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Review

Hydrogen sulfide/polysulfides signaling and neuronal diseases

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ABSTRACT

Hydrogen sulfide (H_2S) and polysulfides including H_2S_n (n = 2 or more) regulate neuronal activity, vascular tone, oxytosis/ferroptosis, oxygen sensing, cancer growth and senescence. Cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3MST) produce H_2S. Polysulfides are also produced by various enzymes including 3MST. In addition, transient receptor potential ankyrin 1 (TRPA1) channel-an important polysulfide target-modulates sulfur metabolism (including cysteine, H_2S and polysulfides) and also affects the neurotransmitter GABA. Polysulfides persulfidate the cysteine residues of the target proteins, causing conformational changes that alter their activity. By contrast, H_2S persulfidates oxidized cysteine residues (e.g., S-nitrosylated- and S-sulfinated) in its targets. H_2S/polysulfides protect neurons from oxidative stress and thereby protect cells against various forms of cell death including oxytosis and ferroptosis. A deviation from normal H_2S and polysulfides levels has been suggested to play a role in the pathophysiology of various neuronal- and psychiatric diseases.

Introduction

For many years, hydrogen sulfide (H_2S) was regarded as an environmental toxic gas, until it was identified in mammalian brains [1–3]. This finding prompted the discovery of H_2S as a physiological signaling molecule in both the brain and the vasculature [4–6]. In the early studies, H_2S was considered merely a by-product of the metabolic pathways or as a marker used to assess enzyme activity [7–9]. Cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfur transferase (3MST) produces H_2S [10–14]. CBS produces H_2S from cysteine alone or from cysteine together with homocysteine, and CSE takes cysteine, homocysteine and both as substrates [12,13]. 3MST produces H_2S and polysulfides from 3-mercaptopyruvate (3 MP), which is produced from L-cysteine and α-ketoglutarate by cysteine aminotransferase as well as from D-cysteine by D-amino acid oxidase [10,11,14]. D-cysteine is identified in high concentrations in the embryonic brain [15]. Several other enzymes can also produce polysulfides such as sulfur quinone oxydoreductase (SQR), superoxide dismutase (SOD), myoglobin, catalase, myeloperoxidase, and cysteinyl tRNA synthetase (CARS) [16–21].

H_2S exerts various physiological effects. H_2S facilitates the induction of hippocampal long-term potentiation (LTP), a synaptic model of memory formation by enhancing the activity of N-methyl D-aspartate (NMDA) receptors [4]. H_2S relaxes vascular smooth muscle in synergy with nitric oxide (NO) [5,6]. H_2S protects neurons from oxidative stress and cardiac muscle from ischemia-reperfusion injury [22–24]. It plays a role as an oxygen sensor [25,26]. H_2S induces Ca^{2+} influx in astrocytes, it was later found that polysulfides rather than H_2S activate TRPA1 channels [27–30]. Physiological roles of polysulfides were subsequently reported such as the regulation of the activity of a tumor suppressor phosphate and tensin homolog (PTEN), protein kinase G1α and Kelch ECH-associating protein 1 (Keap1) [31–33].

S-sulfhydration (persulfidation, S-sulfuration, persulfuration) was proposed by Snyder and his colleagues as a regulation mechanism of target proteins [34–37]. (Nomenclature S-sulfuration was suggested to be used instead of S-sulfhydration in 2012 [35]. In this article widely

Abbreviations: ATP, adenosine triphosphate; CAT, cysteine aminotransferase; CBS, cystathionine β–synthase; CysSSH, cysteine persulfide; CSE, cystathionine γ–lyase; DAO, D-amino acid oxidase; DTT, dithiothreitol; GAPDH, glyceraldehydes-3-phosphate dehydrogenase; GCL, glutamate cysteine ligase; GSH, glutathione; GSSH, glutathione persulfide; HNO, nitroxyl; H_2O_2, hydrogen peroxide; HSNO, thionitrous acid; H_2S, hydrogen sulfide; H_2S_n, hydrogen polysulfides; Keap1, Kelch ECH associating protein 1; LTP, long-term potentiation; 3 MP, 3-mercaptopyruvate; 3MST, 3-mercaptopyruvate sulfurtransferase; NaHS, sodium hydrosulfide; NMDA, N-methyl D-aspartate; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; O_2, oxygen; PERK, PKR-like endoplasmic reticulum kinase; PTEN, phosphatase and tensin homolog; SOD, super oxide dismutase; SQR, sulfur quinone oxydoreductase; $SSNO^-$, nitrosopersulfide; TRPA1, transient receptor potential ankyrin 1.

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accepted 'persulfidation' is used [37]). Persulfidation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) by H_2S increases its catalytic activity by seven fold, and DTT reduces to remove it, resulting in the diminution of the activity, while S-nitrosylation of the same cysteine residue abolishes its catalytic activity [34]. In contrast, the other group suggested that H_2S_n but not H_2S suppress GAPDH activity [38]. The activities of many other proteins have been found to be regulated by persulfidation, including NF-kB to regulate immune responses, protein tyrosine phosphatase to inhibit global protein synthesis, and E3 ubiquitin ligase parkin in Parkinson's disease [39–41].

The human proteome includes 214,000 cysteine residues showed that 5–12 % of total cysteine residues are oxidized, and this can be increased to >40 % by adding oxidants [42]. Of these oxidized cysteine residues such as S-nitrosylated (P-CysSNO) and S-sulfinated (P-CysSOH) ones can be persulfidated by H_2S to P-CysSSH, though the recent systematic analysis of the human proteome shows that cysteine residues which can be both S-nitrosylated and persulfidated are rare or low percentage of S-nitrosylated cysteine residues can be transferred to persulfidated ones [43].

H_2S and polysulfides show neuroprotective effect against oxidative stress induced by high concentrations of glutamate called oxytosis [22,23,44–46]. Oxytosis has recently been proposed to be identical or closely related to ferroptosis, and is implicated in various neurodegenerative diseases, including Alzheimer's disease [47]. Disturbances in H_2S/polysulfide production and in the activity of the cystine/glutamate antiporter (Xc-)—a key target in oxytosis/ferroptosis—have been implicated in the pathogenesis of Parkinson's disease, Huntington's disease, Alzheimer's disease, and other neurological disorders, including schizophrenia [41,48–52]. H_2S and polysulfides may have therapeutic potential for these neurodegenerative and neurological disorders.

Sulfane sulfur and persulfidated molecules

The existence of sulfane sulfur, sulfur bonded sulfur which includes H_2S_n, $CysS_nH$, GS_nH, $CysS_nCys$, GS_nG, PS_nH (Cys:cysteine, G:glutathione, P:protein), in tissues has been predicted from the observations that tissue homogenates release H_2S in the presence of DTT [53–56]. Sulfane sulfur was identified in the brain [53], and it was later designated as bound sulfur [54]. In homogenates the intracellular and extracellular molecules including glutathione an intracellular strong reducing molecule with the reducing potential of −240 mV [55] are mixed. Even at the acidic condition (pH 5.7) to shift the equilibrium ($H_2S \rightleftharpoons H^+ + HS^-$, pK_1 7.04) to H_2S to release H_2S from homogenates, only small amount of H_2S is released [56,57]. However, in the presence of a stronger reducing substance DTT (the reducing potential of −330 mV) tissue homogenates release more H_2S. This category includes free sulfane sulfur (e.g., H_2S_n, cysteine persulfide) as well as per- and polysulfurated cysteine residues on proteins (Fig. 1) [56,58–60]. The levels of bound sulfur in the 3MST-knockout rat brain are similarly decreased to those of H_2S_n and cysteine persulfide measured by LC-MS/MS [48].

The rate and amount of H_2S released under reducing conditions (from bound sulfur) differ among tissues [56]. For example, liver homogenates release larger amounts of H_2S—and at a faster rate—than brain or heart homogenates. In contrast, heart homogenates release far less H_2S than those from the liver or brain, suggesting that both the forms and the amounts of polysulfides differ across tissues.

Molecules in tissue homogenates, in turn, can react with H_2S, and these reaction rates differ among tissues [56]. Liver homogenates quickly react with H_2S, while those brain very slowly and heart in between. Heart homogenates released a little H_2S, while they well react with H_2S. The reacted H_2S exogenously applied increased the levels of bound sulfur, suggesting that H_2S reacted with other molecules to generate persulfidated molecules including persulfidated cysteine residues [56]. Oxidized cysteine residues, such as S-nitrosylated (P-CysSNO) and S-sulfinated (P-CysSOH) forms, can react with and sequester H_2S, whereas thiol cysteine residues do not (Fig. 2). Taken together, these findings suggest that cysteine residues in the heart may be highly oxidized or that the heart contains substantial heme capable of reacting with H_2S. These observations suggest that each tissue possesses specific forms of sulfane sulfur (polysulfides), mostly localized to cysteine residues that vary in redox state and occur at distinct tissue-specific ratios.

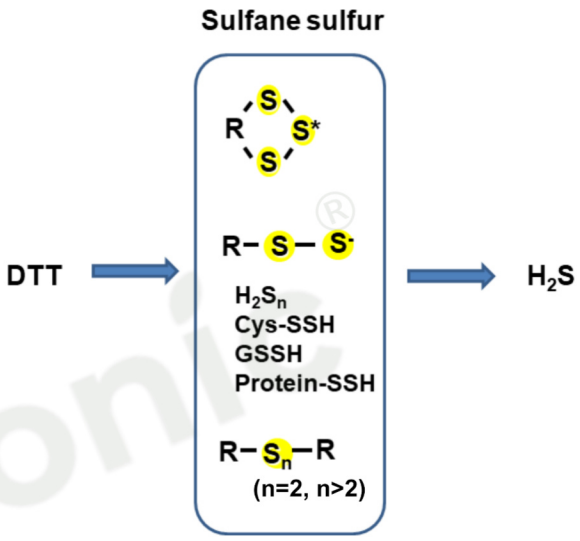


Fig. 1. Release of H_2S from sulfane sulfur (bound sulfur). Sulfane sulfur (sulfur bonded sulfur) including H_2S_n, polysulfides and persulfidated cysteine residues of proteins in tissues homogenates releases H_2S in the presence of DTT.

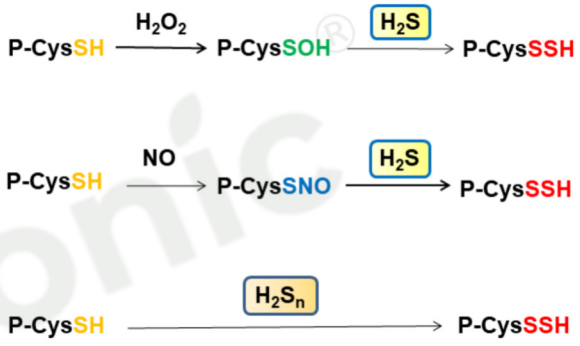


Fig. 2. Persulfidation of cysteine residues. Cysteine residues S-sulfinated by H_2O_2 and those S-nitrosylated by NO can be persulfidated by H_2S. Note that low percentage of S-nitrosylated cysteine residues can be transferred to persulfidated one [43]. This figure is produced by modifying [161].

Persulfidation by diffusible molecules and via sulfur transferase

Nitric oxide (NO) was originally discovered to bind the heme group of soluble guanylyl cyclase and produce cyclic guanosine monophosphate (cGMP) [57]. It was then identified an endogenous signaling molecule, termed endothelium-derived relaxation factor (EDRF), which is produced by nitric oxide synthase (NOS) and diffuses to vascular smooth muscle to induce relaxation [61–64]. In addition to binding to heme, NO also reacts with cysteine thiols in target proteins, leading to S-nitrosylation [65]. It was later found that S-nitrosylation occurs not only through the diffusing NO but also via transnitrosylation between proteins with the enzymatic mechanism [66,67].

H_2S, generated by CBS, CSE, and 3MST, is metabolized by SQR in mitochondria, enhances NMDA receptor activity, and modifies GAPDH function [4,16,34,68]. Meanwhile, polysulfides activate TRPA1 channels and protein kinase G1α, but inhibit PTEN [30–32]. These reactions can be mediated by the diffusion of H_2S and polysulfides. In

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3MST-knockout animals, the levels of persulfidated molecules (detected as bound sulfur) are roughly half those in wild-type animals, whereas CBS-knockout animals show no change. This finding suggests that 3MST, but not CBS, is responsible for producing bound sulfur (persulfidated molecules) [48,60].

There are two potential mechanisms for the production of persulfidated cysteine residues; diffusion of H_2S/polysulfides to the target cysteine residues and persulfidation by enzymes including 3MST as a sulfur transferase [60,69]. Pedre et al. demonstrated that a redox-sensitive green fluorescent protein (roGFP2), containing two cysteine residues, could be fused to 3MST so these cysteine residues would reside in close proximity to the enzyme [69]. By using this roGFP2-3MST fusion protein, 3MST was shown to function as a sulfur transferase, to generate the enzymatic persulfidation.

Regulation of neurotransmitters release by H_2S and polysulfides

The toxic effects of high concentrations of H_2S on the endogenous levels of neurotransmitters *in vivo* have been documented. Exposure of rats to high H_2S levels during perinatal development significantly lowered neurotransmitter levels. Specifically, aspartate, glutamate, and GABA were reduced in the cerebrum, and aspartate and GABA were also reduced in the cerebellum [70]. Aspartate, glutamate, and glutamine levels increased under chronic (but not acute) conditions in the brainstem of saline-treated rats, whereas these increases were suppressed by chronic NaHS treatment [71]. The same study also showed that aspartate, glutamate, and glutamine levels were elevated in female, but not male, mouse brainstems following NaHS treatment. H_2S exerts complex effects on neurotransmitter levels.

Several physiological effects of H_2S on neurotransmitters release have also been reported. In rats, NaHS significantly increased the amplitude of evoked solitary tract (TS)-excitatory post synaptic currents (EPSCs), frequency of miniature (m) EPSCs, and presynaptic terminal calcium influx in the nucleus tractus solitarii (NTS). In contrast, the presence of the CBS inhibitor aminooxyacetate significantly reduced the amplitude of TS-EPSCs and presynaptic calcium influx in the NTS, without altering postsynaptic properties [72]. In the mouse superior mesenteric ganglion (SMG), NaHS selectively potentiated cholinergic fast excitatory post synaptic potentials (F-EPSPs) evoked by splanchnic nerve stimulation but not those evoked by colonic nerve stimulation [73]. Splanchnic F-EPSPs, but not colonic F-EPSPs, were reduced by the CSE blocker DL-propargylglycine and were also reduced in CSE knockout mice. NaHS increased the frequency of miniature end-plate potentials and the amplitude of the evoked postsynaptic responses to a single stimulation in the mouse diaphragm's motor nerve ending [74]. The same group observed a similar result at the neuromuscular junction [75]. These observations suggest that H_2S facilitates the release of neurotransmitters.

Both Na_2S and Na_2S_2 induce the release of neurotransmitters—including GABA, glutamate, D-serine, a co-agonist of NMDA receptors, and glycine—in *in vivo* microdialysis experiments [48]. Na_2S induced the release of GABA and glutamate more strongly than Na_2S_2, while both compounds induced the release of D-serine and glycine to a similar degree. This difference is likely due to distinct release mechanisms for GABA and glutamate compared with those for D-serine and glycine. In a brain cell suspension containing both neurons and glial cells, serotonin suppressed the release of H_2S while increasing that of H_2S_3 [48]. Intracellular H_2S levels were elevated by acetylcholine, and cysteine persulfide release was increased by acetylcholine, norepinephrine, and GABA. Thus, H_2S/H_2S_2 facilitate the release of neurotransmitters, while neurotransmitters in turn regulate the release of H_2S and cysteine persulfide [48].

Transporters such as the alanine-serine-cysteine transporter (Asc-1), a neutral amino acid transporter in neurons, and Slc38a1, found in GABAergic hippocampal neurons, are predicted to be involved in D-serine release [76–78]. Because the time course of neurotransmitter release observed in *in vivo* microdialysis is much longer than that seen in synaptic transmission, it is possible that transporters—rather than vesicular exocytosis—mediate this slower release of transmitters.

Enhancement of NMDA receptors by H_2S and polysulfides

H_2S facilitates the activity of N-methyl D-aspartate (NMDA) receptors to induce hippocampal long-term potentiation (LTP) [4]. The reduction of cysteine disulfide bond at the hinge of the ligand binding domain localized to the extracellular side of NMDA receptors by dithiothreitol (DTT) enhances the activity of the receptors [79]. Although H_2S is a reducing substance, its reducing activity did not fully explain the facilitating activity of H_2S on LTP, for lower concentration of H_2S facilitates LTP induction much greatly than the higher concentration of a strong reducing substance DTT [4].

The activation of astrocytes, which surround synapse and release gliotransmitters to regulate the synaptic activity, was found to be induced through the activation of TRPA1 channels by polysulfides [27–30]. Shigetomi et al. demonstrated that the activation of TRPA1 channels by its specific agonist allyl isothiocyanate induced the release of D-serine from astrocytes to facilitate the induction of LTP [80].

Recently, it was reported that D-serine is released mainly from neurons [81]. In *in vivo* microdialysis Na_2S_2 induced the release of D-serine even in TRPA1-knockout rats, while LTP was suppressed in TRPA1-knockout similarly to that observed in 3MST-knockout rat brain, suggesting that TRPA1 channels play a role in the induction of LTP but not involved in the release of D-serine [48]. H_2S induces the release of D-serine [48], and $GABA_A$ receptor activation induces the release of D-serine [82]. It is possible that D-serine released induced directly by H_2S via unknown mechanism and/or D-serine through the activation of GABA released by H_2S enhance(s) the activity of NMDA receptors, leading to the facilitation of LTP induction [48].

Endothelium-derived hyperpolarizing factor (EDHF)

Endothelium-derived relaxation factor (EDRF) was subsequently identified as NO [62,83]. Another factor distinct from EDRF, known as endothelium-derived hyperpolarizing factor (EDHF) released by the stimulation of acetylcholine, was also discovered. Although prostacyclin, H_2O_2, and K^+ have been proposed as candidates, the definitive identity of EDHF remains elusive [84–87]. EDHF is particularly important in small arteries which influence blood pressure and its signal is mediated by Ca^{2+}-sensitive K^+-channels but not by ATP-sensitive K^+-channels (K_{ATP}) [88–91].

H_2S weakly relaxes vascular smooth muscle, but its effect is greatly augmented in the presence of NO [5]. A similar synergistic effect of H_2S with NO was observed in the ilium [92]. H_2S was reported to activate K_{ATP}, and later it was also found to activate the endothelial Ca^{2+} dependent intermediate K^+ conductance (IK_{Ca}) and small conductance (SK_{Ca}) K^+ channels, as selective IK_{Ca} and SK_{Ca} channel inhibitors, charybdotoxin and apamin, inhibit glibenclamide-insensitive H_2S-induced vasorelaxation, and hyperpolarization was virtually abolished in blood vessels of CSE-deficient mice [6,93]. We previously reported that 3MST localizes to both vascular endothelium and smooth muscle, whereas CBS and CSE are confined primarily to smooth muscle [94]. 3MST produces H_2S_n and polysulfides, which activate TRPA1 channels. Earley showed that the activation of TRPA1 channels induce Ca^{2+} influx in endothelium and subsequently activate IK_{Ca} and SK_{Ca} to hyperpolarize the membrane (Fig. 3) [30,94,95]. The change in membrane potential is conducted via gap junction to hyperpolarize the smooth muscle plasma membrane [95]. Polysulfides are released by acetylcholine stimulation in brain cells derived from wild-type rat brains, but not in

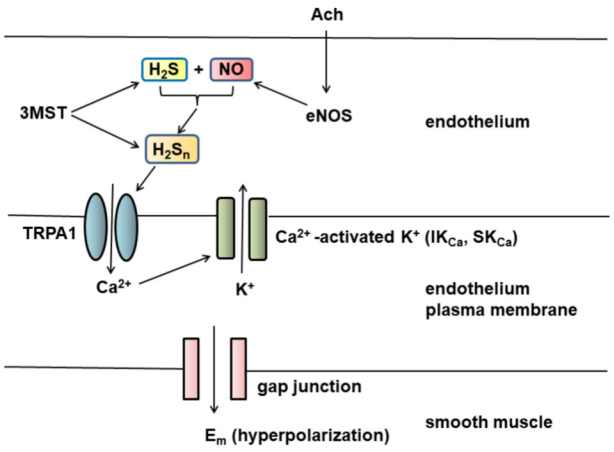


Fig. 3. H_2S and polysulfides are potential Endothelium-derived hyperpolarizing factor (EDHF). 3MST localizes to vascular endothelium produces H_2S and polysulfides including H_2S_n. The chemical interaction of H_2S and NO produced by endothelial NO synthetase (eNOS) activated by acetylcholine also generates H_2S_n. Polysulfides activate TRPA1 channels to induce Ca^{2+} influx which activates Ca^{2+}-activated K^+ channels to hyperpolarize the membrane that transmit via gap junction to hyperpolarized the smooth muscle plasma membrane. This figure is produced by modifying [161].

those from 3MST-knockout rats [48]. It is intriguing to know if endothelium release polysulfides in response to acetylcholine.

H_2S itself can be EDHF as proposed by Snyder and colleagues [93]. H_2S can persulfidate TRPA1 channels, of which the cysteine residues have to be S-nitrosylated to react with H_2S, though the possibility is low as described previously [43,96]. H_2S may persulfidate S-sulfenylated TRPA1 channels. H_2O_2 reacts very slowly with free cysteine (2-20 M^{-1} s^{-1}), while its reactivity significantly increases to cysteine residues (10-10^6 M^{-1} s^{-1}) [97]. Although H_2O_2 poorly reacts with H_2S (0.73 M^{-1} s^{-1}), P–SOH react two orders of magnitude faster with H_2S than with GSH at pH7.4 (Fig. 2) [98,99]. TRPA1 channel is activated by the covalent modification of cysteine residues within the cytoplasmic amino terminus of the channel by H_2O_2 [100,101]. Although sulfenylation of TRPA1 has not been elucidated by selective persulfide labeling methods or mass spectrometry, cysteine residue of TRPM2 is S-sulfenylated by H_2O_2 [102].

Chemical interaction between H_2S and NO

H_2S_n can be produced not only by enzymes but by the chemical interaction of H_2S with NO. Whiteman et al. [103] demonstrated that the reaction of H_2S with NO produces nitrosothiol. We and others identified H_2S_n, HNO, and $SSNO^-$ [104–107]. Based on the observations that the endogenous cysteine disulfide bonds but not persulfidated cysteine residues were found in TRPA1 channels, it was suggested that HNO is the chemical entity produced from NO and H_2S [104]. The cysteine disulfide bond is produced by H_2O_2 to activate TRPA1 channels [108,109]. H_2S_n as well as H_2O_2 produce cysteine disulfide bond in PTEN [31]. It is possible that one cysteine residue is S-sulfenylated or persulfidated which reacts with free cysteine residue to generate the disulfide bond too fast to detect persulfidation.

H_2S_n and the active molecule(s) produced by the interaction between H_2S and NO, which activate TRPA1 channels, are degraded by cyanolysis (degradation in the presence of cyanide) and by reduction with thiols [107]. In contrast, HNO is resistant to cyanolysis and $SSNO^-$ is to thiols. These observations suggest that the chemical entity produced by the interaction between H_2S and NO may be H_2S_n rather than HNO or $SSNO^-$ [86]. Bogdandi et al. [110] recently suggested that H_2S_n transiently activate TRPA1 channels at the early phase of the production, while more stable $SSNO^-$ induces sustained activation of the channels.

Cytoprotective effect of H_2S/polysulfides/sulfite against oxytosis/ferroptosis

There are two forms of glutamate toxicity on neurons; receptor-initiated excitotoxicity [111] and non-receptor mediated oxidative toxicity [112]. The latter was renamed as oxytosis [44]. Oxytosis is initiated by high concentrations of extracellular glutamate and is not suppressed by the antagonists of ionotropic glutamate receptors. Both oxytosis and ferroptosis decrease GSH levels through suppression of cystine/glutamate antiporter Xc^-, require iron, increase reactive oxygen species, lipid peroxidation, and lipoxygenase activity, induce mitochondrial alteration and calcium dysregulation [47]. H_2S, polysulfides and sulfite each exerts a neuroprotective effect against the oxidative stress induced by high extracellular glutamate, a process known as oxytosis (Fig. 4) [22,23,45,46]. Polysulfides also suppress ferroptosis by scavenging radicals with decreasing lipid peroxidation [113].

Although sulfite protects neurons at low concentrations, it together with cystine produces S-cysteinesulfonate which activates NMDA receptors as does glutamate [114]. Two to 5 μM glutamate causes excitotoxic injury [115], and in human traumatic brain injury brains of patients contains approximately 20 μM glutamate [116]. A low concentration of sulfite (1 μM) is enough to protect neurons from oxytosis, and only approximately 0.5 μM S-cysteinesulfonate can be produced at this concentration of sulfite. However, the administration of sulfite would need special attention in individuals sensitive to sulfite and those with molybdenum cofactor deficiency whose sulfite oxidase is deficient [114,117].

H_2S_n activate Kelch ECH-associating protein 1 (Keap1) to release nuclear factor-erythroid 2-related factor 2 (Nrf2) from Keap1/Nrf2 complex to enter into nucleus where Nrf2 upregulates the transcription of antioxidant genes including GCL (Fig. 4) [33]. Accumulation of defective proteins in the endoplasmic reticulum (ER) called ER stress is sensed by PKR-like ER kinase (PERK), inositol-requiring transmembrane kinase/endoribonuclease 1a (1RE1a), and activating transcription factor 6 (ATF6) that are activated by polysulfides [40,118]. The overproduction of methylglyoxal, a highly reactive dicarbonyl compound produced during glycolysis, induce ER stress and cell death [119]. H_2S_n protect neuronal cells from methylglyoxal-induced toxicity by inducing sestrin2, an antioxidative protein of which the expression is regulated by the PERK eIF2a-ATF4 pathway [118].

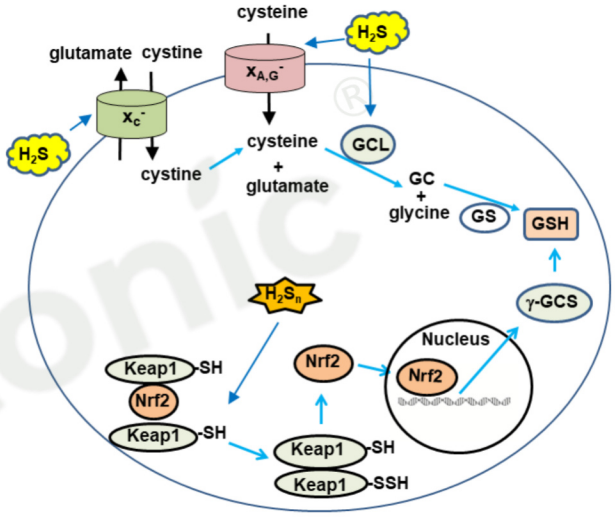


Fig. 4. H_2S/polysulfide protect neurons from oxytosis/ferroptosis. H_2S enhances the activity of cystine glutamate antiporter (Xc^-) to import cystine, which is reduced to cysteine in the cell and used for the production of glutathione (GSH). H_2S also enhances the activity of glutamate cysteine ligase (GCL), the first step enzyme to produce GSH. Polysulfides persulfidate Keap1 to release Nrf2, which enters into the nucleus to activate transcription of antioxidant genes including GCL. This figure is produced by modifying [162].

TRPA1 channels regulate sulfur metabolism and neurotransmitter levels

TRPA1 channels are notable targets of polysulfides; however, they also regulate sulfur metabolism, including the production of H_2S and polysulfides. We found that the levels of 3MST and cysteine were significantly lower in TRPA1-knockout rat brain than in the wild type [48]. Cysteine serves as a substrate for cysteine aminotransferase (CAT), producing 3-mercaptopyruvate, which in turn is a substrate for 3MST. The levels of 3MST products—including H_2S, H_2S_2, and cysteine persulfide—were lower in TRPA1-knockout rat brains [48]. A similar observation was made in neurons of TRPA1-deficient Drosophila, where methionine and cysteine levels were only 15 % and 50 %, respectively, of those in wild-type flies [120]. Resiniferatoxin, an ultrapotent capsaicin analogue that antagonizes TRPV1 and TRPA1 channels, has been shown to regulate the transcription of sulfur-metabolizing enzymes, including rhodanese, sulfur dioxygenase, and molybdenum cofactor synthesis 2 [121].

TRPA1 channels are also involved in regulating neurotransmitter levels. A deficiency in TRPA1 channels increases GABA levels by ~1.25-fold in rat brains and by ~1.44-fold in the Drosophila nervous system compared to the wild-type [48,120]. Resiniferatoxin upregulates spermidine/spermine N(1)-acetyltransferase2 (SAT2), which regulates glutamate uptake at the synaptic terminal, while it suppresses regulator of G protein signaling 7 (RGS7), which controls synaptic plasticity and GABA signaling [121].

H_2S/polysulfides and neurological diseases

Schizophrenia

Schizophrenia is a chronic mental disorder that affects a person's thinking, feeling, and behaviors. Symptoms fall into three categories; positive, negative and cognitive symptoms. Plasma H_2S levels are significantly lower in patients with schizophrenia than in healthy controls, and these lower levels correlate positively with working memory, visual memory, and executive function [122]. Thiol homeostasis is disturbed by a shift to the disulfide bond formation (oxidized) compared to thiol (reduced) in patients [123] (Fig. 5).

MK-801 is a potent non-competitive NMDA receptor antagonist frequently used for rodent schizophrenia models [124]. We recently found that applying MK-801 to 3MST-knockout rats, whose brains contain lower levels of H_2S, H_2S_2, H_2S_3, and cysteine persulfide than wild-type rats, led to augmented behavioral hyperactivity compared to the wild-type. No significant difference in the behavior was observed between 3MST-KO and the wild-type rats before the application of MK-801 (Fig. 5). This result suggests that a lack of H_2S/polysulfides makes them more susceptible to schizophrenic-like behavior [48]. Although another NMDA receptor antagonist, FDA approved drug, memantine showed a similar effect with MK-801 on early life stress-induced aggression in mice [125], it had no effects on the locomotor parameters of zebrafish larvae [126].

As described previously, H_2S induces the release of GABA and the activation of $GABA_A$ receptors induces the release of D-serine, which enhances the activity of NMDA receptors [48,82]. This may be one of the mechanisms in which glutamatergic and GABAergic neurons maintain balance their activity. Disturbance of this balance has been reported to be involved in the pathophysiology of schizophrenia [82,127,128].

Modulation of cystine/glutamate antiporter Xc^- expression has been related to many neurological and psychiatric disorders including schizophrenia [129,130]. Xc^- imports cystine, while it export glutamate from the cell. Hypoglutamatergic hypothesis concerns the contribution to schizophrenia, and Xc^- is suppressed in white blood cells of schizophrenia patients, suggesting that the extracellular levels of glutamate are decreased in this disease as well as intracellular cysteine [131]. GSH levels are decreased in the cerebrospinal fluid of schizophrenia patients [132], while those oxidants (nitric oxide radicals) increased compared to the normal individuals [133]. H_2S/polysulfides increase the levels of GSH by enhancing the activity of Xc^- [23,46]. Striatal cell lines derived from Huntington's disease (HD) model mice have decreased levels of Xc^- [134]. It is also involved in the pathogenesis of Pakinson's disease (PD), and Alzheimer's disease (AD) [47,135]. Cystine deprivation induced cell death is suppressed by the transport of cystathionine, a product of CBS and a substrate of CSE, by this transporter [130,136].

It has also been reported that 3MST levels in schizophrenia were positively correlated with symptom severity scores [50] (Fig. 5). Watanabe et al., demonstrated that C57BL/6 N strain mice exhibited greater scores of prepulse inhibition, which is the normal suppression of startle response, the C3H/HeN mice did [137]. The impaired prepulse inhibition is regarded as an endophenotype for schizophrenia [138], and the expression of 3MST is increased C3H/HeN mice compared to C57BL/6 N [137].

Alzheimer's disease

AD is the leading cause of dementia and characterized by accumulation of amyloid plaques and neurofibrillary tangles in the brain. Suppression of β-secretase and γ-secretase by H_2S prevents the production of amyloid β protein via activating PI3K/Akt and NF-κB pathways as well as suppression of hyperphosphorylation of tau by inhibiting glycogen synthase kinase 3β (GSK3β) via persulfidation in AD [49,139] (Fig. 5). Plasma levels of H_2S as well as serum levels of cysteine and glutathione are decreased in AD patients [140,141]. CSE binds wild type Tau which enhances its catalytic activity, while CSE fails to bind to TauP301L [142]. CSE levels are decreased in postmortem human brain and AD mouse model with TauP301L, amyloid precursor protein with Swedish mutation, and presenilin 1M146V. H_2S prevents hyperphosphorylation of Tau by persulfidating GSK3β, and the application of H_2S donor GYY4137 to the AD model mice ameliorates motor and cognitive deficits [142]. The recent study using a familial AD model mice with five FAD mutations [APP K670 N/M671L (Swedish) + I716V (Florida) + V717I (London) and PS1 M146L + L286V] in which there is no significant difference in the expression levels of CBS, CSE, CARS1 and CARS2, showed lower levels of total polysulfides and protein polysulfides in the brain than those in the wild-type mouse brain, while there is no significant difference in the levels of GSH, GSSH and H_2S between the model mice and the wild-type [143] (Fig. 5).

Down's syndrome

Down's syndrome (DS) is the most common genetic cause of cognitive disability. In DS a trisomy of chromosome 21 where CBS is encoded increases the levels of CBS mRNA 12 times greater in myeloblasts of patients than those of normal individuals [144], and CBS protein levels in the brains are approximately three times greater than the normal individuals [145]. The greater levels of thiosulfate, a metabolite of H_2S, were detected in patient urine than that of normal individuals [146]. Kamoun hypothesized that the high levels of H_2S causes dementia [147]. The levels of CBS and H_2S are elevated in DS fibroblast cells where the mitochondrial electron transport, oxygen consumption and ATP generations are greatly suppressed, and causes neurobehavioral disfunction in a rat model of DS [148] (Fig. 5). H_2S levels were increased in DS model mice in which the levels of not only CBS but also 3MST, rhodanese, and ETHE1 are increased, while persulfidated protein levels were decreased [149].

In AD H_2S levels are low, while those are high in DS. It is interesting to note that DS are prone to age related neurological conditions including an early-onset AD and that CBS is localized to astrocytes that surround senile plaques in the brain of elderly adults of DS associated with an AD type of dementia [145].

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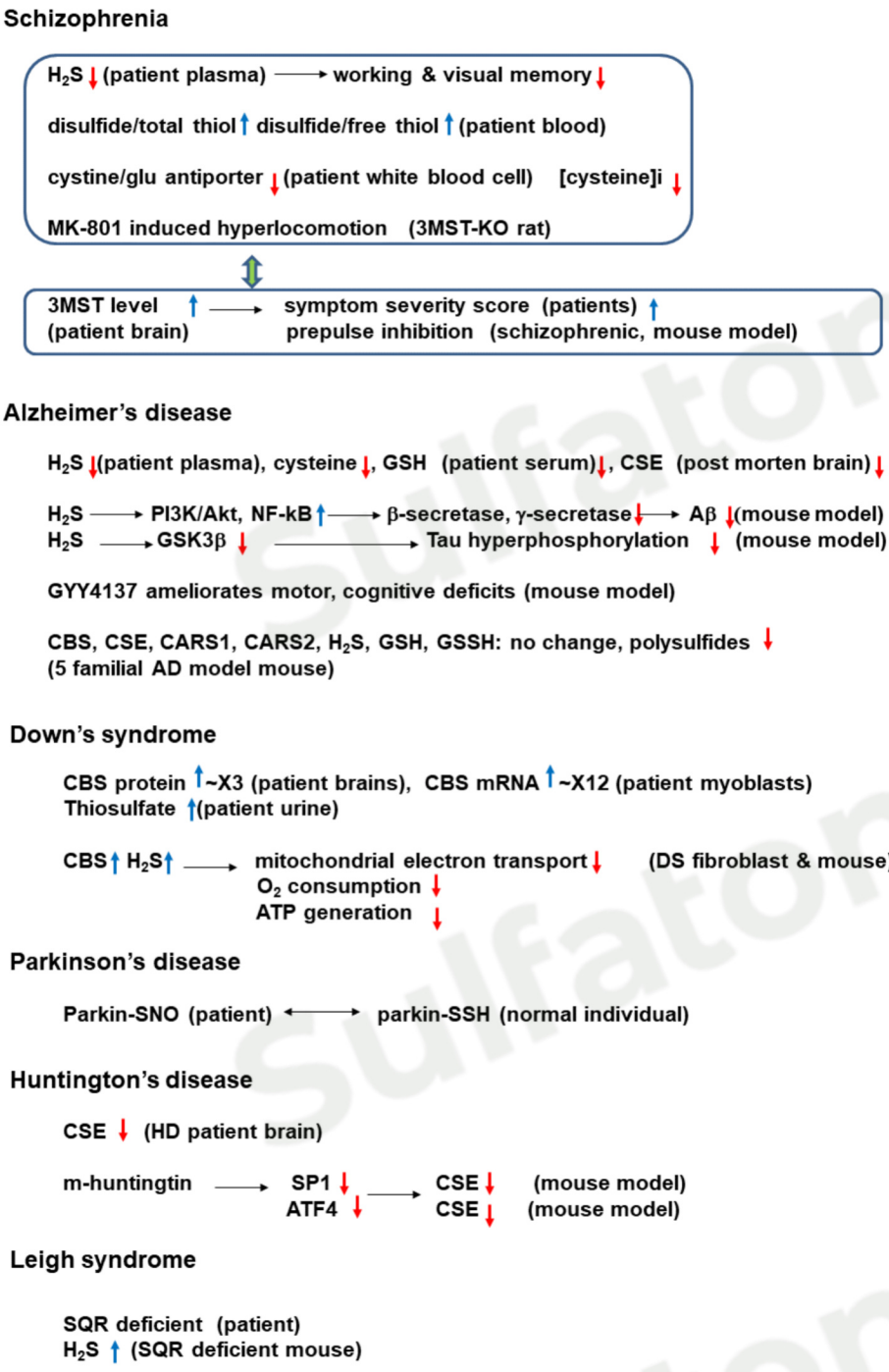


Fig. 5. Diseases caused by unbalanced H_2S and polysulfides. In schizophrenia plasma levels of H_2S are significantly lower in patient compared to the normal individuals and correlate positively with working and visual memory. Thiol homeostasis is disturbed by a shift to 'oxidized' compared to 'reduced' in patients. Cystine/glutamate antiporter is suppressed in patients, leading to decreasing the intracellular levels of cysteine. Excess production of polysulfides has also been proposed to be involved in the pathogenesis of schizophrenia. 3MST levels were positively correlated with symptom severity scores in patients, and mice with higher levels of 3MST showed the impaired prepulse inhibition, which is regarded as an endophenotype for this disease. In Alzheimer's disease the levels of H_2S, cysteine, GSH, and CSE are lower in patients. H_2S suppresses β-secretase and γ-secretase through the activation of PI3K/Akt and NF-κB pathways to prevent the production of amyloid β protein. It also suppresses the hyperphosphorylation of tau by inhibiting GSK3β. In 5 familial AD model mice the levels of CBS, CSE, CARS1, and CARS2 are not significantly different and no significant changes are observed in the levels of H_2S, GSH, and GSSH, but those of polysulfides are decreased. In Down's syndrome CBS protein levels in the postmortem brain of patients were approximately 3 times greater than those of normal individuals, and CBS mRNA levels were approximately 12 times greater in patients myoblasts than those of normal individuals. Thiosulfate levels in patient urine were higher than those of normal individuals. The levels of CBS and H_2S were greater, while mitochondrial electron transport, O_2 consumption, and ATP generation were suppressed in DS fibroblasts and the model mise. In Parkinson's disease cysteine residues of parkin in patients are S-nitrosylated, while those are persulfidated in the normal individuals. In Huntington's disease CSE levels are decreased in patient brains. Mutant huntingtin suppresses transcription factor SP1, leading to the decrease in CSE. Activating transcription factor 4 (ATF4), which also regulate CSE expression, is dysfunctional in HD. The mutation of Leigh syndrome was recently identified in SQR, and its mutant mice showed increased levels of H_2S.

Parkinson's disease and Huntington's disease

PD is a neurodegenerative disorder mainly causing motor dysfunction. Parkin and α-synuclein are associated with pathophysiology of Parkinson's disease. Parkin, an E3 ubiquitin ligase, is responsible for clearance of misfolded proteins including α-synaclein and its mutations cause autosomal recessive PD. The activity of parkin is suppressed by S-nitrosylation, while it is active and persulfidated in normal individuals [41,150] (Fig. 5).

HD is a devastating neurodegenerative disorder characterized by the progressive development of involuntary movements, neuropsychiatric symptoms, and cognitive impairment. CES levels are low in the brains of HD where transcription factor specificity protein 1, which regulate the transcription of CSE, is suppressed by mutant huntingtin [150,151] (Fig. 5). Although activating transcription factor 4 (ATF4), which also regulate CSE expression, is dysfunctional in Huntingtin's disease, the Golgi stressor monensin up-regulates ATF4 via PKR-like endoplasmic reticulum kinase (PERK) pathway to increase the expression of CSE [152,153].

Hypoxic insults and SQR

H_2S is metabolized by SQR, and further metabolized to ETHE1, rhodanese and sulfite oxidase to thiosulfate and sulfuric acid [16,68]. Landry et al. proposed that SQR utilizes CoA as well as GSH as an alternate acceptor generating CoA-SSH, which inhibit butyryl-CoA dehydrogenase and blocks electron flow from butyrate oxidation [154]. Sulfide oxidation by SQR protects against hypoxia-induced injury in the brain [155], while SQR inhibition protects against adverse cardiac remodeling and heart failure [156]. Kumar et al. suggested that hypoxia induced NO reprograms to increase the production of H_2S and its oxidation via SQR promotes angiogenesis and neovascularization induced in hypoxia [157].

Leigh syndrome is the common inherited mitochondrial disease in children and its mutation was recently identified in SQR [158]. The SQR mutant mice in which SQR does not enter into mitochondria showed increased levels of H_2S [159] (Fig. 5). The application of metronidazole to suppress gut microbiota and sulfur-restricted diet prolonged the survival of the mutant mice, suggesting the therapeutic approach to treat patients with Leigh syndrome.

Perspectives

TRPA1 channels are initially found to be activated by H_2S [27], but polysulfides were later identified to much more potently activate the channels [28–30]. Polysulfides, rather than H_2S, have been proposed as the primary chemical species that persulfidate target proteins to regulate their activities. However, H_2S exerts a greater effect on neurotransmitter release than H_2S_2, implying that certain H_2S-mediated mechanisms may have been overlooked. One of the potential mechanism is the persulfidation of S-nitrosylated or S-sulfenylated cysteine residues by H_2S. However, the recent systematic analysis of the human proteome suggest that low percentage of S-nitrosylated cysteine residues can be transferred to persulfidated [43]. Systematic analysis of reciprocal effects of S-sulfenylation and persulfidation is awaited.

Regarding the mechanism underlying neurotransmitter release by H_2S and polysulfides, it remains unclear whether these molecules facilitate vesicular exocytosis or activate specific transporters. By contrast, neurotransmitter-induced release of H_2S and polysulfides was not observed in 3MST-knockout mice. It remains intriguing to discover how neurotransmitters activate 3MST and which specific signaling pathways mediate this process.

TRPA1 channels were not initially predicted to participate in sulfur metabolism or the regulation of neurotransmitter levels [48,120,121,160], but mounting evidence indicates they play a significant role in both processes. There may be other functional proteins not previously expected to regulate sulfur metabolism that also participate in reciprocal regulation. Their activation by H_2S and polysulfides could, in turn, affect sulfur metabolism itself.

Disturbances in H_2S/polysulfide signaling, persulfidation, and the cystine/glutamate antiporter are implicated in the pathophysiology of various neurological and psychiatric diseases. Advancing our understanding of these molecules' physiological roles—and developing therapeutic approaches based on them—remains a key future challenge.

Author contributions

Hideo Kimura: Writing – original draft preparation, reviewing and editing (all sections).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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