effects of Aβ1–42 or AGEs [73].

Therefore, physiological H_2S may possess neuroprotective effects against glucose overexposure through the regulation of oxidative stress and neuroinflammation, as well as AGE formation and toxicity. At the same time, H2S-mediated neuroprotection may also be indirectly associated with its antidiabetic effects [74].

3.3. Homocysteine

Homocysteine (Hcy) is a non-essential S-containing amino acid formed as an intermediate product during the transformation of methionine to cysteine. One of the steps of this process, the formation of cystathionine from Hcy, is catalyzed by CBS, which also forms H_2S as a byproduct. Concomitantly, decreased CBS activity is associated with increased homocysteine levels, thus providing a mechanistic link between Hcy overload and H_2S metabolism [75]. Although Hcy is a physiological molecule formed *in vivo*, at higher accumulation rates, it possesses a broad spectrum of toxic effects associated with cardiovascular, endocrine, renal diseases, cancer, as well as neurological diseases [76]. Hcy was also shown to possess neurotoxic properties through the induction of neuronal oxidative stress, DNA damage, and apoptosis, thus contributing to neurodegeneration [77].

H_2S was shown to ameliorate Hcy-induced down-regulation of bcl2 expression as well as ROS-dependent mitochondrial dysfunction, thus decreasing proapoptotic signaling [78]. Taken together with up-regulation of Bax expression and DNA damage [79], these H_2S-associated changes result in a significant decrease in mitochondrial cytochrome c release and caspase 3 activation underlying the inhibition of Hcy-induced mitochondria-dependent apoptosis [80]. The particular mechanism of protective H_2S effects in Hcy-induced mitochondrial dysfunction may involve up-regulation of NADH dehydrogenase, cytochrome c oxidase, and F0-F1 ATPase activity in brain mitochondria, as well as increased oxygen consumption at mitochondrial complexes I, II, and IV, thus resulting in reduced ROS production and mitochondrial damage [81].

Given the role of ROS overproduction in mitochondrial dysfunction, one of the key mechanisms of protective action of H_2S upon Hcy exposure may include up-regulation of Nrf2 signaling that prevents Hcy-associated decrease in antioxidant enzyme activity [82]. In addition, H_2S was shown to prevent Hcy-induced inhibition of paraoxonase 1 expression and activity in PC12 cells that also suppresses ROS accumulation and oxidative damage [83]. Given the role of oxidative stress with the generation of reactive aldehydes, 4-HNE and MDA, in Hcy neurotoxicity, up-regulation of ALDH2 by H_2S may also be considered as the potential neuroprotective mechanism of the latter [84].

Protective effects of H_2S upon Hcy overexposure may also involve up-regulation of SIRT1 expression, a key regulator of redox homeostasis, as well as inhibition of ER stress, as evidenced by the down-regulation of GRP78 and cleaved caspase−12 protein expression in PC12 cells [85]. Similar effects were observed in HT22 cells, being associated with reduced Hcy-induced cellular senescence [86]. In turn, the up-regulation of BDNF expression and BDNF/TrkB signaling by H_2S significantly reduced hippocampal ER stress and apoptosis in Hcy-exposed rats [87], thus preventing cognitive decline in response to Hcy [88]. Correspondingly, a Hcy-induced inhibition of CBS activity resulting in lower H_2S production was shown to be associated with ER stress, altogether contributing to impaired learning and memory [89]. Taken together, these data suggest that H_2S may up-regulate SIRT1 expression with subsequent TORC1 deacetylation and its interaction with CREB, being considered as a

regulator of BDNF expression [90] altogether resulting in the reduction of Hcy-induced ERS.

Neuroinflammation with microglia activation due to STAT3 signaling was shown to be a significant contributor to Hcy neurotoxicity [91]. In turn, H2S was shown to ameliorate Hcy-induced microglia activation, as evidenced by reduced glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor molecule 1 (Iba1) expression, as well as the resulting expression of proinflammatory IL-6, TNFa, and MCP-1 in the cortex and hippocampus [92].

Another mechanism of H_2S-mediated neuroprotection against Hcy-induced neurodegeneration may involve the reduction of BBB permeability through the inhibition of MMPs' (MMP2, MMP9) activity and improvement of tissue inhibitor of metalloproteinase and tight junction protein (zonula occludens 1) expression [93]. In turn, increased BBB permeability may be involved in stimulated leukocyte extravasation and brain edema upon Hcy neurotoxicity [94]. The modulation of NMDAR expression may also be involved in neuroprotective effects of H_2S in Hcy-induced BBB permeability [95]. Down-regulation of NMDA receptor signaling and prevention of Ca^{2+} overload by H_2S may also mediate the protective effect of the latter against Hcy neurotoxicity [96].

Being in agreement with the indications of a tight association between Hcy and H_2S metabolism, the down-regulation of CBS expression and activity leading to reduced H_2S generation through ERK1/2 pathway activation may contribute significantly to Hcy neurotoxicity [97]. Concomitantly, maternal hyperhomocysteinemia also results in reduced H_2S production through the inhibition of CBS, whereas H_2S supplementation significantly improved neurobehavioral effects of Hcy exposure [98, 99].

3.4. Lipopolysaccharide (LPS) Endotoxin

Lipopolysaccharide (LPS) is a component of Gram-negative bacteria cell wall that is known to be a potent proinflammatory molecule, causing a significant impact on gut health [100]. However, in the case of increased gut wall permeability, translocation of LPS into the bloodstream underlies metabolic endotoxemia that may induce systemic inflammatory response [101]. In turn, LPS was shown to affect the structural integrity of the blood-brain barrier with subsequent development of LPS-induced neuroinflammation that is known to play a significant role in neurotoxicity and neurodegeneration [102].

LPS exposure was shown to induce anxiety-like behavior along with oxidative stress and neuroinflammation in the cortex and hippocampus in parallel with reducing H_2S production. In turn, H_2S ameliorated behavioral deficits and promoted microglia polarization from pro-inflammatory M1 phenotype expressing IL-1β and TNF-α to an anti-inflammatory M2 phenotype characterized by up-regulated IL-4 and TGF-β expression, thus being indicative of the potential role of H_2S in the regulation of neuroinflammation [103]. Moreover, the modulation of LPS-induced microglia activation is considered as the key mechanism in neuroprotection, whereas the direct effect of H_2S-releasing compounds on neuronal SH-S5Ys cell viability was not significant [104]. In contrast to other studies, it has been demonstrated that the anti-inflammatory effects of H_2S in BV2 microglial cells are accompanied by ROS overproduction [105].

In view of the key role of NF-κB transcription factor in LPS-induced inflammation [106], the anti-inflammatory effect of H_2S was shown to be dependent on the inhibition of LPS-induced IkB degeneration, thus preventing NF-κB activation and nuclear translocation and down-regulation of downstream signaling genes, including TNFa and TNFR [107]. In addition to the direct regulation of NF-κB signaling, the anti-inflammatory effect of H_2S in LPS-exposed microglia and astrocytes was shown to be dependent on the inhibition of p38 MAPK phosphorylation [108]. Other neuroinflammatory mechanisms involved in H_2S anti-inflammatory effects upon LPS exposure may involve the down-regulation of JAK-STAT3, cytokine-receptor interactions, TLR, NOD-like receptor, and chemokine signaling pathways, all being associated with H_2S-induced up-regulation of genes involved in sulfur metabolism, HSP production, and DNA replication [109].

In addition to the inhibition of LPS-induced neuroinflammation and oxidative stress upon LPS exposure in mice, H_2S also reduced neuronal apoptosis through the modulation of c-Jun and caspase 3 activation [110].

3.5. Ammonia

Ammonia is a physiological product of amino acid metabolism, although significant amounts of ammonia originate from the metabolic activity of gut microbiota. Being highly toxic, ammonia is detoxified in two pathways, the urea cycle, and the glutamine-glutamate cycle, with the liver playing a key role in NH3 removal [111]. Liver dysfunction due to a wide spectrum of pathologies, including cirrhosis and hepatitis, results in impaired NH_3 detoxification, hyperammonemia, and its toxic effects on target tissues, especially the brain. A particular case of liver dysfunction-induced neurotoxicity is hepatic encephalopathy [112].

In rats with hepatic encephalopathy, H_2S significantly reduced liver damage and inflammation, as well as decreased circulating ammonia levels, altogether resulting in decreased hippocampal NMDA receptor subtype 2B protein levels [113]. Concomitantly, in a model of acute liver failure, a significant H_2S-mediated decrease in ammonia levels prevented cognitive deficiency [114]. In a culture of rat astrocytes, H2S treatment ameliorated NH4Cl-induced apoptosis by decreasing caspase-3 and Bax expression along with up-regulation of Bcl2 expression. The observed effects were found to be dependent on Nrf2/ARE signaling and subsequent up-regulation of downstream antioxidant genes [115].

4. EXOGENOUS NEUROTOXICANTS

4.1. Alcohol

Although ethanol is formed physiologically in minor levels during metabolism [116], toxicologically valuable doses originate from external exposure, most commonly due to alcoholism causing significant health hazards [117]. Excessive doses of ethanol cause significant neurotoxicity, especially during neurodevelopment through a variety of pathways [118]. Alteration of neuronal cystathionine β synthase

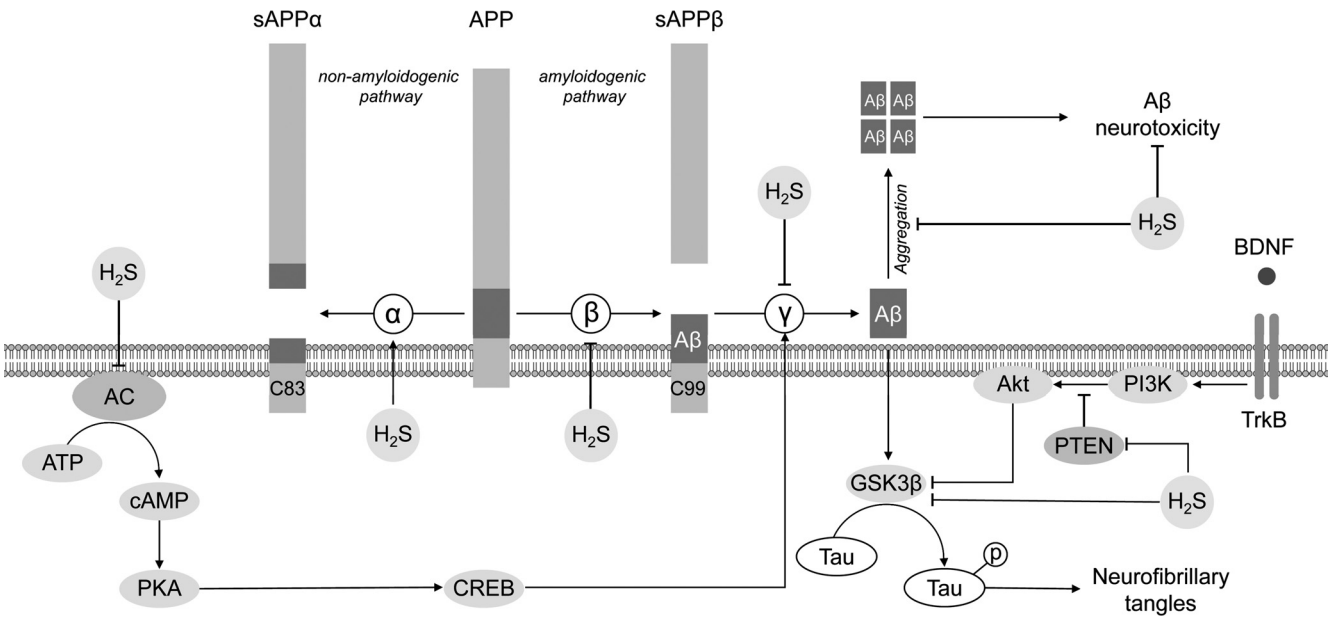

Fig. (4). Interference of endogenous H_2S with RAGE signaling and NF-κB activation.

(CBS) and cystathionine γ lyase (CSE) activity, as well as cellular H2S levels, is also considered as the potential mechanism of ethanol neurotoxicity [119].

In view of the high sensitivity of the developing brain to ethanol toxicity, special focus was made on the protective role of H_2S in fetal alcohol syndrome. Specifically, in a rat model of fetal alcohol disorder, H_2S significantly increased the reduced glutathione levels and the activity of antioxidant enzymes in parallel with the reduction of TNF-α and IL-1β levels, altogether resulting in decreased pro-apoptotic signaling and necrosis in hippocampal neurons [120]. Therefore, the inhibition of NF-κB pro-inflammatory signaling was proposed as the potential mechanism of anti-inflammatory effects of H_2S upon alcohol and cigarette smoke exposure [121]. In addition, H_2S was shown to increase hippocampal neurogenesis in a model of fetal alcohol disorders through the up-regulation of BrdU and BDNF expression in dentate gyrus area, in parallel with reduced apoptosis rate, altogether resulting in improved spatial memory [122].

It has been also demonstrated that exercise-induced amelioration of endoplasmic reticulum stress upon alcohol exposure was associated with the improvement of cystathionine β synthase (CBS) and cystathionine γ lyase (CSE) activity and the resulting increase in H_2S production [123]. It is, therefore, hypothesized that H_2S may possess a protective effect against alcohol-induced neurotoxicity through the inhibition of oxidative and endoplasmic reticulum stress [124].

Given the role of alcohol exposure in hyperhomocysteinemia, it is proposed that neuroprotective mechanisms of H_2S may be shared between hyperhomocysteinemia and alcoholism [124].

4.2. Formaldehyde

Formaldehyde is a reactive aldehyde with high toxicity that is considered a human carcinogen. Significant amounts of FA are formed endogenously during metabolism, although being tightly regulated under physiological conditions [125]. In turn, exogenous FA exposure possesses significant health hazards, especially in view of increased emissions [126]. In addition to carcinogenic effects, FA toxicity also affects other adverse health effects [127]. FA neurotoxicity [128, 129] was shown to be linked to neurodegeneration and other neurological disorders [130]. As in the case of the earlier reviewed endogenous neurotoxicants, H2S was shown to be tightly associated with FA neurotoxicity.

On the one hand, disturbance of H_2S metabolism was considered the potential mechanism of formaldehyde neurotoxicity. Specifically, formaldehyde exposure was shown to induce NO-mediated inhibition of cystathionine-beta-synthase activity with a subsequent decrease in endogenous H_2S production and intracellular ROS overproduction, altogether resulting in neurotoxicity in the PC12 cell model [131]. Similar effects were observed *in vivo*. Specifically, formaldehyde-induced inhibition of hippocampal CBS activity with reduced H_2S production is associated with altered learning and memory functions in rats that may be at least partially mediated by the induction of oxidative stress and apoptosis [132].

On the other hand, H_2S significantly modulates FA toxicity pathways, including neuronal apoptosis. Specifically, activation of BDNF production and TrkB-mediated signaling contributing to the reduction of proapoptotic signals through the up-regulation of Bcl-2 and the inhibition of Bax protein expression is considered as a potential neuroprotective mechanism of H_2S upon FA overexposure [133]. Moreover, H_2S-induced improvement of mitochondrial membrane potential in FA-exposed cells may also contribute to reduced cytochrome c release and inhibition of caspase 3 activation [134]. These TrkB-dependent effects on apoptosis may be mediated through MAPK/ERK and Akt signaling pathways [135]. Concomitantly, the up-regulation of hippocampal BDNF expression, reduction of oxidative stress, and apopto-

sis upon H_2S (as a donor, NaHS) treatment significantly reversed learning and memory dysfunctions in rats exposed to FA [136].

Moreover, it has been demonstrated that protective effects of H2S against formaldehyde neurotoxicity may be dependent on H_2S-induced SIRT1 and subsequent amelioration of ER-stress in PC12 cells [137], thus being indicative of the role of the SIRT1/TORC1/CREB/BDNF-TrkB pathway in the promotion of neuronal survival by H_2S upon FA neurotoxicity.

As an additional protective mechanism, H_2S-induced up-regulation of leptin signaling in HT-22 cells was shown to ameliorate apoptosis and senescence associated with FA exposure through the inhibition of p16INK4a and p21CIP1 pathways [138].

4.3. Acrylonitrile

Acrylonitrile is used in the production of plastics and resins, being highly toxic even at low-dose exposure [139]. Acrylonitrile was shown to be toxic for both neuronal and glial cells [140]. Therefore, the search for neuroprotective agents to be used to counteract acrylonitrile neurotoxicity is of particular importance [141].

Acrylonitrile exposure was found to decrease H_2S production in primary rat astrocytes in a dose-dependent manner, while the inhibition of the cystathionine-β-synthase (CBS)/3-mercaptopyruvate sulfurtransferase (3-MST)-H_2S pathway predisposed to acrylonitrile neurotoxicity. At the same time, supplementation with NaHS significantly reduced acrylonitrile cytotoxicity, thus being indicative of the significant role of H2S as a target for acrylonitrile-induced neurotoxicity [142]. In turn, H_2S significantly ameliorated acrylonitrile neurotoxicity through the up-regulation of Nrf2 signaling and the resulting increase in heme oxygenase-1 and γ-glutamylcysteine synthetase expression and the resulting decrease in ROS formation, as well as the activation of autophagy in primary rat astrocytes [143]. Taken together, these findings are indicative of the role of H_2S metabolism as a mediator of acrylonitrile-induced oxidative stress and subsequent neurotoxicity.

4.4. Laboratory Neurotoxicants for the Modeling of Parkinson's Disease (6-hydroxydopamine and MPTP)

4.4.1. 6-hydroxydopamine

6-hydroxydopamine is a neurotoxic compound that is frequently used for Parkinson's disease modeling due to dopaminergic neuron damage through the induction of oxidative stress, apoptosis, neuroinflammation, and dopaminergic neurodegeneration [144]. In turn, H_2S significantly attenuated the 6-OHDA-induced decrease in striatal dopamine levels, tyrosine hydroxylase-positive neuronal death in substantia nigra pars compacta, as well as behavioral disorders [145, 146]. Amelioration of 6-OHDA-induced loss of nigral tyrosine-hydroxylase positive neurons and striatal dopamine decline was shown to be dependent on H_2S-induced Nrf2 activation and nuclear translocation, resulting in the up-regulation of downstream antioxidant enzyme expression [147]. Correspondingly, cystathionine-beta-synthase overexpression also had neuroprotective effects on 6-OHDA-exposed rats by decreasing neuronal apoptosis, oxidative stress, and α-synuclein expression [148].

In addition to oxidative stress and apoptosis, targeting 6-OHDA-induced ERS was also shown to mediate neuroprotective effects of H2S. Specifically, in SH-SY5Y cells exposed to 6-OHDA, NaHS treatment significantly reduced ER stress, as evidenced by a decrease in CHOP, phospho-eIF2α, and GRP78 expression, being dependent on H2S-induced Akt-Hsp90 pathway activation [149]. Activation of PKCα and PKCε was shown to play a significant role in H_2S-induced Akt/PI3K activation and neuroprotection in 6-OHDA-treated SH-SY5Y cells [150].

H_2S may also contribute to neuroprotection upon 6-OHDA exposure through the modulation of neuroinflammation. Specifically, in 6-OHDA-exposed rats, H_2S significantly reduced NF-κB signaling along with the inhibition of microglial activation and proinflammatory cytokine levels. Experimental studies using BV-2 microglial cells demonstrated that the impact of H_2S on NF-κB signaling may be mediated by the stabilization of IkB [151].

It is also notable that H_2S-mediated prevention of 6-OHDA dopaminergic neuron loss and PD-like behavior is associated with increased nigral leptin expression and aerobic glycolysis (Warburg effect), as evidenced by increased expression of hexokinase 1, pyruvate kinase M-2, pyruvate dehydrogenase kinase 1, and lactate dehydrogenase, whereas the inhibition of leptin signaling ameliorated both H2S neuroprotection and Warburg effect [152]. It has been also demonstrated that leptin signaling is involved in antiapoptotic effects of H_2S and the induction of autophagy response. Specifically, H_2S reduced 6-OHDA-induced neuronal apoptosis characterized by increased Bax expression, caspase 3 activation, and down-regulated Bcl2 expression. These effects, as well as H_2S-induced autophagy, were reduced by the inhibition of leptin receptor signaling [153]. Autophagy flux induced by H_2S was shown to be related to AMPK sulfhydration at Cys302 with its subsequent activation as well as mTOR inhibition [154].

4.4.2. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its Metabolite 1-methyl-4-phenyl Pyridine Ion (MPP)

MPTP is a neurotoxic agent widely used for the development of Parkinson's disease that is metabolized by monoamine oxidase B to a more toxic 1-methyl-4-phenylpyridinium ion (MPP^+) [155]. MPP^+ possesses dopaminergic neurotoxicity through the induction of mitochondrial dysfunction, as well as oxidative stress, apoptosis, neuroinflammation, and excitotoxicity [156].

Induction of PD-like phenotype upon MPTP/MPP^+ exposure is also associated with the dysregulation of H_2S production. Specifically, motor deficits and dopaminergic neurotoxicity of MPTP were also shown to be associated with the down-regulation of CBS, thus reducing endogenous H_2S levels, whereas CBS overexpression ameliorated these changes as well as the reduced α-synuclein level and glial activation in MPTP-exposed rats [157]. MPP^+ was shown to down-regulate CBS expression and activity, thus resulting in decreased H_2S production in PC12 cells, whereas the improvement of H_2S levels ameliorated MPP^+ cytotoxicity and oxidative stress [158]. Concomitantly, the prevention of oxidative stress, mitochondrial membrane potential loss, cytochrome c release, and decreased Bcl2 expression followed by improved cell viability by asymmetric dimethylarginine in

MPP^+-exposed PC122 cells was shown to be dependent on CBS expression and subsequent release of H2S [159], thus being indicative of the beneficial role of H2S in protection against MPP^+-induced neuronal apoptosis [160].

The observed H_2S-induced increase in cell viability, autophagic flux, and inhibition of oxidative stress in MPP^+-exposed SH-S5Y5 cells was shown to be dependent on the increase in SIRT1 expression and sulfhydration [161]. Concomitantly, these effects were also accompanied by the up-regulation of antioxidant enzyme expression, including heme oxygenase-1 and glutamate-cysteine ligase producing reduced glutathione [162].

Being in agreement with the observed increase in SIRT1 expression, BDNT/TrkB signaling was shown to be critical for observed antioxidant effects and reduction of ER stress by H_2S in MPP^+-treated PC12 cells [163].

Certain studies revealed the role of Akt signaling in H2S-induced neuroprotection against MPTP/MPP^+ toxicity. Specifically, it has been demonstrated that H2S treatment significantly ameliorated dopaminergic neurotoxicity of MPTP through AKT-dependent inhibition of nNOS expression and activity with a subsequent decrease in NO production and α-synuclein nitration [164]. In turn, H_2S-induced up-regulation of the PI3K/AKT pathway, resulting in the up-regulation of Bcl2 expression, was shown to be mediated by an increase in KATP channel activity [165]. At the same time, another study demonstrated that the modulation of UCP2 activity may be considered as a more significant factor in the mediation of H_2S-induced neuroprotection against MPP oxidative stress in dopaminergic neurons as compared to the KATP-dependent mechanism [166].

Finally, MPTP exposure was found to increase ROCK2 expression, being involved in microglia activation and cytotoxicity, whereas H_2S exposure significantly ameliorated MPTP-induced effects through the up-regulation of miR-135a-5p possessing an inhibitory effect on ROCK2 mRNA translation [167].

4.3. Metals

4.3.1. Toxic Metals

Toxic metals, arsenic, mercury, lead, aluminium, possess significant neurotoxic effects due to their prooxidant, pro-inflammatory, and immunotoxic activity [168], being associated with the development of neurodevelopmental [169] and neurodegenerative diseases [170]. Certain studies aimed to estimate whether H_2S may counteract metal-induced toxicity.

Protective effects of H_2S upon MeHg overexposure were shown to involve the up-regulation of antioxidant system with the increase of GPX and TrxR activity, as well as the prevention of mitochondrial dysfunction with a subsequent decrease in the release of cytochrome C and apoptosis-inducing factors, thus preventing mitochondrial-dependent apoptosis in rat cortex [171]. In addition, direct interaction between methylmercury and H_2S may also significantly contribute to neuroprotective effects of the latter. Specifically, in SH-SY5Y cells, the H_2S-dependent transformation of MeHg to bismethylmercury sulfide ($(MeHg)_2S$) was shown to reduce MeHg toxicity [172]. Such interaction may result from the role of the H2S molecule as an equivalent of the thiol group, being a target for electrophilic Hg binding [173]. It is also notable that Hg species were considered as cystathionine γ-lyase inhibitors [174], which may underlie reduced cellular H_2S levels upon Hg exposure.

In contrast to Hg, evidence on neuroprotective effects of H2S upon exposure to other toxic metals are rather insufficient, being limited to single studies. Specifically, in As-exposed mice characterized by reduced cortical GSH levels along with Nrf2 and NF-κB activation, the increase in H_2S production may be associated with glial glutamate transporter 1 up-regulation that may result in increased glutamate uptake [175]. H2S was also shown to ameliorate cognitive deficits and reduce neuronal apoptosis, neuroinflammation, as well as oxidative stress through the up-regulation of the antioxidant system in Pb-exposed rats [176]. In the $AlCl_3$-induced model of AD, application of tacrine–H_2S donor hybrid was shown to increase hippocampal H_2S levels, as well as inhibit AChE activity, reduce neuroinflammation, and improve synaptogenesis, altogether resulting in improved cognitive and locomotor functioning [177].

4.3.2. Biometals

Although biologically essential metals (biometals), zinc, iron, and copper, are required for adequate development and functioning of the brain, their overaccumulation also results in neurotoxicity [178]. Particularly, iron, zinc, and copper overload were found to be associated with Alzheimer's disease [179] and other neurodegenerative diseases [180]. Therefore, the potential neuroprotective effect of H2S against metal neurotoxicity was investigated in several studies.

In Zn-exposed neuroblastoma SH-SY5Y cells, H_2S significantly reduced mitochondrial dysfunction, resulting in increased intracellular ATP and NAD levels, as well as preventing Zn-induced cell death. It is notable that these effects were also associated with H_2S-induced inhibition of metal-responsive transcription factor-1 (MTF1) and metallothionein gene expression, thus being indicative of interference with intracellular Zn signaling [181]. In addition to direct binding to Zn^{2+} and prevention of its intracellular accumulation, H2S-dependent amelioration of Zn-induced phosphorylation of glycogen synthase kinase-3β and protein kinase C may also contribute to H_2S-induced prevention of Zn^{2+} neurotoxicity [182].

In contrast to other metals discussed, copper toxicity may be aggravated by H_2S, which should also be discussed. Specifically, H_2S promoted intracellular Cu accumulation in SH-S5Y5 cells through the down-regulation of the exported ATP7A without any significant impact on ATP7B and Cu^{2+} importer Ctr1. The resulting reduction in Cu export from the cell was associated with the induction of oxidative stress, mitochondrial dysfunction, and reduced ATP production, altogether leading to reduced cell viability [183]. These findings corroborate findings from a culture of HeLa cells indicating a higher rate of apoptosis upon H_2S and Cu co-exposure [184].

Direct data on the impact of H_2S on iron neurotoxicity are lacking, although certain indications provide evidence for the significance of the interplay between H_2S and iron for the brain. Specifically, in type 1 diabetic mice, H2S was shown

to reduce iron accumulation in the prefrontal cortex and prevent ferroptosis, being associated with the up-regulation of GPX4, SLC7A11, and Sirtuin 6 expression, and the prevention of microglia activation, altogether resulting in reduced anxiety-like and depressive-like behaviors [185]. These findings generally corroborate the earlier observed role of cystathionine β-synthase, a source of H_2S, as a negative regulator of ferroptosis [186]. Similarly, cystathionine gamma-lyase (CSE) activity and H2S production were inversely associated with ferroptosis in myoblasts [187]. It should also be notable that H_2S is involved in systemic iron metabolism regulation [188]. H_2S was shown to inhibit IL-6-induced hepcidin secretion through the down-regulation of JAK2/STAT3 signaling [189]. The latter may be associated with inhibition of STAT3 acetylation due to H_2S-induced SIRT1 activation [190]. At the same time, a more recent study revealed the key contribution of IL-6/pSTAT3/hepcidin mechanism to H_2S-induced changes in iron metabolism only upon proinflammatory conditions. Oppositely, in normal non-inflammatory conditions, the up-regulation of TfR1 and a decrease in Fpn1 expression in response to H_2S treatment may be mediated by the modulation of IRP/IRE and Nrf2 pathways [191]. Correspondingly, the deficiency of cystathionine β-synthase is also associated with hemochromatosis-like phenotype due to hepcidin dysregulation [192]. Although these findings do not provide a direct indication of the impact of H_2S on iron neurotoxicity, these data allow hypothesizing the potential involvement of H_2S dysregulation in the neurotoxicity of systemic iron overload.

5. OTHER NEUROTOXIC AGENTS

In *in vitro* and *in vivo* experimental studies, H_2S treatment was shown to possess protective effects through the inhibition of oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation against neurotoxicity of a variety of physiological and exogenous agents, including sodium azide [193], 3-nitropropionic acid [194], metamphetamine [195], and corticosterone [196]. Given a wide spectrum of biological effects of endogenous H2S in the neural system, it is highly likely that it may possess protective activity against other neurotoxicants, although direct data are lacking.

CONCLUSION

The existing data demonstrate that H_2S has neuroprotective effects upon exposure to endogenous and exogenous neurotoxicants. On the one hand, neuroprotective effects are mediated by S-sulfhydration of key regulators of antioxidant (Sirt1, Nrf2) and inflammatory response (NF-κB), resulting in the modulation of the downstream signaling, such as SIRT1/TORC1/CREB/BDNF-TrkB, Nrf2/ARE/HO-1, or other pathways. On the other hand, H_2S appears to have a direct detoxicative effect by binding endogenous (ROS, AGEs, Aβ) and exogenous (MeHg) neurotoxicants, thus reducing their toxicity. Moreover, alteration of H_2S metabolism through the inhibition of H_2S-synthetizing enzymes in the brain (CBS, 3-MST) is expected to be considered as a significant mechanism of neurotoxicity. Taken together, the existing data indicate that the modulation of cerebral H_2S metabolism may be used as a neuroprotective strategy to counteract neurotoxicity of a wide spectrum of endogenous and exogenous neurotoxicants associated with neurodegeneration (Alzheimer's and Parkinson's disease), fetal alcohol syndrome, hepatic encephalopathy, environmental neurotoxicant exposure, *etc*. However, additional studies from relevant animal models are required, including Parkinson's disease models of mice overexpressing α-synuclein instead of chemically induced Parkinson's disease models. In this particular case, the modulation of H_2S-synthetizing enzymes or the use of H_2S-releasing drugs should be considered as the potential tools against toxic exposure-associated diseases. However, the translation of the findings to humans is quite questionable due to the origin of the data from cell cultures and rodent models, while the efficiency, tolerability, and safety of H_2S donors in humans are unclear and should be studied additionally.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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