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Signaling by hydrogen sulfide (H_2S) and polysulfides (H_2S_n) in the central nervous system

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A B S T R A C T

Hydrogen sulfide (H_2S) is a signaling molecule used to modify neuronal transmission, regulate vascular tone, protect tissues from oxidative stress, sense oxygen, and generate ATP. Hydrogen polysulfides (H_2S_n) have recently been identified as signaling molecules that mediate the activation of ion channels, regulation of tumor growth, and the transcriptional regulation of oxidative stress; some of which were previously ascribed to H_2S. Cystathionine β-synthetase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST) are known as H_2S-producing enzymes. 3MST also produces H_2S_n and other persulfurated molecules such as cysteine persulfide, glutathione persulfide, and persulfurated proteins. The chemical interaction of H_2S and nitric oxide (NO) also produces H_2S_n, which may be the mechanism underlying the synergistic effect of H_2S and NO that was initially reported on vascular relaxation. H_2S_n and other persulfurated molecules elicit their effect via S-sulfuration (S-sulfhydration) of specific cysteine residues of the target proteins. This review article focuses on the production and roles of H_2S_n as well as H_2S in the central nervous system.

1. Introduction

Memory loss is often observed in individuals exposed to toxic levels of hydrogen sulfide (H_2S), and the levels of neurotransmitters change in animals intoxicated with this molecule (Reiffenstein et al., 1992; Warenycia et al., 1989). The endogenous levels of H_2S were evaluated in the brains of bovines, humans, and rats, though the levels were overestimated because of the method used (Goodwin et al., 1989; Warenycia et al., 1989; Savage and Gould, 1990; Ishigami et al., 2009). They have been re-evaluated but still show significantly different values (Furne et al., 2008; Ishigami et al., 2009; Koike et al., 2017). H_2S is produced by cystathionine β-synthetase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST) in various tissues (Stipanuk and Beck, 1982; Abe and Kimura, 1996; Hosoki et al., 1997; Zhao et al., 2001; Shibuya et al., 2009; Chiku et al., 2009; Singh et al., 2009).

H_2S facilitates the induction of hippocampal long-term potentiation (LTP) by enhancing the activity of N-methyl-D-aspartate (NMDA) receptors (Abe and Kimura, 1996). In addition, we found that H_2S activates transient receptor potential ankyrin 1 (TRPA1) channels in astrocytes, which regulate synaptic transmission by releasing gliotransmitters to the synaptic cleft to facilitate LTP induction (Nagai et al., 2004; Oosumi et al., 2010; Shigetomi et al., 2012, 2013; Kimura et al., 2013). Subsequently, we identified H_2S_n ($n \geq 2$) which induce Ca^{2+} influx in astrocytes more potently than H_2S (Nagai et al., 2006; Oosumi et al., 2010; Kimura et al., 2013). H_2S_n are produced by 3MST, and H_2S_2 and H_2S_3 have been identified in the brain (Kimura et al., 2013, 2015; Koike et al., 2017; Nagahara et al., 2018).

Several other targets of H_2S_n have been found; a tumor suppresser phosphatase and tensin homolog (PTEN) (Greiner et al., 2013), a transcription factor complex consisting of Kelch ECH-associating protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) complex that up-regulates antioxidant genes (Koike et al., 2013), a vascular tension regulator protein kinase G1α (Stubbert et al., 2014), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an enzyme that catalyzes glycolysis (Jarosz et al., 2015).

The chemical interaction of H_2S and NO also generates H_2S_n (EberhardtDux et al., 2014; Cortese-KrottKuhnle et al., 2015; Moustafa and Habara, 2016; Miyamoto et al., 2017). We identified synergy between H_2S and nitric oxide (NO) during the relaxation of vascular smooth muscle (Hosoki et al., 1997), and a similar effect was observed in the ileum (Teague et al., 2002). A mechanism of the synergy has been studied, and several potential chemical entities generated from H_2S and NO have been proposed: nitrosothiol (Whiteman et al., 2006), thionitrous acid (HSNO) (Filipovic et al., 2012), nitroxyl (HNO) (EberhardtDux et al., 2014), nitrosopersulfide (SSNO-) (Cortese-KrottKuhnle et al., 2015), and H_2S_n (EberhardtDux et al., 2014; Cortese-KrottKuhnle et al., 2015; Moustafa and Habara, 2016; Miyamoto et al., 2017). Concerning the characteristics of the product, such as the sensitivity to cyanide and reducing substances, H_2S_n may be a potential chemical entity that is produced from H_2S and NO to activate TRPA1 channels (EberhardtDux et al., 2014; Cortese-KrottKuhnle et al., 2015; Miyamoto et al., 2017).

H_2S protects neurons from oxidative stress by enhancing the activity

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of the cystine/glutamate antiporter and cysteine transporter to increase the intracellular levels of cysteine, a substrate for the production of glutathione (GSH), a major intracellular antioxidant (Kimura and Kimura, 2004). H_2S also enhances the activity of glutamate cysteine ligase (GCL) also known as γ-glutamyl cysteine synthetase (γ-GCS), a rate limiting enzyme for GSH production (Kimura and Kimura, 2004; Kimura et al., 2006, 2010). By these integrated effects, H_2S increases the production of GSH.

It has been reported that H_2S also up- or down-regulates genes that are activated by NMDA to induce excitotoxicity in neurons (Chen et al., 2011). Although its mechanism is not well understood, the application of H_2S in diseases caused by oxidative stress may require the co-administration of inhibitors of NMDA receptors to prevent excitotoxicity.

H_2S_n also involved in the protection of neurons against oxidative stress (Koike et al., 2013). H_2S_4 releases Nrf2 from the Keap1/Nrf2 complex so it can be transferred to the nucleus where Nrf2 upregulates the transcription of antioxidant genes including enzymes involved in the production of GSH. Recently, we demonstrated that sulfite (H_2SO_3) protects neurons from oxidative stress by potentially reacting with extracellular cystine to generate cysteine that is more efficiently transported into cells and used for GSH production (Kimura et al., 2018).

H_2S and H_2S_n may be involved in neurodegenerative diseases such as Parkinson's disease (PD), Huntington's diseases (HD), ethylmalonyl encephalopathy, and even in cancer (Vandiver et al., 2013; Shiota et al., 2018). Mutations encoded in the gene parkin cause hereditary PD. Parkin of PD patients is nitrosylated, while that of healthy individuals is S-sulfurated (S-sulfhydrated) (Chung et al., 2004; Yao et al., 2004; Vandiver et al., 2013). The expression of CSE in the brains of patients with HD is significantly lower than that of normal individuals (Paul et al., 2014). Patients with ethylmalonyl encephalopathy are defective in ETHE1, persulfide dioxygenase, and are unable to metabolize H_2S. The increased levels of H_2S exert its toxic effect on organs such as the brain and skeletal muscle (Tiranti et al., 2009). A recent study showed that the higher concentrations of polysulfides including H_2S_n are contained in glioblastoma cells but not in glioblastoma-free control hemispheres (Shiota et al., 2018).

2. Modulation of neurotransmission

H_2S facilitates induction of hippocampal long-term potentiation (LTP), a synaptic model of memory formation, by enhancing the activity of N-methyl D-aspartate (NMDA) receptors (Abe and Kimura, 1996). The reduction of a cysteine disulfide bond located at the hinge of a ligand binding domain of NMDA receptors by dithiothreitol (DTT) enhances their activity of the receptors (Aizenman et al., 1989). Because H_2S is a reducing molecule, the same mechanism was predicted. However, H_2S with a one-tenth concentration of DTT induced LTP more efficiently than DTT (Abe and Kimura, 1996). This observation suggested that H_2S may have an additional effect rather than the reduction of NMDA receptors.

Astrocytes, a type of glia, surround synapses and release gliotransmitters to modulate synaptic activity (Araque et al., 1999). NaHS, sodium salt of H_2S, induces Ca^{2+} influx in astrocytes (Nagai et al., 2004). During this study, a batch of NaHS with a yellowish color showed much greater activity than that of colorless NaHS (Nagai et al., 2006). We identified H_2S_n as a source of the color. H_2S_3 activates TRPA1 channels by S-sulfurating two cysteine residues, which are redox sensitive and localized to the amino terminus (Oosumi et al., 2010; Kimura et al., 2013; Hatakeyama et al., 2015). Shigetomi et al. demonstrated that the activation of TRPA1 channels in astrocytes induces a release of a gliotransmitter D-serine, which binds to a glycine site of NMDA receptors to enhance their activity (Shigetomi et al., 2012, 2013). H_2S and H_2S_n enhance the activity of NMDA receptors by these distinct mechanisms to facilitate the induction of LTP (Kimura, 2013).

3. S-sulfuration and bound sulfane sulfur

S-sulfuration (S-sulfhydration) was proposed by Snyder and colleagues as a mode of action of H_2S where H_2S adds a sulfur atom to thiol of cysteine residues (R-Cys-SH) to make R-Cys-SSH (Mustafa et al., 2009). However, this requires theoretical revision (Kimura, 2015). The oxidation state of sulfur in H_2S and cysteine is -2 and atoms with the same oxidation state do not react with each other. In contrast, the oxidation state of sulfur in H_2S_n is -1 or 0 and can S-sulfurate cysteine residues. In contrast, under oxidative conditions some cysteine residues are oxidized to become R-Cys-SOH, and at the exposure to NO, R-Cys-SH is oxidized to R-Cys-SNO. Both R-Cys-SOH and R-Cys-SNO can be S-sulfurated by H_2S to R-Cys-SSH (Kabil et al., 2014).

Because Cys-SH has a pKa of 8.29 and the predicted pKa for Cys-SSH is 4.34 (Cuevasanta et al., 2015), CysSSH dissociates to $CysSS^-$ and H^+, while CysSH exists as non-dissociated form at physiological pH. S-sulfuration increases mass of 32 and adds one negative charge to the target proteins. Compared to protein phosphorylation, which increases mass of 95 and adds two negative charges, S-sulfuration may induce less conformational changes in target proteins. However, some of the known target proteins such as TRPA1 channels, PTEN, and protein kinase G1α have two cysteine residues responsible for their activity regulation. It is possible that one of the two cysteine residues could be S-sulfurated and reacts with the remaining non-S-sulfurated cysteine residue to produce a disulfide bond, which may induce greater conformational change than a simple S-sulfuration in TRPA1 channel and PTEN and also enables two monomers of protein kinase G1α to generate its dimer.

Bound sulfane sulfur, which is measured as H_2S released from tissues or cells by reduction, includes H_2S_n, Cys-SSH, GSSH, and S-sulfurated cysteine residues (WarenyciaGoodwin et al., 1990; Ogasawara et al., 1993, 1994; Ishigami et al., 2009; Shibuya et al., 2009). Cells expressing 3MST contain greater levels of bound sulfane sulfur than control cells (Shibuya et al., 2009), and oral administration of D-cysteine, which is metabolized by D-amino acid oxidase to 3-mercaptopyruvate a substrate of 3MST, is given to mice to increase the levels of bound sulfane sulfur (Shibuya et al., 2013). The brains of 3MST knockout mice contain less than half of bound sulfane sulfur compared to those of the wild-type mice (Kimura et al., 2017). These observations suggest that 3MST can produce persulfurated molecules.

4. Production of H_2S_n

Hylin and Wood reported that protein-bound polysulfides (R-Cys-SSH) are produced from 3-mercaptopyruvate (3 MP), a substrate of 3MST (Hylin and Wood, 1959). Considering this observation together with the fact that 3MST can produce bound sulfane sulfur, we predicted the production of H_2S_n by this enzyme. We identified H_2S_n in the brain and they can be produced by 3MST (Kimura et al., 2013, 2015, 2017; Koike et al., 2017; Nagahara et al., 2018; Kimura, 2019).

In addition to the production of H_2S_n, 3MST also generates Cys-SSH, and GSSH (Kimura et al., 2017). Two mechanisms have been proposed. The active site cysteine of 3MST receives sulfur from 3 MP to produce per- or poly-sulfide, which is released as H_2S_n (mainly H_2S_2) by the interaction with thioredoxin (Kimura, 2016; Kimura et al., 2017; Koike et al., 2017; Nagahara, 2018; Nagahara et al., 2018). H_2S_2 and H_2S_3 immediately react with cysteine and GSH to produce Cys-SSH and GSSH (Kimura et al., 2017). As an alternative mechanism, 3MST transfers sulfane sulfur from its active site to cysteine and GSH to S-sulfurate them without intermediation by H_2S_n.

3MST thiolates tRNA to ensure accuracy of the genetic code and stabilization of tRNA structure. It was initially identified by Wong et al., that 3MST from rat brains transfers sulfur from 3 MP to thiolate tRNA (Wong et al., 1974). Two isoforms of 3MST localized to cytosol and mitochondria were identified in humans (Frasdorf et al., 2014). Recently, it was demonstrated that cysteinyl tRNA synthetase (CARS)

produces Cys-SSH (Akaike et al., 2017). 3MST receives sulfur from 3 MP, while CARS from cysteine. Both 3MST and CARS accept cysteine as an acceptor of sulfur to produce Cys-SSH.

Hemoproteins such as hemoglobin, myoglobin, neuroglobin, and catalase can oxidize H_2S to produce polysulfides. Centrally located iron (Fe^{3+}) of hemoglobin binds to H_2S to generate sulfhemoglobin (Fe^{2+}). The ratio of sulfide and oxygen may determine the oxidation products. At low sulfide concentrations, thiosulfate may be the predominant product, while polysulfides are favored at high concentrations of sulfide (Vitvitsky et al., 2012). Myoglobin, a monomeric heme protein found in most animal muscles, neuroglobin, primarily expressed in neurons, and catalase oxidize H_2S to polysulfides (Bostelaar et al., 2016; Ruetz et al., 2017; Olson et al., 2017).

Copper/zinc superoxide dismutase (Cu/ZnSOD), located in cytosol can produce H_2S_2, and to lesser extent, H_2S_3 and H_2S_5 by oxidizing H_2S with O_2 or H_2O_2 as electron acceptors (Searcy et al., 1995, 1996; Olson et al., 2018). Peroxidases such as lactoperoxidase and myeloperoxidase can oxidize H_2S in the presence of H_2O_2 or O_2 with SOD to polysulfides (Nakamura et al., 1984; Garai et al., 2017).

H_2S is metabolized by SQR, which transfers sulfur to cysteine, GSH, and H_2S to produce Cys-SSH, GSSH, and H_2S_2 with GSH as the most preferable acceptor in mitochondria (Hildebrandt and Grieshaber, 2008; Landry et al., 2017). In the brain, the level of SQR is low (Linden et al., 2012), and neuroglobin may play a role in H_2S oxidation in this tissue (Ruetz et al., 2017). Two electrons generated in the process of oxidizing H_2S at SQR are transferred to FADH2 bound to SQR to coenzyme Q (CoQ), resulting in the production of ATP.

H_2S_n are also produced by the chemical interaction between H_2S and NO (EberhardtDux et al., 2014; Cortese-KrottKuhnle et al., 2015; Moustafa and Habara, 2016; Miyamoto et al., 2017). We identified H_2S_2 and H_2S_3 generated from the mixture of H_2S with NO, and the application of the mixture to dorsal rood ganglion (DRG) neurons pre-loaded with SSip-1, a fluorescent probe selective to polysulfides, detected produced H_2S_n (Miyamoto et al., 2017). In this study Ca^{2+} influx through TRPA1 channels was induced by generated H_2S_n in DRG neurons. The application of the H_2S donor or NO donor to peritoneal mast cells pre-loaded SSP4, another fluorescent probe selective to polysulfides, showed the production of H_2S_n by the interaction of endogenous NO and H_2S, respectively (Moustafa and Habara, 2016). Although Ebenhardt et al. and Cortese-Krott et al. also showed the production of H_2S_n from H_2S and NO, they mainly studied HNO or SSNO- rather than H_2S_n (EberhardtDux et al., 2014; Cortese-KrottKuhnle et al., 2015).

Ebenhardt et al. proposed that HNO produced from H_2S and NO activates TRPA1 channels, leading to a release of calcitonin gene-related peptide to relax the vasculature (EberhardtDux et al., 2014). Cortese-Krott et al. showed that the main product is SSNO-, which release HNO, NO, H_2S, and H_2S_n to relax vascular smooth muscle (Cortese-KrottKuhnle et al., 2015). HNO is resistant to cyanolysis (degradation by cyanide), and SSNO- is resistant to both cyanolysis and thiol. In contrast, H_2S_n are sensitive to both cyanolysis and the reduction by thiol. Our study showed that the product of H_2S and NO is sensitive to both cyanolysis and the reduction by thiol. Based on these observations, we concluded that the main product from H_2S and NO to activate TRPA1 channels must be H_2S_n rather than HNO and SSNO- (Miyamoto et al., 2017).

5. Neuroprotection

There are two forms of glutamate toxicity; oxidative toxicity and excitotoxicity (Choi, 1987; Murphy et al., 1989). Oxidative toxicity called oxytosis, which is independent of ionotropic glutamate receptors and can be observed separately from excitotoxicity in neurons that have not yet expressed ionotropic glutamate receptors. Oxytosis is not suppressed by the antagonists of the receptors (Murphy et al., 1990; Tan et al., 2001). High concentrations of glutamate suppress the cystine/glutamate antiporter xCT, leading to a decrease in the transport of cystine, which is reduced in the cytoplasm to cysteine, a substrate for GSH production, an endogenous major antioxidant. In contrast, excitotoxicity is caused by the excessive activation of ionotropic glutamate receptors, resulting in the exceeding influx of Ca^{2+} mainly through NMDA receptors into cells (Choi, 1987).

H_2S protects neurons from oxytosis by enhancing the activity of X_{CT} as well as cysteine transporter (Kimura and Kimura, 2004; Kimura et al., 2010). H_2S also facilitates the activity of glutamate cysteine lyase (GCL), also known as γ-glutamyl cysteine synthetase (γ-GCS), a rate limiting enzyme for GSH production. The activity of ATP-dependent K^+ channels and cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels are enhanced by H_2S to stabilize plasma membrane to prevent excess excitation of neurons (Kimura et al., 2006). By these integrated mechanisms, H_2S protects neurons from oxytosis (Fig. 3).

It was reported that 200 μM H_2S alone induced excitotoxicity similarly to NMDA where 1649 out of 3230 genes were commonly regulated by both H_2S and NMDA (Chen et al., 2011). Although H_2S enhances the effect of glutamate to activate NMDA receptors, it does not directly active the receptors (Abe and Kimura, 1996). It rather suppresses synaptic activity at concentrations greater than 300 μM (Abe and Kimura, 1996). It is possible that the long exposure of H_2S alone may enhance the effect of endogenous glutamate on NMDA receptors that are not observed in a short exposure to H_2S (Fig. 3). Understanding the mechanism of the gene activation common between H_2S and NMDA is important. Considering these observations, co-application of NMDA antagonists may help suppressing excitotoxicity caused by H_2S.

H_2S_n exert their cytoprotective effect through the transcriptional regulation (Koike et al., 2013). H_2S_n S-sulfurates kelch-like ECH-associated protein 1 (Keap1) in Keap1/Nrf2 complex to release nuclear factor-like 2 (Nrf2) which transfers to the nucleus to up-regulate antioxidant genes; some of which are involved in the production of GSH (Fig. 3). Aspirin hybrid with H_2S and NO releasing moiety called NOSH compound has a greater anti-inflammatory and neuroprotective effect than that which releases either H_2S or NO (Lee et al., 2013). H_2S_n generated from H_2S and NO may be one of the active chemical entities involved in the neuroprotective effect of NOSH compound.

We recently identified sulfite (H_2SO_3) as another cytoprotective molecule against oxytosis (Kimura et al., 2018). The concentrations of sulfite in serum are between 0.2 and 4.87 μM (Togawa et al., 1992; Ji et al., 1995; Kajiyama et al., 2000; Meng et al., 2005; Kimura et al., 2018). Sulfite at 1 μM protects neurons against oxytosis by increasing the intracellular concentrations of cysteine and GSH (Kimura et al., 2018). Serum contains approximately 40–77 μM cystine and 11–19 μM cysteine, which is transported into cells more efficiently than cystine (Brigham et al., 1960; Jones et al., 2011; Kimura et al., 2010). Sulfite reacts with cystine to be converted into cysteine and S-cysteinesulfonate (Clarke, 1932), and sulfite converts cystine to cysteine more efficiently than do H_2S and H_2S_n (Kimura et al., 2018) (Fig. 3). It is possible that sulfite may play a physiological role in maintaining cysteine in the extracellular milieu such as serum. Because sulfite is not able to S-sulfurate or oxidize cysteine residues, it may not induce translocation of Nrf2 to the nucleus through S-sulfuration of Keap1, as does H_2S_n (Kimura et al., 2018).

S-cysteinesulfonate and glutamate (Kumar et al., 2018) activate NMDA receptors, which may cause excitotoxicity. Our observation showed that following the application of sulfite to culture medium, approximately half the concentration of cysteine and S-cysteinesulfonate, are released from cystine (Kimura et al., 2018). One micromolar sulfite, which is enough to protect neurons from oxytosis, can generate approximately 0.5 μM S-cysteinesulfonate in the medium. Substantial neuronal excitotoxic injury is caused by 2–5 μM glutamate (Mark et al., 2001), and the pathophysiological extracellular concentrations of glutamate in human traumatic brain injury patients are approximately 20 μM (Bullock et al., 1998). Considering these observations, any

excitotoxic effect caused by S-cysteinesulfonate produced by sulfite in serum may be minimal (Fig. 3). However, the administration of sulfite requires special attention in individuals sensitive to sulfite and those with molybdenum cofactor deficiency whose sulfite oxidase is deficient (Vally and Misso, 2012; Kumar et al., 2018).

Thiosulfate was reported to protect neurons from oxygen glucose deprivation and reoxygenation (Marutani et al., 2015). However, it showed relatively weak protection against oxytosis with only weak reinstating effect on GSH levels (Kimura et al., 2018).

6. Neuronal diseases and H_2S and H_2S_n

6.1. Parkinson disease

Parkinson's disease (PD) is a common neurodegenerative disorder with the progressive loss of dopamine neurons (Martin et al., 2011). The majority of PD cases are sporadic with rare familial causes of PD. The most common cause of hereditary PD involves mutations in parkin, E3 ubiquitin ligase, which has been proposed to have a neuroprotective function. Several specific cysteine residues in Parkin are S-nitrosylated in a mouse model of PD and in brains of patients with PD (Chung et al., 2004; Yao et al., 2004). S-nitrosylation inhibits ubiquitin E3 ligase activity of parkin and its neuroprotective activity, suggesting that S-nitrosylation of parkin may be involved in the pathogenesis of PD (Chung et al., 2004; Yao et al., 2004). In contrast, S-sulfuration of parkin activates its E3 ubiquitin ligase activity, and H_2S S-sulfurates parkin to elicit its cytoprotective effect on neurons (Vandiver et al., 2013). Moreover, S-sulfuration of parkin is markedly depleted in the brains of patients with PD, suggesting that the loss of S-sulfuration may be pathologic.

Whether the exact cysteine residues are S-nitrosylated or S-sulfurate have not been clarified. However, because S-nitrosylated cysteine residues can be S-sulfurated by H_2S, S-sulfuration of S-nitrosylated parkin may be regulated by H_2S (Fig. 1A) (Vandiver et al., 2013; Kimura, 2016). When the S-nitrosylated cysteine residues are distinct from those S-sulfurated, H_2S_n and other per- or poly-sulfides may be involved in the S-sulfuration of cysteine residues (Fig. 1B).

6.2. Huntington disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by glutamine repeats in the protein huntingtin (Htt). Although mutant Htt is toxic, the mechanisms for mutant Htt disrupting cellular function in HD has not been well understood. Mutant Htt binds to SP1 to sequestrate it from SP1 binding site of a CSE promoter, which leads to decreased levels of CSE and H_2S (Ishii et al., 2004; Paul et al., 2014). In HD, it is also defective in activating transcription factor 4 (ATF4), which regulates gene encoding synthetic enzymes such as CSE and transporters of several amino acids, including cysteine (Sbodio et al., 2016). Golgi stress is also involved in the pathogenesis of HD via the PKR-like endoplasmic reticulum kinase (PERK)/ATR4 pathway (Sbodio et al., 2018). Regulation and restoration of cysteine balance through the activation of PERK/ATF4 pathways, which leads to the activation of CSE and increases the production of H_2S, may be beneficial for HD and provide a novel therapeutic approach for disease management.

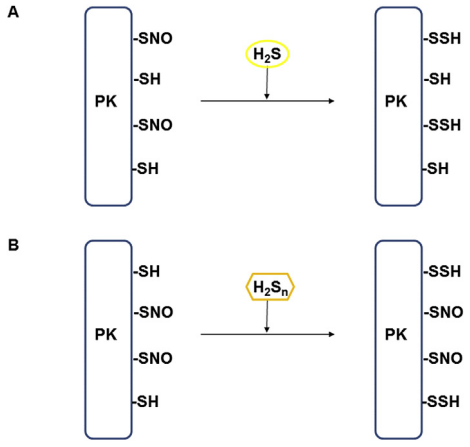


Fig. 1. Regulation of S-sulfuration by H_2S and H_2S_n. A. S-nitrosylated cysteine residues of parkin (PK) can be S-sulfurated by H_2S. B. In contrast, H_2S_n S-sulfurates thiol of cysteine residues.

6.3. Ethylmalonyl encephalopathy

Ethylmalonyl encephalopathy is an autosomal recessive disorder characterized by early-onset encephalopathy, progressive neurological failure, defective cytochrome c oxidase in muscle and the brain, and high excretion of ethylmalonic acid in urine (Tiranti et al., 2009). H_2S is mainly metabolized in mitochondria. The first step is oxidation by SQR to produce Cys-SSH at its active site. SQR includes a variety of acceptor molecules such as GSH to produce GSSH, cysteine to CysSSH, and H_2S to H_2S_2 (Hildebrandt and Grieshaber, 2008; Libiad et al., 2014). The ETHE1 gene that encodes persulfide dioxygenase is mutated in this disorder, and GSSH is the only known substrate for ETHE1, which produces GSH and sulfite. High concentrations of H_2S as well as thiosulfate were detected in the brain, liver, and muscle in Ethe1-knockout mice, and H_2S toxicity may be involved in the pathogenesis of this disorder.

7. Cancer

It has recently been demonstrated that H_2S producing enzymes CBS and CSE are relatively highly expressed in various types of cancer cells (Hellmich and Szabo, 2015). Colon, ovarian, and breast cancers lead to overexpressed CBS and increased levels of H_2S, which enhance tumor growth and spread by stimulating angiogenesis, and two electrons derived from two H_2S molecules by SQR enter the mitochondrial electron transport chain, promoting mitochondrial ATP generation (Lagoutte et al., 2010). CSE is significantly highly expressed in melanoma cells (Panza et al., 2014), while other studies show that exogenously applied H_2S exerted antitumor activity (Hellmich and Szabo, 2015). This discrepancy may be due to the difference in concentrations of H_2S. Endogenous levels of low concentrations of H_2S may promote cancer cell growth, while exogenously applied higher concentrations of H_2S may inhibit cancer cell proliferations (Hellmich and Szabo, 2015).

In contrast to colon, ovarian, breast, and melanoma cancers, CBS silenced glioma cells show greater tumor volume, increased depth of invasion, and angiogenesis as well as cell proliferation. This observation suggests that the CBS expression is antitumor in glioma (Takano et al., 2014). These glioma cells show increased VEGF, which induces angiogenesis, and higher expression of HIF2a, which makes cells resistant to hypoxia, and increases anchorage-dependent cell growth.

A recent study with surface-enhanced Raman spectroscopy in the presence of reporter metal gold enables us to understand the metabolic intermediates between cancer cells and surrounding tissues (Shiota et al., 2018). In this study, the glioblastoma-bearing ipsilateral hemispheres exhibited greater amounts of polysulfides such as H_2S_n than the glioblastoma-free control hemispheres in vivo. Although the exact molecular entities of polysulfides are not determined, they may be involved in the pathogenesis of glioma.

The NOSH compound, which releases H_2S and NO, has been reported to have suppressive effects on colon cancer (Vannini et al., 2015). This observation suggests that H_2S_n generated from H_2S and NO may have a suppressive effect on cancer. It is also distinct from the effect on glioma described earlier.

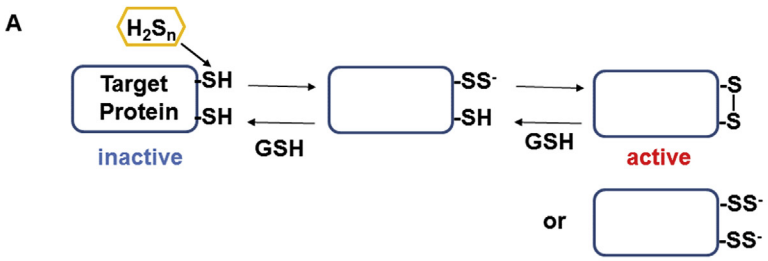
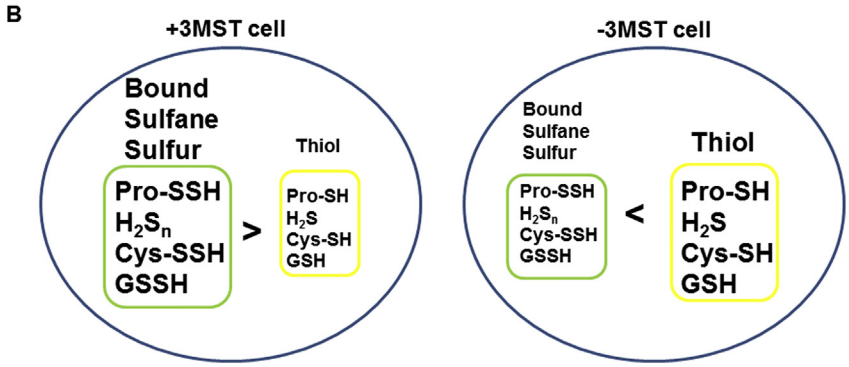


Fig. 2. Signaling through S-sulfuration of target proteins and S-sulfuration maintained in cells. (A) H_2S_n activate various target proteins through S-sulfuration, while the activation ceases when H_2S_n are retracted and GSH reduces S-sulfuration or disulfide bonds. (B) Cells contain certain amounts of S-sulfurated proteins and per- or poly-sulfurated molecules or have bound sulfane sulfur that depend on the expression of 3MST. The role of these per- or poly-sulfurated molecules that constantly maintain a certain level has not been well understood.



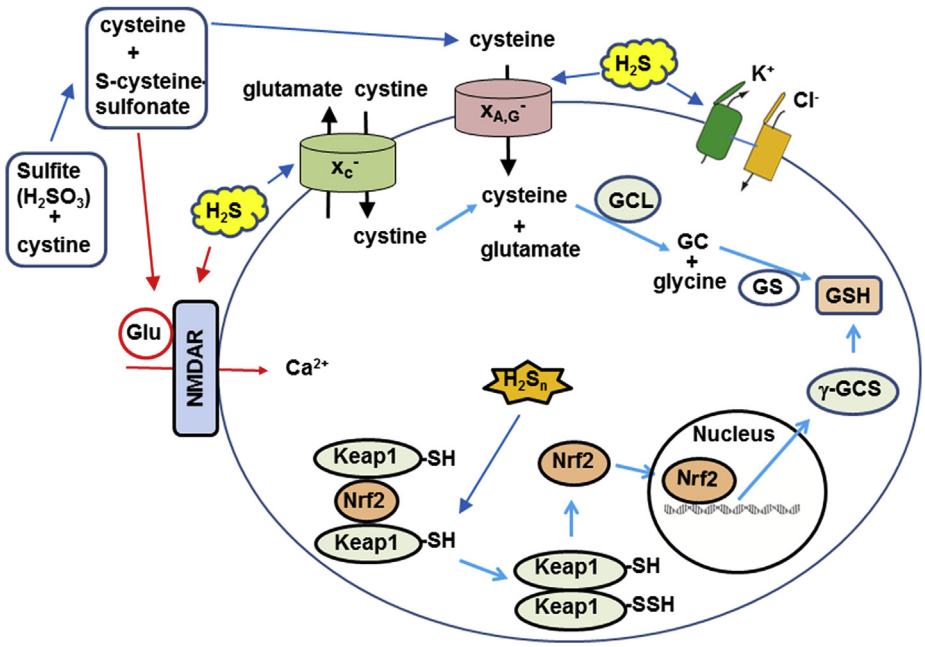


Fig. 3. Protection of neurons from oxidative stress by H_2S and H_2S_n. H_2S protects neurons from oxidative stress by increasing the intracellular concentrations of glutathione (GSH) by enhancing the transport of cystine and cysteine, and the activity of glutamate cysteine ligase (GCL), a rate limiting enzyme for GSH production. In addition, H_2S stabilizes membrane potential by enhancing the activity of ATP-dependent K^+ channels and CFTR Cl^- channels. H_2S_n S-sulfurate Keap1 to release Nrf2, which enters into the nucleus to up-regulate antioxidant genes including GCS gene, leading to the increased production of GCL. H_2S has been reported to induce excitotoxicity by enhancing the activity of NMDA receptors. Sulfite (H2SO3) also protects neurons from oxidative stress. It reacts with cystine to produce cysteine, which is more efficiently transported into cells than cystine, and S-cysteinesulfonate, an agonist of NMDA receptors.

7.1. Perspective

The endogenous concentrations of H_2S have been measured by several methods but are still not well understood. The initial measurement 50–160 μM in the brain was determined via the methylene blue method, which uses high concentrations of acids and releases H_2S as an artifact from the iron-sulfur clusters located at the active site of enzymes belonging to the respiratory chain (Goodwin et al., 1989; Warenycia et al., 1989; Savage and Gould, 1990). This method can be applied to in vitro production of H_2S where the amount of H_2S produced by the enzymes and that released from acid-labile sulfur can be corrected by subtracting a value obtained by the reaction without a substrate cysteine, in which H_2S is released only from acid-labile sulfur (Abe and Kimura, 1996). In contrast, it should not be used to measure endogenous H_2S where H_2S released from acid-labile sulfur cannot be separated.

Another method, where H_2S evaporated from brain homogenates was measured by gas chromatography, indicated an H_2S concentration of 14 nM (Furne et al., 2008). In this method, H_2S may bind to proteins during the procedure of homogenate production, leading to the underestimation of concentrations. A recent measurement of H_2S using HPLC and LC-MS/MS show 0.030 + 0.004 μmol/g-protein (pH 7.0), which is approximately 3 μM in the brain (Koike et al., 2017). In the same study, the levels of H_2S_n are 0.026 + 0.002 μmol/g-protein, indicating that almost the same concentrations exist with those of H_2S in the brain.

The regulation of the levels of H_2S and H_2S_n has not been well understood. H_2S production by CSE is enhanced by Ca^{2+}/calmodulin in one study, while it is suppressed by Ca^{2+} and calmodulin in another study (Mustafa et al., 2009; Mikami et al., 2013). H_2S_n is produced by

3MST, and their release from the active site of 3MST can be regulated by thioredoxin (Nagahara et al., 2007; MikamiShibuya et al., 2011; Yadav et al., 2013; Kimura et al., 2015, 2017). Because the activity of thioredoxin is regulated by changes in redox states including oxidative stress, it is possible that the production of H_2S_n may be regulated by redox states of cells. The production of H_2S_n and H_2S by 3MST can be regulated by cysteine aminotransferase (CAT), whose activity to produce 3 MP, a substrate of 3MST, is controlled by Ca^{2+} (Mikami et al., 2013). The activity of CAT is suppressed by 150 nM Ca^{2+}, and this regulation is effective in cells such as retinal neurons in which the intracellular Ca^{2+} concentrations are maintained between 10 and 600 nM (Krizaj and Copenhagen, 2002; Hayashida and Yagi, 2002)that are lower than those in regular cells. Cellular signaling that regulates the production and concentrations of H_2S and H_2S_n still need to be addressed.

S-sulfuration (S-sulfhydration) regulates the activity of various target proteins of H_2S and H_2S_n that may also be involved in cellular redox homeostasis. Certain amounts of cysteine residues in cells are S-sulfurated or have bound sulfane sulfur (WarenyciaGoodwin et al., 1990; Ogasawara et al., 1993; Ishigami et al., 2009; Mustafa et al., 2009). The levels of bound sulfane sulfur in cells are less than half in the brains of 3MST knockout mice compared to the wild-type mice, suggesting that 3MST is one of enzymes S-sulfurate proteins (Kimura et al., 2017). Although the activation of target proteins by S-sulfuration with a short period of time is well understood, the role of S-sulfurated proteins or bound sulfane sulfur in constantly maintaining high or low levels has not been well understood. For example, H_2S_n activate TRPA1 channels by S-sulfurating two cysteine residues in amino terminus located in cytosol, while the channels return to the quiescent condition once H_2S_n retract and the S-sulfurated cysteine residues are reduced by GSH abundant in cells (Fig. 2A). In contrast, the levels of S-sulfurated proteins or bound sulfane sulfur are maintained low in 3MST knockout animals (Fig. 2B).

A similar observation was obtained in parkin in the brains of patients with Parkinson's disease. Parkin is less S-sulfurated in the brains of patients than that of healthy individuals (Vandiver et al., 2013). It is intriguing to understand the role of S-sulfuration with a short period such as the one observed in the activation of TRPA1 channels (Kimura et al., 2013) and that with a long-period of time, such as that observed in parkin and 3MST knockout mice (Fig. 2) (Vandiver et al., 2013; Kimura et al., 2017).

H_2S_n are also signaling molecules that modify cysteine residues of target proteins whose redox state is different from those regulated by H_2S. H_2S_n are produced not only by enzymes but also from H_2S and NO. Other per- and poly-sulfide molecules such as Cys-SSH and GSSH may also be involved in the cellular redox homeostasis. By addressing the physiological and pathophysiological roles of these molecules, their therapeutic potential will be unveiled.

Conflicts of interest

The author declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.01.027.

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