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Redox regulation in hydrogen sulfide action: From neurotoxicity to neuroprotection

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1. Introduction

Hydrogen sulfide (H_2S) is an environmental poisonous gas that smells like rotten eggs and is toxic to humans at high concentrations (Smith and Gosselin, 1979). The primary target of acute H_2S poisoning is the brain, although it is also toxic to the respiratory and cardiovascular systems (Rumbeiha et al., 2016). A distinct and incapacitating feature of H_2S poisoning is sudden loss of consciousness and collapse, known as “knockdown”, which often renders victims unable to escape, resulting in death (Nogue et al., 2011). More recently, positive effects of H_2S in physiological systems have been identified related to signaling mechanisms similar to those of nitric oxide (NO) and carbon monoxide (CO). H_2S has been shown to function as a neuromodulator in the brain that contributes to long-term potentiation (LTP) at physiological concentrations (Abe and Kimura, 1996). Furthermore, H_2S has been shown to participate in many physiological and pathophysiological processes *in vitro* and *in vivo*. These findings suggest that maintenance of H_2S homeostasis is critical for overall organismal homeostasis. This is supported by the fact that the effects of H_2S in the human body are closely related to its concentration. H_2S is generally cytoprotective at lower concentrations (ranging from 100 to 800 nM in human plasma), but toxic at higher levels (Polhemus et al., 2014). In some brain disorders, endogenous H_2S generation is blunted, and H_2S deficiency has been implicated in the progression of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and traumatic brain injury (TBI) (Eto et al., 2002; Hu et al., 2010; Paul et al., 2014; Zhang et al., 2013). H_2S supplementation has been shown to confer protective effects against these disorders in the central nervous system (CNS). Although the mechanisms of action of H_2S have not been fully characterized, redox regulation has been identified as a critical player in H_2S-mediated neuroprotection and toxicity. In this review, we summarized the signaling pathways and potential therapeutic effects of H_2S, and discussed the oxidative and anti-oxidant mechanisms that underlie the action of H_2S in the brain.

1.1. Synthesis and metabolism of H_2S

1.1.1. Synthesis of H_2S

Both endogenous and environmental sources contribute to production of H_2S. Biosynthesis of H_2S in mammalian brain tissues primarily occurs via catalysis of L-cysteine (Cys) alone or Cys with homocysteine (Hcy) by two pyridoxal-5′-phosphate (PLP)-dependent enzymes, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) (Chen et al., 2004; Chiku et al., 2009; Singh et al., 2009; Stipanuk and Beck, 1982). Both enzymes are ubiquitously expressed throughout the human body, and CBS is predominantly expressed in astrocytes (Zhang et al., 2017). CBS catalyzes a β-replacement reaction where Cys reacts with Hcy, resulting in production of H_2S in the cytoplasm, which is thought to be the primary source of H_2S in the mammalian brain. Although CSE was first reported in the brain, it mainly contributes to the formation of H_2S in the vascular system. CSE catalyzes the reaction of Cys in the cytoplasm in a similar manner to CBS, producing H_2S and serine (Zhang and Bian, 2014). H_2S can also be generated by cysteine aminotransferase (CAT) in conjunction with 3-mercaptopyruvate sulfurtransferase (3MST). 3-mercaptopyruvate (3 MP) can be produced from Cys and α-ketoglutarate (α-KG) by CAT. Then, 3 MP metabolism by 3MST results in H_2S production in the mitochondria. 3MST is mainly located in the mitochondria of neurons, while CBS and CSE do not exhibit organelle-specific localization (Mikami et al., 2011; Shibuya et al., 2013). H_2S has also been reported to be produced from D-cysteine by the enzyme D-amino acid oxidase (DAO), which is localized in peroxisomes, through the DAO/3MST pathway (Shibuya et al., 2013). Mitochondria and peroxisomes, which are generally in close proximity or maintain physical contact, are the key sites that produce H_2S through

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mutual interactions with the DAO/3MST cascade. In addition, the production of H_2S can result from glucose, glutathione, elemental sulfur, and polysulfide (Kolluru et al., 2013; Polhemus and Lefer, 2014). For example, glucose and phosphogluconate generate H_2S through glycolysis and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase reactions, respectively (Kolluru et al., 2013; Polhemus and Lefer, 2014).

1.1.2. Metabolism of H_2S

H_2S exists in two forms in the body: one-third is H_2S gas and two-thirds is present as hydrosulfide anion at physiological pH (Reiffenstein, 1992). Despite the unclear regulatory processes associated with endogenous H_2S metabolism, H_2S has been shown to be decomposed by several enzymatic and non-enzymatic processes to maintain the proper physiological balance (Kolluru et al., 2013; Stein and Bailey, 2013). Among these, mitochondrial oxidative modification is an important contributor to H_2S metabolism. This includes metabolism by several enzymes such as sulfide quinone oxidoreductase (SQR), s-dioxygenase, and s-transferase, to convert H_2S into thiosulfate ($S_2O_3^{2-}$). $S_2O_3^{2-}$ can be further converted to sulfite (SO_3^{2-}), which is catalyzed by thiosulfate cyanide sulfurtransferase (TSST). SO_3^{2-} is rapidly oxidized to sulfate (SO_4^{2-}) by sulfate oxidase. Alternatively, SO_3^{2-} can be converted by rhodanese to $S_2O_3^{2-}$, which is presumably metabolized to SO_4^{2-} via $S_2O_3^{2-}$ reductase (Muller et al., 2004) and SO_3^{2-} oxidase (Hildebrandt and Grieshaber, 2008). Therefore, SO_4^{2-} is likely the main end-product of H_2S metabolism under physiological conditions. Another mechanism of H_2S metabolism is methylation to methanethiol and dimethylsulfide by thiol S-methyltransferase in the cytoplasm (Hildebrandt and Grieshaber, 2008; Kabil and Banerjee, 2010; Stein and Bailey, 2013). The third pathway of H_2S metabolism is through interaction between H_2S and methemoglobin, which leads to sulfhemoglobin, a possible plasma H_2S biomarker (Hildebrandt and Grieshaber, 2008; Kabil and Banerjee, 2010; Stein and Bailey, 2013). These pathways are believed to be the main metabolic mechanisms of mammalian H_2S. Furthermore, a small amount of H_2S is exhaled as a gas, and the amount is modulated by distinct pharmacological interventions (Insko et al., 2009) (Fig. 1).

1.2. Physiological function of H_2S

H_2S is abundant in various tissues and is important in many human systems. The mechanisms of the physiological functions of H_2S have been widely studied (Fig. 2). Many studies have shown that sulfhydration by H_2S (addition of a sulfhydryl (−SH) group to a cysteine residue, resulting in an -SSH group) is a major mechanism of action. This modification may result in changes in protein conformation and activity, contributing to many physiological processes such as LTP, intracellular calcium homeostasis, and pH regulation (Zhang and Bian, 2014). For example, Kimura and colleagues first reported that H_2S acted on N-methyl D-aspartate (NMDA) receptors to augment hippocampal LTP in a synaptic model of learning and memory (Abe and Kimura, 1996). H_2S treatment stimulated the activity of adenylyl cyclase (AC), resulting in enhanced cAMP generation, phosphorylation of protein kinase A (PKA), stimulation of the NMDA receptor, and induction of LTP (Chen et al., 2017; Kimura, 2000). NMDA receptor-mediated LTP can be induced when a disulfide bond is reduced to free Cys (Aizenman et al., 1989), suggesting an important role of H_2S in NMDA receptor activation via sulfhydration of Cys residues (Kimura, 2013). The involvement of NMDA receptors was also shown in a study that inhibition of NMDA receptors can block H_2S-induced LTP (Paul and Snyder, 2015). In contrast, other gas transmitters such as NO and CO promote LTP in an NMDA-independent manner (Hawkins et al., 1994).

Recent studies have shown that H_2S is involved in modulation of Ca^{2+} concentrations to maintain homeostasis in microglia (Lee et al., 2006), astrocytes (Nagai et al., 2004), and neuronal SH-SY5Y cells (Yong et al., 2010). H_2S can open transient receptor potential (TRP) channels (Nagai et al., 2004; Tsugane et al., 2007) in astrocytes to assist Ca^{2+} influx. In addition, H_2S triggers the opening of L-type and T-type Ca^{2+} channels and activates NMDA receptors, facilitating Ca^{2+} influx to regulate neural function through the cAMP/PKA and phospholipase C (PLC)/protein kinase C (PKC) pathways (Lee et al., 2006; Yong et al., 2010). Furthermore, H_2S triggers release of Ca^{2+} from intracellular stores as the endoplasmic reticulum (Nagai et al., 2004).

Due to the inconvenience of using gas in experimental studies (the biological half-life of H_2S is seconds to minutes), H_2S salts such as sodium hydrosulfide (NaHS), sodium sulfide (Na_2S), and GYY-4137 are often used as H_2S donors (Li et al., 2008, 2009; Zhang and Bian, 2014). Lu et al. showed that NaHS (10–200 μM) led to an intracellular pH decrease by increasing activity of the Cl^-/HCO_3^- exchanger while suppressing the activity of the Na^+/H^+ exchanger, which prevented excessive activation of microglia and reduced neuroinflammation (Lu et al., 2010). Therefore, H_2S is capable of regulating intracellular pH in primary cultured microglia and astrocytes, although the mechanisms underlying the interactions between H_2S with these exchangers are not clear (Cao et al., 2018b).

1.3. Neurotoxicity of H_2S

H_2S is toxic gas by-product in many industries such as petroleum, agriculture, and sewage processing. The acute toxic effects of H_2S poisoning in humans are conjunctivitis, pulmonary edema, apnea, headache, immediate knockdown, and coma (Rumbeiha et al., 2016). H_2S poisoning can result in death from central nervous dysfunction or respiratory paralysis at 1000 ppm. Concentrations of H_2S ranging from 100 to 1000 ppm cause acute H_2S poisoning-induced neurological deficits including olfactory fatigue, nausea, headache, vomiting, dizziness, seizures, coma, and sometimes death (Reiffenstein, 1992). In some cases, a single exposure to H_2S may trigger long-term neurological dysfunction (Kilburn, 2003; Tvedt et al., 1991). Acute H_2S-induced brain lesions have been reported in various brain regions including the thalamus, cortex, colliculus, and basal ganglia (Schneider et al., 1998; Snyder et al., 1995). Although the mechanisms have only been partially characterized (Jiang et al., 2016), H_2S-induced neurotoxic effects resemble brain injury caused by ischemic hypoxia or addictive drugs (Doujaiji and Al-Tawfiq, 2010; Rumbeiha et al., 2016; Xiong et al., 2016, 2017; Yang et al., 2018). It is generally accepted that ischemic hypoxia and the direct effects of H_2S are both triggers of toxic sequelae. The cellular and molecular mechanisms that link the upstream effects of hypoxia and H_2S with neurotoxicity have been largely attributed to oxidative stress, glutamate excitotoxicity, and inflammation in the brain (Kim et al., 2018).

Oxidative stress is the result of an imbalance in pro-oxidant/anti-oxidant homeostasis, resulting in generation of toxic reactive oxygen species (ROS) (Mittler, 2002) including superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^{\cdot}$) (Lan et al., 2011; Liu et al., 2010). Generally, large amounts of $O_2^{\cdot -}$ and H_2O_2 are produced as by-products during synthesis of ATP by mitochondrial oxidative phosphorylation. In addition, NADPH oxidases are major contributors to ROS production (Stefanatos and Sanz, 2018). Many antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase, and antioxidant cofactors such as glutathione (GSH) and vitamin C contribute to maintenance of redox balance (Ren et al., 2017). Due to a high metabolic rate, the mammalian brain requires a constant supply of ATP, resulting in greater sensitivity to oxidative stress than other tissues (Wang et al., 2014a). At submicromolar concentrations, H_2S-induced oxidative stress results in inhibition of cytochrome C oxidase (complex IV) enzymatic activity by binding to the ferric heme a_3 of mitochondria complex IV in a manner similar to that of cyanide (Chenuel et al., 2015; Haouzi et al., 2015; Smith et al., 1977). Inhibition of key electron transport chain components may lead to reduced ATP production. However, studies of the

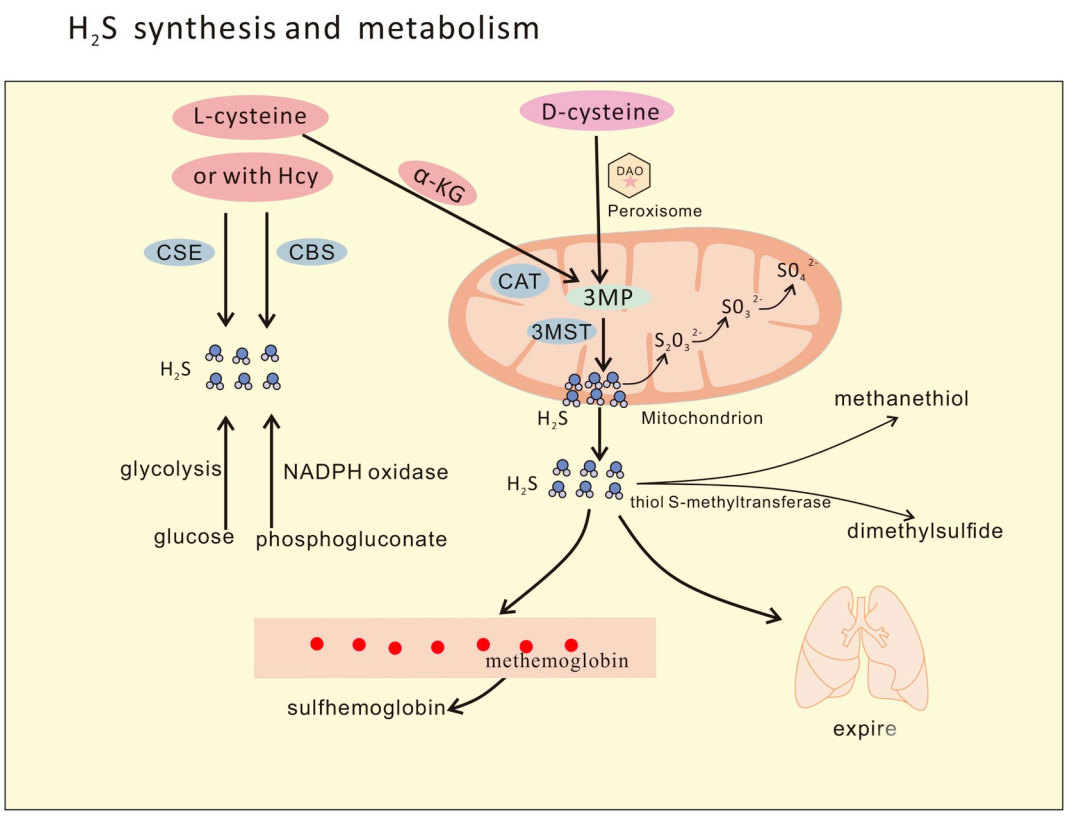

Fig. 1. Synthesis and metabolism of H_2S. In the cytoplasm, L-cysteine, either alone or with Hcy as substrate, generates H_2S through CSE and CBS, respectively. In the mitochondria, L-cysteine and D-cysteine generate H_2S through 3-MST dependent pathway. A small amount of H_2S can be produced through glycolysis and oxidation of phosphogluconate. Metabolism of H_2S mainly occurs in mitochondria, where H_2S is converted successively to $S_2O_3^{-}$, SO_3^{2-}, and finally SO_4^{2-} via SQR, TSST, and sulfate oxidase. Furthermore, H_2S can be metabolized to methanethiol and dimethylsulfide, form sulfhemoglobin with methemoglobin, and it can be exhaled in small amounts.

toxicity of cyanide and H_2S have shown that ATP levels are unchanged in rat brain or *in vitro*. Even so, oxidative stress is likely an important component of H_2S-induced toxicity because mitochondrial damage resulting from complex IV inhibition promotes ROS production and neuronal apoptosis (Jiang et al., 2016; Kurokawa et al., 2011; Rumbeiha et al., 2016; Shaul and Seger, 2007; Snyder et al., 1995). The ROS production was primarily due to the fact that inhibition of complex IV results in the accumulation of upstream complexes in a reduced form and thus enhances superoxide formation (Bouillaud and Blachier, 2011). Although complex IV activity was inhibited throughout the course of H_2S treatment, it was decreased only in the inferior colliculus, thalamus, and cortex of mice, indicating that complex IV inhibition might be region-specific in the CNS. As such, oxidative stress may not be the only mechanism of H_2S-elicited neurotoxicity and neurodegeneration (Anantharam et al., 2017).

Glutamate-induced excitotoxicity and neuroinflammation are also believed to contribute to H_2S-induced toxicity. In an *in vitro* model of cerebellar granule neurons (CGN) (Garcia-Bereguiain et al., 2008), treatment with 250 μM H_2S elevated the glutamate concentration in the extracellular medium. This resulted in activation of NMDA receptors, thus leading to excessive calcium influx into the neuronal cytosol and excitotoxic CGN death. This activity was L-type calcium channel and NMDA receptor dependent, as demonstrated by reduced CGN cell death resulting from co-treatment with blockers of these calcium channels (Garcia-Bereguiain et al., 2008). Furthermore, some reports have indicated that H_2S induced neuroinflammation through activation of glial cells and modulation of cytokine production (Rumbeiha et al., 2016). Evidence for inflammation included increased levels of ionized calcium-binding adaptor molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP), which are markers of microglial and astrocyte activation, in a mouse model of acute H_2S exposure (Anantharam et al., 2017). Furthermore, pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α), cytoplasmic FMR1-interacting protein 2 (Cyfip2), and nuclear hormone receptor and transcriptional repressor family (Nr1d2) were significantly activated or increased, while the anti-inflammatory protein macrophage migration inhibition factor (MIF) was downregulated in the brains of mice after acute H_2S exposure (Kim et al., 2018).

Current understanding of H_2S-induced neurotoxicity is limited. For example, the mechanism of H_2S-induced neural apoptosis is not well-understood. However, H_2S-induced neurotoxicity is of clinical relevance because, in the case of severe poisoning, toxic symptoms persist even when all free H_2S has been eliminated. These observations suggest that the negative effects of H_2S persist long after removal of soluble H_2S, resulting in alterations in brain pathophysiology (Haouzi et al., 2016). Therefore, further investigations are needed to characterize the pathways that underlie these effects. A summary of the mechanisms involved in acute H_2S-induced neurotoxicity is presented in Fig. 3.

1.4. Neuroprotection of H_2S

Physiological concentration of H_2S is an important contributing factor to cellular homeostasis in the body. Abnormal H_2S concentrations are often associated with various pathological states. A variety of neurological diseases such as AD, PD, TBI, and stroke are closely related to H_2S dysregulation, and exogenous H_2S supplementation exerts protective effects in brain disease models (Eto et al., 2002; Hu et al., 2010; Paul et al., 2014). The mechanisms that underlie these effects are believed to relate to anti-oxidant, anti-glutamate, and anti-inflammatory processes (Sommer et al., 2018) (see Table 1).

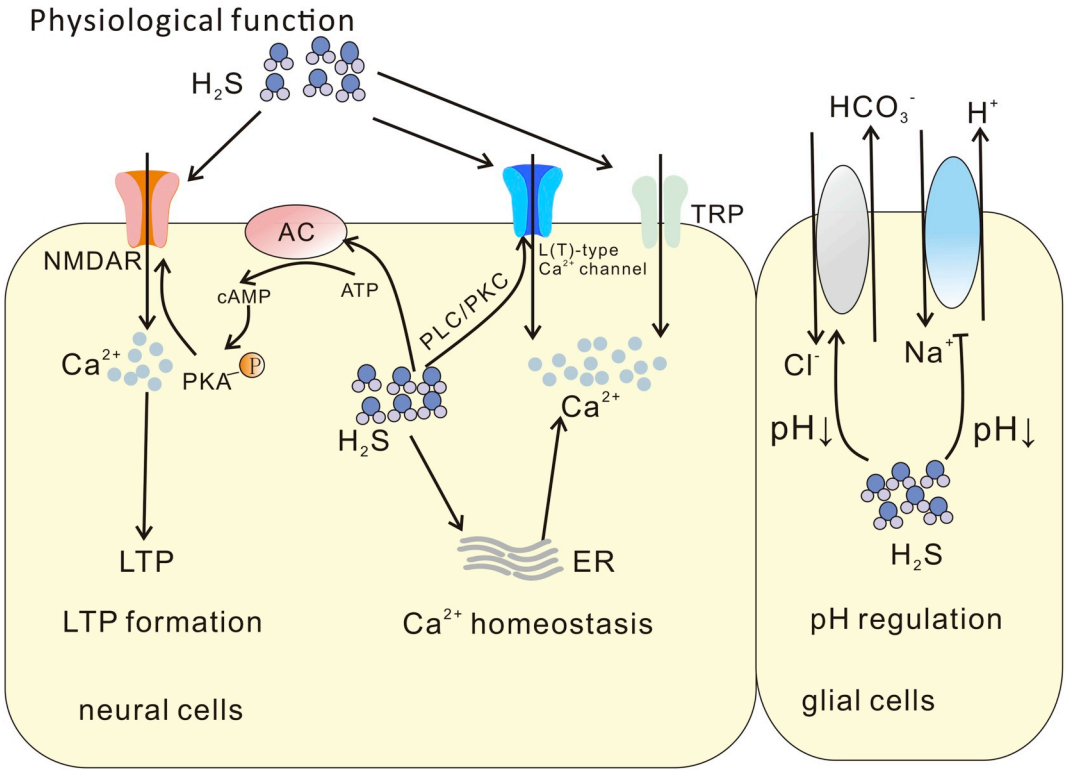

Fig. 2. Physiological function of H_2S. H_2S promotes LTP through the cAMP/PKA pathway or direct action on the NMDA receptor to promote the influx of Ca^{2+}. In addition, H_2S activates L (T)-type Ca^{2+} channels through the PLC/PKC pathway and acts on the ER to regulate intracellular Ca^{2+} homeostasis of. In microglia, H_2S regulates intracellular pH by inhibiting the Na^+/H^+ exchanger and activating the HCO_3^-/Cl^- exchanger.

1.5. The anti-oxidative role of H_2S

In a PC12 model of hypoxic injury, H_2S prevented decreased cell viability via regulating ROS-activated MAPK cascades (Lan et al., 2011; Meng et al., 2011), suggesting a protective role of H_2S against oxidative stress (Wang et al., 2014a). This anti-oxidative effect has been shown in various models and various pathways, including direct quenching of ROS production, and modulation of cellular levels of anti-oxidants such as GSH and nuclear factor erythroid 2-related factor 2 (Nrf2) (Kobayashi and Yamamoto, 2005; Wang et al., 2014a; Whiteman et al., 2004).

H_2S inhibits ROS production through NADPH-dependent and mitochondrial pathways. H_2S may suppress extracellular signal-regulated kinase (ERK) phosphorylation, resulting in decreased NOX2 expression, which inhibits NADPH oxidase activity. NOX2, a primary membrane subunit of NADPH oxidase, can produce excessive amounts of superoxide upon activation, resulting in downstream production of ROS (Hu et al., 2010). While it is unknown whether H_2S reacts with NADPH oxidase in a manner similar to NO, which acts directly on NADPH oxidase (Clancy et al., 1992), H_2S suppresses the formation of mitochondrial ROS through s-sulfhydration of cysteine-59 on p66Shc (an upstream activator of mitochondrial redox signaling), resulting in inhibition of p66Shc translocation into mitochondria where it participates in ROS production (Xie et al., 2014).

Administration of H_2S protects neural cells from oxidative stress through recovery of GSH levels (Kimura et al., 2010; Tyagi et al., 2009), which supports the involvement of GSH in H_2S-elicited neuroprotection. GSH is a major scavenger of ROS and lipid peroxides in the brain at 1–10 mM concentrations. Synthesis of GSH includes two main enzymatic steps: 1) Cys reacts with glutamate via glutamate cysteine ligase (GCL, formerly γ-GCS) to form γ-glutamyl cysteine, which is the rate limiting step in glutathione formation, and 2) formation of GSH from γ-glutamyl cysteine and glycine, which is catalyzed by GSH synthetase (GS) (Lu, 2013). Kimura et al. first reported the protective effects of H_2S in neurons against oxidative stress through increased levels of substrates of GSH formation, including the cystine/glutamate antiporter, intracellular cysteine, and γ-glutamyl cysteine (Kimura and Kimura, 2004; Mikami et al., 2016; Zhang et al., 2017). H_2S has no effect on GS, but it can regulate the production of GSH by increasing the activity of GCL (Liu et al., 2010). Increased GCL activation may be mediated through some cell surface receptor activation by H_2S (Kimura and Kimura, 2004). H_2S might be more effective in scavenging ROS through regulating intracellular GSH levels than by directly scavenging ROS because intracellular concentrations of GSH are much higher than those of H_2S (Furne et al., 2008; Ishigami et al., 2009; Wintner et al., 2010). Nrf2 regulate genes that encode antioxidant proteins by binding to antioxidant response elements and triggering downstream gene transcription to protect cells from oxidative stress insults (Kobayashi and Yamamoto, 2005). Kelch-like ECH associated protein 1 (Keap1) is a negative regulator of Nrf2. H_2S can protect mammalian cells through s-sulfhydration of cysteine-151 of Keap1, which subsequently induces Nrf2 dissociation from Keap1 and nuclear translocation, resulting in stimulation of Nrf2-targeted gene expression of GCL, leading to increased GSH production (Yang et al., 2013). Furthermore, polysulfide, a bound sulfur species derived from H_2S, reversibly modified Keap1 and induced Nrf2 translocation into the nucleus, caused acceleration of GSH synthesis in a model of t-butylhydroperoxide-induced cytotoxicity (Koike et al., 2013; Kumar and Sandhir, 2018). Nrf2-mediated benefits were also observed in other studies of H_2S-elicited neuroprotection (Koike et al., 2013; Kumar and Sandhir, 2018).

These findings provide strong evidence for the anti-oxidant effects of H_2S *in vivo* and *in vitro*. Given that a common characteristic of neurodegenerative diseases is increased oxidative stress (Yuan et al., 2018), and that H_2S metabolic disorders, generally resulting in decreased concentrations, occur in these disorders, a number of studies have suggested that H_2S is linked to the pathogenesis of neurodegeneration (Eto et al., 2002; Hu et al., 2010; Paul et al., 2014). Although previous studies have not established a causal link between abnormal

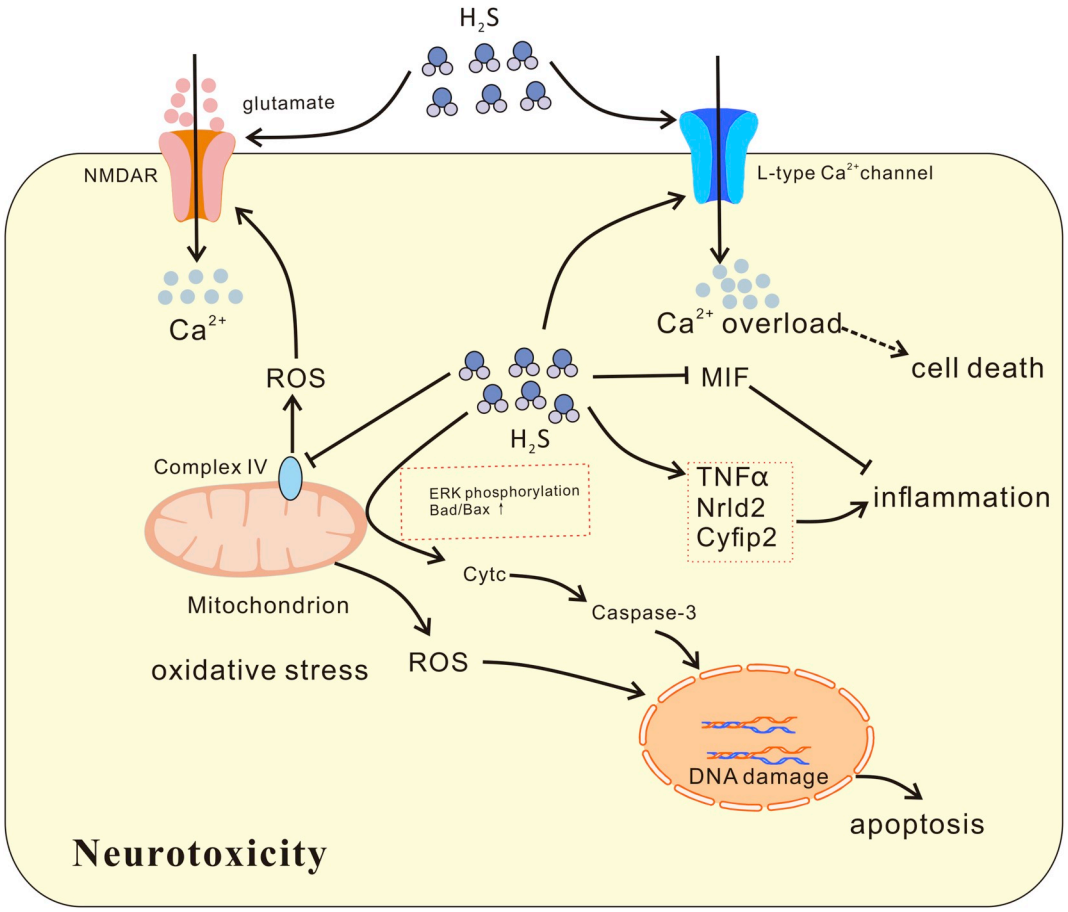

Fig. 3. Neurotoxic mechanism of H_2S. The toxic mechanism of H_2S is mainly related to oxidative stress, excitatory glutamate toxicity, and inflammation. H_2S exposure leads to mitochondrial dysfunction through inhibition of complex IV, producing a large amount of ROS, resulting in neural cell apoptosis. H_2S can also trigger excessive levels of glutamate in the synaptic cleft, thus stimulating the L-type calcium channel and NMDA receptor, which results in calcium overload and cell death. In addition, H_2S promotes neuroinflammation by increasing proinflammatory factors such as TNFα, Nrld2, and Cyfip2, and inhibiting the anti-inflammatory factor MIF.

metabolism of H_2S and these disorders, H_2S supplementation is a potential therapeutic strategy for treatment of these disorders due to its anti-oxidative properties, which is evidenced by findings that H_2S prevents ROS accumulation and neuronal death in animal models (Kimura and Kimura, 2004; Whiteman et al., 2004, 2005).

AD is one of the most common progressive neurodegenerative diseases, and is characterized by clinical symptoms such as cognitive dysfunction, memory impairment, and personality changes, and biochemical changes such as increased oxidative stress, neuronal inflammation, and neuronal apoptosis (Henstridge et al., 2019). It is characterized by formation of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain (Ballard et al., 2011). H_2S levels in the brains of patients with AD are lower than those of age-matched healthy individuals (Eto et al., 2002), and plasma H_2S levels are negatively correlated with the severity of AD (Wang et al., 2014a). Tang et al. reported that NaHS administration protected PC12 cells against Hcy-mediated cytotoxicity by preventing dissipation of the mitochondrial membrane potential (MMP) and by reducing intracellular ROS (Tang et al., 2010, 2011). These results agreed with those in another study which showed that treatment with spa-water rich in H_2S content delayed AD progression, potentially through an anti-oxidative pathway, as evidenced by the finding that malondialdehyde (MDA) concentration is prominently deceased in the experiment (Giuliani et al., 2013).

The brain of patients with PD is characterized by accumulation of aggregated α-synuclein and severe pars-compacta nigral cell loss (Lees et al., 2009; Rajput, 1993). Although the molecular mechanism of PD pathogenesis is unclear, mitochondrial dysfunction and oxidative stress are the key processes that lead to dopaminergic neuron death (Sarukhani et al., 2018). Since elimination of ROS has long been considered a promising strategy for treatment of PD (Cao et al., 2018b), several studies have evaluated the effects of H_2S supplement in PD models (Hu et al., 2010; Lu et al., 2012; Xie et al., 2013). Increased H_2S production through CBS overexpression specifically inhibited 6-hydroxydopamine (OHDA)-induced oxidative stress, down-regulated α-synuclein, and decreased the number of apoptotic nigral dopamine neurons in rats (Yin et al., 2017). In rodents, 6-OHDA reduced the levels of SOD and GPx, and increased the formation of MDA in the damaged hemisphere. NaHS treatment did not improve the decreased levels of SOD and GPx resulting from 6-OHDA treatment, but significantly reduced the overproduction of MDA in dopaminergic neurons in the substantia nigra (Sarukhani et al., 2018). In contrast, CO treatment increased the expression of SOD in a 6-OHDA-induced PD model. These findings indicated that there might be distinct mechanisms of redox regulation between H_2S and CO. H_2S plays a neuroprotective role through anti-oxidative pathways in PD models, as demonstrated by the finding that systemic administration of H_2S partly ameliorated dopaminergic neuronal injury and behavioral symptoms in experimental study (Yuan et al., 2018). This dopaminergic protective effect has also been shown in a study of methamphetamine. Methamphetamine is a widely abused psychostimulant with great neurotoxic potential due to increased oxidative damage in dopaminergic neurons (Yang et al., 2018). In an *in vivo* model of methamphetamine-induced neurotoxicity, NaHS treatment significantly increased the levels of SOD and GSH, and reduced MDA levels in the CA1 region of the hippocampus (Ghanbari

Table 1
The summary of neuroprotective effects of H_2S in brain disease models.

Mechanism	Species	Treatment agent	Dose regimen	Key results	Reference
Anti-oxidative stress	bEnd3 cell lines	NaHS	50 μM for 24 h	attenuated the production of free radical and recovered GSH levels	Tyagi et al. (2009)
	MEFs	NaHS	30 μM for 2 h	stimulated mRNA expressions of Nrf2-targeted downstream genes and enhanced the anti-oxidative capacity	Yang et al. (2013)
	Neuro2A cells	Na_2S_4	25 μM for 6 h,12 h	activation of Nrf2 signaling	Koike et al. (2013)
	PC12 cells	NaHS	400 μmoL/L for 30 min	inhibited ROS and prevented cell viability decrease	Lan et al. (2011)
	PC12 cells (AD model)	NaHS	200 μmoL/L for 24 h	prevented both the loss of MMP and the increase of intracellular ROS	Tang et al. (2010)
	Primary cortical neurons	NaHS	100 μM for 24 h	increased the activity of γ-GCS and recovered GSH levels	Kimura and Kimura (2004)
	SH-SY5Y cells	NaHS	60, 125, 250 μM for 5 min	scavenged $ONOO^-$	Whiteman et al. (2004)
	SH-SY5Y cells	NaHS	100 μM for 30 min	decreased mitochondrial ROS production and protected neuronal cells against stress-induced senescence	Xie et al. (2014)
	Mice and primary mesencephalic neurons	NaHS	Mice (5.6 mg/kg/day for 7 days), neurons (100 μM for 15 min)	rescued MPTP-induced loss of dopamine neurons in mice and protected primary mesecephalic neurons against cytotoxicity	Lu et al. (2012)
	Mice model of MCAO	ADT/NaHS	ADT (50 mg/kg/day) or NaHS (1.4 mg/kg/day) i.p for 24 h or 48 h	inhibited expression of pro-inflammatory factors	Wang et al. (2014a)
	Rats model of PD	NaHS	1.68 or 5.6 mg/kg/day, i.p. for 3 weeks	inhibited NADPH oxidase activation and oxygen consumption.	Hu et al. (2010)
	Rats model of AD	sodium hydrosulfide, Tabiano's spa-water	Sodium hydrosulfide (0.25, 0.5, 1 mg/kg/day) for 15 days i.p.; spa-water (3, 6, 12 ml/kg/day) for 15 days, i.p.	deceased MDA concentration	Giuliani et al. (2013)
	Rats	NaHS	1.68 or 5.6 mg/kg, i.p once a day for 3 weeks	decreased the loss of the nigral dopamine neurons and inhibited oxidase stress injury	Yin et al. (2017)
	Rats	NaHS	3 and 5.6 mg/kg for 7 days, i.p. daily	reduced the decreasing effect of 6-OHDA on striatal dopamine level and MDA overproduction	Sarukhani et al. (2018)
	Rats	NaHS	3 mg/kg, i.p. once	increased the activity of endogenous antioxidant enzymes SOD and CAT, decreased the levels of MDA	Jiang et al. (2013)
	Rats	NaHS	1 and 5 mg/kg, i.p. once	reduced brain injuries and post-ischemic cerebral edema	Gheibi et al. (2014)
	Rats	NaHS	0.0112 or 0.0224 mg/kg i.p. once	increased SOD activity and reduced the MDA content	Yin et al. (2013)
	Rats	NaHS	5, 10 mg/kg, three times at 30 min, 24 h, and 48 h	increased the level of SOD and GSH	Ghanbari et al. (2018)
Anti-glutamate toxicity	HEK 293T cells	H_2S	100 μM for 10 min	inhibited PTP1B activity and promoted PERK activity during the response to ER stress	Krishnan et al. (2011)
	PC12 cells	NaHS	200 μM or 400 μM for 30 min	upregulated BDNF and inhibited ER stress	Xiao et al. (2016)
	Primary cultures of astrocytes	NaHS	100 μM for 30 min	promoted glutamate uptake activity via decreasing ROS generation	Lu et al. (2008)
	primary cultures of cortical cells	NaHS	100 μM for 8 h, 30 and 100 μM for 4 h	increased the level of GSH	Kimura et al. (2010)

(*continued on next page*)

Table 1 (*continued*)

Mechanism	Species	Treatment agent	Dose regimen	Key results	Reference
Anti-inflammation	Mice model of MCAO	ADT/NaHS	ADT (50 mg/kg/day) or NaHS (1.4 mg/kg/day), i.p for 24 h or 48 h	reduced inflammation-induced MMP-9, iNOS and IL-1β, and enhanced of the arginase-1 and IL-10	Wang et al. (2014a)
	Mice model of SCI	ATB-346	30 μmoL/kg once daily for 10 d, orally	decreased the inflammatory component including iNOS, TNF-α and IL-1β, and accelerated the recovery of lost motor function	Campolo et al. (2013)
	Rats model of I/R	NaHS	0.0112 or 0.0224 mg/kg, i.p. once	reduced the production of TNF-α and MCP-1, increased the expression of anti-inflammatory cytokine IL-10	Yin et al. (2013)
	Rats model of AD	NaHS	5 mg/kg for 15 days, i.p. continuously	upregulated the expression of PPAR-α and PPAR-γ that antagonize the effects of the proinflammatory factors	Li et al. (2016)

Abbreviation.
ATB-346: 2-(6-methoxynapthalen- 2-yl)-propionic acid 4-thiocarbamoyl-phenyl ester.
AD: Alzheimer's disease.
BDNF: brain derived neurotrophic factor.
bEnd3: brain endothelial cells.
ER: endoplasmic reticulum.
GSH: glutathione.
HEK: human embryonic kidney.
IL-1β: interleukin-1β.
iNOS: nitric oxide synthase.
i.p.: intraperitoneally injected.
I/R: cerebral ischemia/reperfusion injury.
MCAO: middle cerebral artery occlusion.
MCP-1: monocyte chemotactic protein-1.
MDA: malondialdehyde.
MEFs: mouse embryonic fibroblasts.
MMP: mitochondrial membrane potential.
MMP-9: metallopeptidase-9.
NaHS: sodium hydrosulfide.
Na_2S_4: sodium tetrasulfide
Nrf2: nuclear factor erythroid 2-related factor 2.
$ONOO^-$: peroxynitrite.
PD: Parkinson's disease.
PERK: protein kinase-like ER kinase.
PPAR: peroxisome proliferator-activated receptor.
PTP1B: protein tyrosine phosphatase1B.
SCI: spinal cord injury.
SOD: superoxide dismutase.
TBI: traumatic brain injuries.

et al., 2018), implying that the observed neuroprotective effects were partly due to antioxidant activity.

Production of ROS is a major factor in the neuropathology of TBI and stroke (Arvin et al., 1995; Zhang et al., 2014, 2017). When TBI occurs, endogenous H_2S in the cerebral cortex and hippocampus of mice was decreased, which paralleled CBS mRNA and protein expression in the brain (Zhang et al., 2013). While causality between increased ROS and low H_2S levels has not been established, H_2S treatment substantially reduced oxidative stress and lesion volume resulting from TBI (Karimi et al., 2017; Zhang et al., 2013). Some studies have demonstrated the benefits of H_2S on controlled cortical impact injury in rats via increased activity of endogenous antioxidant enzymes (SOD and catalase), and decreased levels of oxidative products (MDA and 8-iso-prostaglandin F2α (8-iso-PGF2α)) (Jiang et al., 2013). In addition, H_2S supplementation activated the mitochondrial ATP-sensitive potassium (K_{ATP}) channel and reduced oxidative stress in a rat model of TBI (Jiang et al., 2013). K_{ATP} channels are widely expressed in excitatory cells and are located in the surface of the plasmalemmal membrane and the inner mitochondrial membrane (Farkas et al., 2004; Seino, 1999; Zawar et al., 1999). These channels play an important role in synaptic transmission by coupling cellular metabolism to electrical activity within the brain (Sun et al., 2008). Mitochondrial K_{ATP} channel activation can lead to K^+ influx, which enhances mitochondrial respiration through mitochondria matrix swelling, which results in faster electron transport and decreased ROS production (Jezek et al., 2004; Starkov, 1997). Thus, the anti-oxidant effects of H_2S may partially occur through K_{ATP} channel dependent pathways in TBI models. One study has shown that H_2S effectively protected neurons from serious cerebral damage caused by transient middle cerebral artery occlusion (Gheibi et al., 2014). H_2S can serve as an antioxidant, resulting in significantly increased SOD activity and reduced MDA content in the brain of stroke model (Yin et al., 2013). These results suggested the therapeutic potential of H_2S supplementation to improve the pathological course of TBI and stroke by antagonizing oxidative stress.

In brief, these results demonstrated robust anti-oxidant properties of H_2S, which have shown considerable benefits in brain disease models (Fig. 4). However, these studies are unsystematic, and they have only evaluated *in vitro* or animal models. In particular, no studies have concluded whether disruption of H_2S contributes to the pathogenesis of these diseases. If H_2S is involved with pathogenesis of neurological diseases, regulation of key enzymes in H_2S production would be a potential strategy to prevent the progression of these disorders. Future studies should focus on characterization of the role of H_2S in pathogenesis of neurological diseases.

1.6. H_2S-mediated protection against glutamate toxicity

As the primary excitatory neurotransmitter, glutamate plays a pivotal role in synaptic plasticity, neuronal development, and neuronal modulation in the CNS (Suzuki et al., 2006). Glutamate dysregulation has been implicated in various brain disorders, particularly neurodegenerative diseases, learning and functional disabilities, and addictive behaviors (Hertz, 2006). When excessive glutamate accumulates in the synaptic cleft, neuronal toxicity or neuronal death can occur via receptor-initiated glutamate excitotoxicity (Choi, 1988) and non-receptor mediated oxidative glutamate toxicity (Murphy et al., 1989) (Fig. 5).

In general, glutamate is absorbed into cells for reuse or conversion into glutamine via glutamate transporters (GluTs). Glutamate transporter (GLT)-1 is the main glutamate transporter and GluTs are highly expressed in astrocytes (Lu et al., 2008; Trotti et al., 1998). Lu and coworkers first demonstrated that the protective effects of H_2S in astrocytes were mediated by up-regulation of GLT-1 expression, resulting in increased glutamate uptake, which was partially mediated by decreased ROS production in a model of H_2O_2-induced cell injury (Lu et al., 2008). In addition, H_2S improved the function of GluTs via activation of K_{ATP} channels and increased uptake of extracellular glutamate into astrocytes (Sun et al., 2008). These results agreed with studies that neurons with decreased expression of K_{ATP} channels showed enhanced glutamate release (Soundarapandian et al., 2007), and activation of K_{ATP} channels prevented opening of the NMDA receptor channel and Ca^{2+}

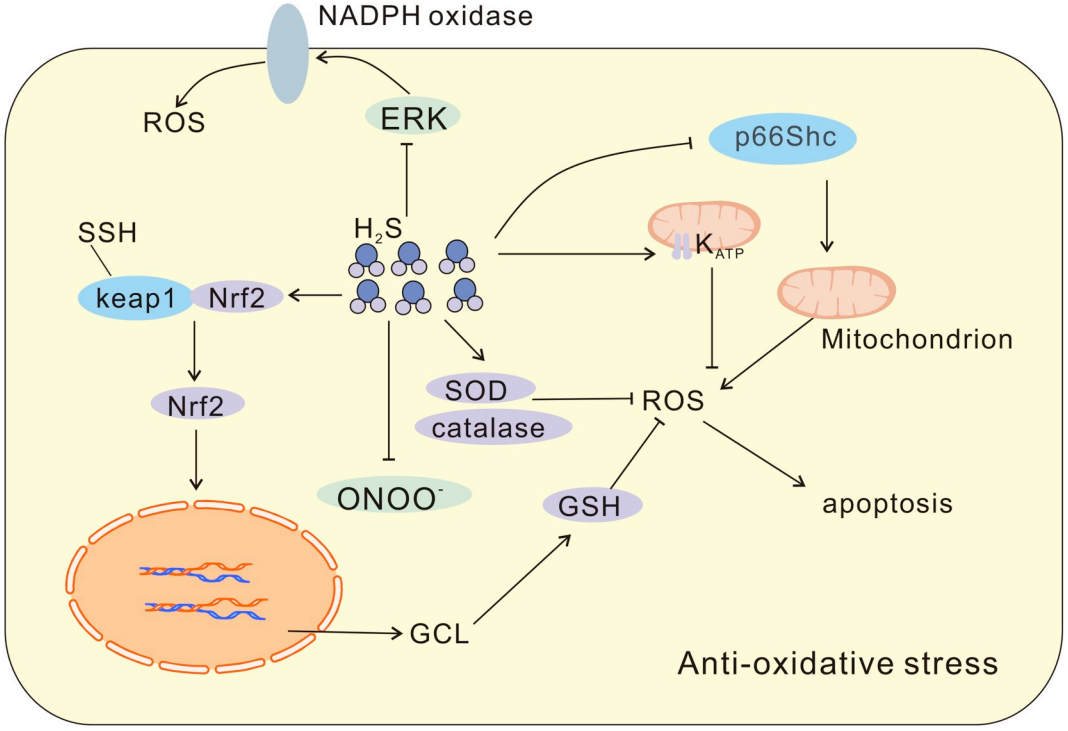

Fig. 4. Anti-oxidative stress mechanism of H_2S. H_2S may suppress ERK phosphorylation to inhibit the activity of NADPH oxidase, reducing downstream production of ROS. H_2S also suppresses the formation of mitochondrial ROS via activation of K_{ATP} channels and s-sulfhydration of p66Shc. In addition, H_2S protects neural cells from oxidative stress by increasing SOD, catalase, and Keap1/Nrf2/GCL mediated GSH production.

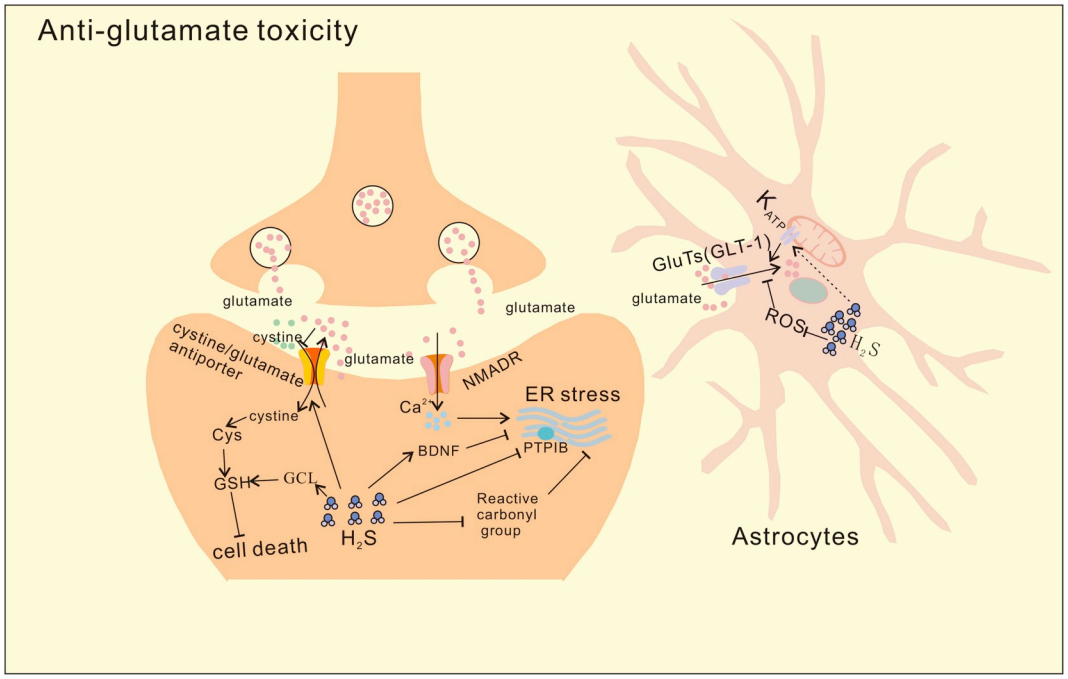

Fig. 5. Anti-glutamate toxicity mechanism of H_2S. H_2S activates K_{ATP} channels to reduce glutamate release, recovers cystine transport, and increases the activity of GCL, resulting in GSH production and protection of neurons from cell death. H_2S alleviates ER stress through pathways involving PTP1B, BDNF, and reactive carbonyl group. In astrocytes, H_2S up-regulates GLT-1 expression and increases glutamate reuptake, which is partly mediated by decreased ROS production and activation of K_{ATP} channels.

influx (Jiang et al., 2013).

NMDA receptors are typically overactivated by synaptic glutamate accumulation, which can induce Ca^{2+} influx and endoplasmic reticulum (ER) stress, eventually resulting in excitatory toxicity. Several studies have shown that H_2S inhibits ER stress in mammalian neural cells. H_2S alleviated ER stress through sulfhydration of the Cys residue of protein tyrosine phosphatase 1B (PTP1B) or by clearing reactive carbonyl groups during alcohol-mediated neuronal damage (Koike and Ogasawara, 2016; Krishnan et al., 2011), thus improving brain function. Furthermore, H_2S improved the expression of brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, in 1-methyl-4-phenylpyridinium (MPP^+)-treated PC12 cells. This effect was reversed by blocking the BDNF receptor TrkB, implying that this protection was mediated by BDNF (Xiao et al., 2016).

Oxidative glutamate toxicity, a form of oxidative stress-induced programmed neural cell death independent of ionotropic glutamate receptors (Maher and Davis, 1996; Murphy et al., 1989; Tan et al., 2001), is triggered by high concentrations of glutamate (Maher and Davis, 1996; Murphy et al., 1989; Tan et al., 2001). Through the cystine/glutamate antiporter, elevated extracellular glutamate inhibits intracellular transport of cystine, which is the key source of cysteine to produce GSH within the cell. GSH depletion by over 80% for several hours may result in an increase in ROS production and massive influx of Ca^{2+}, resulting in cell death (Tan et al., 2001). Neuro2A cells expressing 3MST and CAT showed significant resistance to oxidative glutamate toxicity via maintenance of GSH levels (Kimura et al., 2010). This result agreed with the observation that H_2S protected neurons through enhanced GCL activity and up-regulation of cystine transport in HT22 cells (Kimura and Kimura, 2004), which may explain how H_2S increased GSH production efficiency.

1.7. The anti-inflammatory role of H_2S

H_2S can exert anti-inflammatory or pro-inflammatory effects depending on concentration. Nontoxic levels of H_2S have been shown to exert anti-inflammatory effects on glial cells (Hu et al., 2007; Lee et al., 2016), as demonstrated by inhibition of TNF-α, interleukin (IL)-1β, NADPH oxidase, and inducible nitric oxide synthase (iNOS), and/or enhancement of arginase-1, IL-4, and IL-10 (Campolo et al., 2013; Cao et al., 2018a; Seifert and Pennypacker, 2014; Wang et al., 2014a, 2014b; Yin et al., 2013). Regulation of inflammation by H_2S consists of inhibiting inflammatory factors and promoting the release of anti-inflammatory factors. However, there are some exceptions. For example, NF-κB may facilitate apoptosis of neural cells by inducing the expression of pro-inflammatory cytokines and inducing oxidation (Godinez-Rubi et al., 2013). H_2S inhibits the expression of NF-κB and apoptosis in ischemia reperfusion injury and AD models (Biermann et al., 2011; Li et al., 2016). In contrast, NF-κB also promotes the expression of anti-apoptotic gene products and proteins such as Bcl-2 in the brain (Mattson and Camandola, 2001). In hepatocytes, H_2S sulfhydrates the p65 subunit of NF-κB at cysteine-38 and promotes NF-κB translocating into the nucleus, resulting in activation of several anti-apoptotic genes (Sen et al., 2012). These dual actions of H_2S on NF-κB may have been due to the differences in experimental models or differences in H_2S concentrations. The ability of H_2S to differentially regulate NF-κB in various tissues may suggest complex interactions that result in H_2S-induced anti-apoptotic effects. Whether the anti-inflammatory effects of H_2S are related to its antioxidant effects has not been characterized, but it is possible that they are linked given the fact that oxidative stress plays a critical role in the inflammatory processes (Pattison and Winyard, 2008). In addition, as studies of the anti-inflammatory effects of H_2S have been largely limited to evaluation of inflammatory cytokine levels, further studies focused on regulation of inflammation are necessary.

2. Conclusions and perspectives

H_2S has attracted increased attention in the past decade. Studies have shown that H_2S exerts antioxidant and neuroprotective effects at concentrations in the micromolar range, but induces neurotoxic effects in the millimolar range. The ability of H_2S to act as a protective and toxic mechanism suggests that it plays a role in redox homeostasis

(Kolluru et al., 2013). One of the main goals of developing H_2S-based therapeutics is to improve efficiency and reduce toxic effects. Several clinical trials have evaluated H_2S (e.g., biomarker in asthma, prognostic factor in shock), but none have focused on neuroprotection. Antioxidant therapies often provide little benefit to patients with AD and PD, despite having been effective in experimental models (Angelova and Abramov, 2018). This failure to provide therapeutic benefit is mostly due to obstacles in delivering antioxidants to neural cells or maintaining the chemical stability of antioxidants. Recent studies have suggested that instead of reducing oxidative stress via administration of antioxidants, enhancing the antioxidant capabilities of the brain may provide more benefits (Franco et al., 2019). Thus, H_2S treatment is a promising strategy because it can easily diffuse in a transporter-independent manner in the brain. However, maintenance of H_2S levels at the ideal concentration is a challenge. The dual action of H_2S indicates that H_2S concentrations must be tightly regulated. This can be solved by use of H_2S-releasing prodrugs. Woods et al. recently found that an H_2S-releasing agent based on Ruthenium (II), a compound present in living cells, was able to release H_2S through irradiation with red light without the help of secondary nanoparticle system (Woods et al., 2018). Another challenge is determining of H_2S concentrations in tissues. Fluorescent probes have been developed to address this issue. However, these small cationic molecular probes cannot be used for *in vivo* imaging due to shallow tissue penetration and poor bio-stability (Li et al., 2018). Recently, Wang and colleagues proposed poly (acrylic acid)-modified upconversion nanoparticles assembled with cationic near-infrared cyanine chromophores as a nanoprobe for monitoring H_2S. This nanoprobe showed excellent properties including good selectivity, high sensitivity, and low cytotoxicity in cells and zebra fish (Wang et al., 2018). Li et al. also reported a ratiometric upconversion luminescence nanoprobe with an acid-activated targeting strategy for detecting and bioimaging of mitochondrial H_2S that demonstrated high selectivity and sensitivity (Li et al., 2018). These innovations suggest that nanoprobes may be ideal for monitoring cellular H_2S levels in mammalian tissues. We believe that comprehensive understanding of the mechanisms of action of H_2S and advances in prodrugs and detection methods will aid in translation to therapeutic strategies for treatment of brain disorders in humans.

Conflicts of interest

The authors declare there is no potential conflict of interests.

Acknowledgments

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References

Abe, K., Kimura, H., 1996. The possible role of hydrogen sulfide as an endogenous neuromodulator. J. Neurosci. 16, 1066–1071.
Aizenman, E., Lipton, S.A., Loring, R.H., 1989. Selective modulation of NMDA responses by reduction and oxidation. Neuron 2, 1257–1263.
Anantharam, P., Whitley, E.M., Mahama, B., Kim, D.S., Imerman, P.M., Shao, D., Langley, M.R., Kanthasamy, A., Rumbeiha, W.K., 2017. Characterizing a mouse model for evaluation of countermeasures against hydrogen sulfide-induced neurotoxicity and neurological sequelae. Ann. N. Y. Acad. Sci. 1400, 46–64.
Angelova, P.R., Abramov, A.Y., 2018. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. FEBS Lett. 592, 692–702.
Arvin, B., Neville, L.F., Barone, F.C., Feuerstein, G.Z., 1995. Brain injury and inflammation. A putative role of TNF alpha. Ann. N. Y. Acad. Sci. 765, 62–71 discussion 98-69.
Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., Jones, E., 2011. Alzheimer's disease. Lancet 377, 1019–1031.
Biermann, J., Lagreze, W.A., Schallner, N., Schwer, C.I., Goebel, U., 2011. Inhalative preconditioning with hydrogen sulfide attenuated apoptosis after retinal ischemia/reperfusion injury. Mol. Vis. 17, 1275–1286.
Bouillaud, F., Blachier, F., 2011. Mitochondria and sulfide: a very old story of poisoning, feeding, and signaling? Antioxidants Redox Signal. 15, 379–391.
Campolo, M., Esposito, E., Ahmad, A., Di Paola, R., Wallace, J.L., Cuzzocrea, S., 2013. A hydrogen sulfide-releasing cyclooxygenase inhibitor markedly accelerates recovery from experimental spinal cord injury. FASEB J. 27, 4489–4499.
Cao, L., Cao, X., Zhou, Y., Nagpure, B.V., Wu, Z.Y., Hu, L.F., Yang, Y., Sethi, G., Moore, P.K., Bian, J.S., 2018a. Hydrogen sulfide inhibits ATP-induced neuroinflammation and Abeta1-42 synthesis by suppressing the activation of STAT3 and cathepsin S. Brain Behav. Immun. 73, 603–614.
Cao, X., Cao, L., Ding, L., Bian, J.S., 2018b. A new hope for a devastating disease: hydrogen sulfide in Parkinson's disease. Mol. Neurobiol. 55, 3789–3799.
Chen, H.B., Wu, W.N., Wang, W., Gu, X.H., Yu, B., Wei, B., Yang, Y.J., 2017. Cystathionine-beta-synthase-derived hydrogen sulfide is required for amygdalar long-term potentiation and cued fear memory in rats. Pharmacol. Biochem. Behav. 155, 16–23.
Chen, X., Jhee, K.H., Kruger, W.D., 2004. Production of the neuromodulator H2S by cystathionine beta-synthase via the condensation of cysteine and homocysteine. J. Biol. Chem. 279, 52082–52086.
Chenuel, B., Sonobe, T., Haouzi, P., 2015. Effects of infusion of human methemoglobin solution following hydrogen sulfide poisoning. Clin. Toxicol. 53, 93–101.
Chiku, T., Padovani, D., Zhu, W., Singh, S., Vitvitsky, V., Banerjee, R., 2009. H2S biogenesis by human cystathionine gamma-lyase leads to the novel sulfur metabolites lanthionine and homolanthionine and is responsive to the grade of hyperhomocysteinemia. J. Biol. Chem. 284, 11601–11612.
Choi, D.W., 1988. Glutamate neurotoxicity and diseases of the nervous system. Neuron 1, 623–634.
Clancy, R.M., Leszczynska-Piziak, J., Abramson, S.B., 1992. Nitric oxide, an endothelial cell relaxation factor, inhibits neutrophil superoxide anion production via a direct action on the NADPH oxidase. J. Clin. Investig. 90, 1116–1121.
Doujaiji, B., Al-Tawfiq, J.A., 2010. Hydrogen sulfide exposure in an adult male. Ann. Saudi Med. 30, 76–80.
Eto, K., Asada, T., Arima, K., Makifuchi, T., Kimura, H., 2002. Brain hydrogen sulfide is severely decreased in Alzheimer's disease. Biochem. Biophys. Res. Commun. 293, 1485–1488.
Farkas, E., Institoris, A., Domoki, F., Mihaly, A., Luiten, P.G., Bari, F., 2004. Diazoxide and dimethyl sulphoxide prevent cerebral hypoperfusion-related learning dysfunction and brain damage after carotid artery occlusion. Brain Res. 1008, 252–260.
Franco, R., Navarro, G., Martinez-Pinilla, E., 2019. Antioxidant Defense Mechanisms in Erythrocytes and in the Central Nervous System. Antioxidants, vol. 8.
Furne, J., Saeed, A., Levitt, M.D., 2008. Whole tissue hydrogen sulfide concentrations are orders of magnitude lower than presently accepted values. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R1479–R1485.
Garcia-Bereguiain, M.A., Samhan-Arias, A.K., Martin-Romero, F.J., Gutierrez-Merino, C., 2008. Hydrogen sulfide raises cytosolic calcium in neurons through activation of L-type Ca2+ channels. Antioxidants Redox Signal. 10, 31–42.
Ghanbari, F., Khaksari, M., Vaezi, G., Hojati, V., Shiravi, A., 2018. Hydrogen sulfide protects hippocampal neurons against methamphetamine neurotoxicity via inhibition of apoptosis and neuroinflammation. J. Mol. Neurosci. 67, 133–141.
Gheibi, S., Aboutaleb, N., Khaksari, M., Kalalian-Moghaddam, H., Vakili, A., Asadi, Y., Mehrjerdi, F.Z., Gheibi, A., 2014. Hydrogen sulfide protects the brain against ischemic reperfusion injury in a transient model of focal cerebral ischemia. J. Mol. Neurosci. 54, 264–270.
Giuliani, D., Ottani, A., Zaffe, D., Galantucci, M., Strinati, F., Lodi, R., Guarini, S., 2013. Hydrogen sulfide slows down progression of experimental Alzheimer's disease by targeting multiple pathophysiological mechanisms. Neurobiol. Learn. Mem. 104, 82–91.
Godinez-Rubi, M., Rojas-Mayorquin, A.E., Ortuno-Sahagun, D., 2013. Nitric oxide donors as neuroprotective agents after an ischemic stroke-related inflammatory reaction. Oxid Med Cell Longev 297357.
Haouzi, P., Chenuel, B., Sonobe, T., 2015. High-dose hydroxocobalamin administered after H2S exposure counteracts sulfide-poisoning-induced cardiac depression in sheep. Clin. Toxicol. 53, 28–36.
Haouzi, P., Sonobe, T., Judenherc-Haouzi, A., 2016. Developing effective countermeasures against acute hydrogen sulfide intoxication: challenges and limitations. Ann. N. Y. Acad. Sci. 1374, 29–40.
Hawkins, R.D., Zhuo, M., Arancio, O., 1994. Nitric oxide and carbon monoxide as possible retrograde messengers in hippocampal long-term potentiation. J. Neurobiol. 25, 652–665.
Henstridge, C.M., Hyman, B.T., Spires-Jones, T.L., 2019. Beyond the neuron-cellular interactions early in Alzheimer disease pathogenesis. Nat. Rev. Neurosci. 20, 94–108.
Hertz, L., 2006. Glutamate, a neurotransmitter–and so much more. A synopsis of Wierzba III. Neurochem. Int. 48, 416–425.
Hildebrandt, T.M., Grieshaber, M.K., 2008. Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. FEBS J. 275, 3352–3361.
Hu, L.F., Lu, M., Tiong, C.X., Dawe, G.S., Hu, G., Bian, J.S., 2010. Neuroprotective effects of hydrogen sulfide on Parkinson's disease rat models. Aging Cell 9, 135–146.
Hu, L.F., Wong, P.T., Moore, P.K., Bian, J.S., 2007. Hydrogen sulfide attenuates lipopolysaccharide-induced inflammation by inhibition of p38 mitogen-activated protein kinase in microglia. J. Neurochem. 100, 1121–1128.
Insko, M.A., Deckwerth, T.L., Hill, P., Toombs, C.F., Szabo, C., 2009. Detection of exhaled hydrogen sulphide gas in rats exposed to intravenous sodium sulphide. Br. J. Pharmacol. 157, 944–951.

Ishigami, M., Hiraki, K., Umemura, K., Ogasawara, Y., Ishii, K., Kimura, H., 2009. A source of hydrogen sulfide and a mechanism of its release in the brain. Antioxidants Redox Signal. 11, 205–214.
Jezek, P., Zackova, M., Ruzicka, M., Skobisova, E., Jaburek, M., 2004. Mitochondrial uncoupling proteins–facts and fantasies. Physiol. Res. 53 (Suppl. 1), S199–S211.
Jiang, J., Chan, A., Ali, S., Saha, A., Haushalter, K.J., Lam, W.L., Glasheen, M., Parker, J., Brenner, M., Mahon, S.B., Patel, H.H., Ambasudhan, R., Lipton, S.A., Pilz, R.B., Boss, G.R., 2016. Hydrogen sulfide–mechanisms of toxicity and development of an antidote. Sci. Rep. 6, 20831.
Jiang, X., Huang, Y., Lin, W., Gao, D., Fei, Z., 2013. Protective effects of hydrogen sulfide in a rat model of traumatic brain injury via activation of mitochondrial adenosine triphosphate-sensitive potassium channels and reduction of oxidative stress. J. Surg. Res. 184, e27–35.
Kabil, O., Banerjee, R., 2010. Redox biochemistry of hydrogen sulfide. J. Biol. Chem. 285, 21903–21907.
Karimi, S.A., Hosseinmardi, N., Janahmadi, M., Sayyah, M., Hajisoltani, R., 2017. The protective effect of hydrogen sulfide (H2S) on traumatic brain injury (TBI) induced memory deficits in rats. Brain Res. Bull. 134, 177–182.
Kilburn, K.H., 2003. Effects of hydrogen sulfide on neurobehavioral function. South. Med. J. 96, 639–646.
Kim, D.S., Anantharam, P., Hoffmann, A., Meade, M.L., Grobe, N., Gearhart, J.M., Whitley, E.M., Mahama, B., Rumbeiha, W.K., 2018. Broad spectrum proteomics analysis of the inferior colliculus following acute hydrogen sulfide exposure. Toxicol. Appl. Pharmacol. 355, 28–42.
Kimura, H., 2000. Hydrogen sulfide induces cyclic AMP and modulates the NMDA receptor. Biochem. Biophys. Res. Commun. 267, 129–133.
Kimura, H., 2013. Physiological role of hydrogen sulfide and polysulfide in the central nervous system. Neurochem. Int. 63, 492–497.
Kimura, Y., Goto, Y., Kimura, H., 2010. Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. Antioxidants Redox Signal. 12, 1–13.
Kimura, Y., Kimura, H., 2004. Hydrogen sulfide protects neurons from oxidative stress. FASEB J. 18, 1165–1167.
Kobayashi, M., Yamamoto, M., 2005. Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. Antioxidants Redox Signal. 7, 385–394.
Koike, S., Ogasawara, Y., 2016. Sulfur atom in its bound state is a unique element involved in physiological functions in mammals. Molecules 21.
Koike, S., Ogasawara, Y., Shibuya, N., Kimura, H., Ishii, K., 2013. Polysulfide exerts a protective effect against cytotoxicity caused by t-buthylhydroperoxide through Nrf2 signaling in neuroblastoma cells. FEBS Lett. 587, 3548–3555.
Kolluru, G.K., Shen, X., Bir, S.C., Kevil, C.G., 2013. Hydrogen sulfide chemical biology: pathophysiological roles and detection. Nitric Oxide 35, 5–20.
Krishnan, N., Fu, C., Pappin, D.J., Tonks, N.K., 2011. H2S-Induced sulfhydration of the phosphatase PTP1B and its role in the endoplasmic reticulum stress response. Sci. Signal. 4, ra86.
Kumar, M., Sandhir, R., 2018. Neuroprotective effect of hydrogen sulfide in hyperhomocysteinemia is mediated through antioxidant action involving Nrf2. NeuroMolecular Med. 20, 475–490.
Kurokawa, Y., Sekiguchi, F., Kubo, S., Yamasaki, Y., Matsuda, S., Okamoto, Y., Sekimoto, T., Fukatsu, A., Nishikawa, H., Kume, T., Fukushima, N., Akaike, A., Kawabata, A., 2011. Involvement of ERK in NMDA receptor-independent cortical neurotoxicity of hydrogen sulfide. Biochem. Biophys. Res. Commun. 414, 727–732.
Lan, A., Liao, X., Mo, L., Yang, C., Yang, Z., Wang, X., Hu, F., Chen, P., Feng, J., Zheng, D., Xiao, L., 2011. Hydrogen sulfide protects against chemical hypoxia-induced injury by inhibiting ROS-activated ERK1/2 and p38MAPK signaling pathways in PC12 cells. PLoS One 6, e25921.
Lee, M., McGeer, E.G., McGeer, P.L., 2016. Sodium thiosulfate attenuates glial-mediated neuroinflammation in degenerative neurological diseases. J. Neuroinflammation 13, 32.
Lee, S.W., Hu, Y.S., Hu, L.F., Lu, Q., Dawe, G.S., Moore, P.K., Wong, P.T., Bian, J.S., 2006. Hydrogen sulphide regulates calcium homeostasis in microglial cells. Glia 54, 116–124.
Lees, A.J., Hardy, J., Revesz, T., 2009. Parkinson's disease. Lancet 373, 2055–2066.
Li, L., Salto-Tellez, M., Tan, C.H., Whiteman, M., Moore, P.K., 2009. GYY4137, a novel hydrogen sulfide-releasing molecule, protects against endotoxic shock in the rat. Free Radic. Biol. Med. 47, 103–113.
Li, L., Whiteman, M., Guan, Y.Y., Neo, K.L., Cheng, Y., Lee, S.W., Zhao, Y., Baskar, R., Tan, C.H., Moore, P.K., 2008. Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): new insights into the biology of hydrogen sulfide. Circulation 117, 2351–2360.
Li, X., Zhao, H., Ji, Y., Yin, C., Li, J., Yang, Z., Tang, Y., Zhang, Q., Fan, Q., Huang, W., 2018. Lysosome-assisted mitochondrial targeting nanoprobe based on dye-modified upconversion nanophosphors for ratiometric imaging of mitochondrial hydrogen sulfide. ACS Appl. Mater. Interfaces 10, 39544–39556.
Li, X.H., Deng, Y.Y., Li, F., Shi, J.S., Gong, Q.H., 2016. Neuroprotective effects of sodium hydrosulfide against beta-amyloid-induced neurotoxicity. Int. J. Mol. Med. 38, 1152–1160.
Liu, W.B., Zhou, J., Qu, Y., Li, X., Lu, C.T., Xie, K.L., Sun, X.L., Fei, Z., 2010. Neuroprotective effect of osthole on MPP+-induced cytotoxicity in PC12 cells via inhibition of mitochondrial dysfunction and ROS production. Neurochem. Int. 57, 206–215.
Lu, M., Choo, C.H., Hu, L.F., Tan, B.H., Hu, G., Bian, J.S., 2010. Hydrogen sulfide regulates intracellular pH in rat primary cultured glia cells. Neurosci. Res. 66, 92–98.
Lu, M., Hu, L.F., Hu, G., Bian, J.S., 2008. Hydrogen sulfide protects astrocytes against H(2)O(2)-induced neural injury via enhancing glutamate uptake. Free Radic. Biol. Med. 45, 1705–1713.
Lu, M., Zhao, F.F., Tang, J.J., Su, C.J., Fan, Y., Ding, J.H., Bian, J.S., Hu, G., 2012. The neuroprotection of hydrogen sulfide against MPTP-induced dopaminergic neuron degeneration involves uncoupling protein 2 rather than ATP-sensitive potassium channels. Antioxidants Redox Signal. 17, 849–859.
Lu, S.C., 2013. Glutathione synthesis. Biochim. Biophys. Acta 1830, 3143–3153.
Maher, P., Davis, J.B., 1996. The role of monoamine metabolism in oxidative glutamate toxicity. J. Neurosci. 16, 6394–6401.
Mattson, M.P., Camandola, S., 2001. NF-kappaB in neuronal plasticity and neurodegenerative disorders. J. Clin. Investig. 107, 247–254.
Meng, J.L., Mei, W.Y., Dong, Y.F., Wang, J.H., Zhao, C.M., Lan, A.P., Yang, C.T., Chen, P.X., Feng, J.Q., Hu, C.H., 2011. Heat shock protein 90 mediates cytoprotection by H(2)S against chemical hypoxia-induced injury in PC12 cells. Clin. Exp. Pharmacol. Physiol. 38, 42–49.
Mikami, Y., Kakizawa, S., Yamazawa, T., 2016. Essential roles of natural products and gaseous mediators on neuronal cell death or survival. Int. J. Mol. Sci. 17.
Mikami, Y., Shibuya, N., Kimura, Y., Nagahara, N., Yamada, M., Kimura, H., 2011. Hydrogen sulfide protects the retina from light-induced degeneration by the modulation of Ca2+ influx. J. Biol. Chem. 286, 39379–39386.
Mittler, R., 2002. Oxidative stress, antioxidants and stress tolerance. Trends Plant Sci. 7, 405–410.
Muller, F.H., Bandeiras, T.M., Urich, T., Teixeira, M., Gomes, C.M., Kletzin, A., 2004. Coupling of the pathway of sulphur oxidation to dioxygen reduction: characterization of a novel membrane-bound thiosulphate:quinone oxidoreductase. Mol. Microbiol. 53, 1147–1160.
Murphy, T.H., Miyamoto, M., Sastre, A., Schnaar, R.L., Coyle, J.T., 1989. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. Neuron 2, 1547–1558.
Nagai, Y., Tsugane, M., Oka, J., Kimura, H., 2004. Hydrogen sulfide induces calcium waves in astrocytes. FASEB J. 18, 557–559.
Nogue, S., Pou, R., Fernandez, J., Sanz-Gallen, P., 2011. Fatal hydrogen sulphide poisoning in unconfined spaces. Occup. Med. (Lond.) 61, 212–214.
Pattison, D.J., Winyard, P.G., 2008. Dietary antioxidants in inflammatory arthritis: do they have any role in etiology or therapy? Nat. Clin. Pract. Rheumatol. 4, 590–596.
Paul, B.D., Sbodio, J.I., Xu, R., Vandiver, M.S., Cha, J.Y., Snowman, A.M., Snyder, S.H., 2014. Cystathionine gamma-lyase deficiency mediates neurodegeneration in Huntington's disease. Nature 509, 96–100.
Paul, B.D., Snyder, S.H., 2015. Modes of physiologic H2S signaling in the brain and peripheral tissues. Antioxidants Redox Signal. 22, 411–423.
Polhemus, D.J., Calvert, J.W., Butler, J., Lefer, D.J., 2014. The cardioprotective actions of hydrogen sulfide in acute myocardial infarction and heart failure. Sci. Tech. Rep. 2014, 768607.
Polhemus, D.J., Lefer, D.J., 2014. Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease. Circ. Res. 114, 730–737.
Rajput, D.R., 1993. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 56, 938–939.
Reiffenstein, R.J., 1992. Toxicology of hydrogen sulfide. Annu. Rev. Pharmacol. Toxicol. 109–134.
Ren, X., Zou, L., Zhang, X., Branco, V., Wang, J., Carvalho, C., Holmgren, A., Lu, J., 2017. Redox signaling mediated by thioredoxin and glutathione systems in the central nervous system. Antioxidants Redox Signal. 27, 989–1010.
Rumbeiha, W., Whitley, E., Anantharam, P., Kim, D.S., Kanthasamy, A., 2016. Acute hydrogen sulfide-induced neuropathology and neurological sequelae: challenges for translational neuroprotective research. Ann. N. Y. Acad. Sci. 1378, 5–16.
Sarukhani, M., Haghdoost-Yazdi, H., Sarbazi Golezari, A., Babayan-Tazehkand, A., Dargahi, T., Rastgoo, N., 2018. Evaluation of the antiparkinsonism and neuroprotective effects of hydrogen sulfide in acute 6-hydroxydopamine-induced animal model of Parkinson's disease: behavioral, histological and biochemical studies. Neurol. Res. 40, 523–531.
Schneider, J.S., Tobe, E.H., Mozley Jr., P.D., Barniskis, L., Lidsky, T.I., 1998. Persistent cognitive and motor deficits following acute hydrogen sulphide poisoning. Occup. Med. (Lond.) 48, 255–260.
Seifert, H.A., Pennypacker, K.R., 2014. Molecular and cellular immune responses to ischemic brain injury. Transl. Stroke Res. 5, 543–553.
Seino, S., 1999. ATP-sensitive potassium channels: a model of heteromultimeric potassium channel/receptor assemblies. Annu. Rev. Physiol. 61, 337–362.
Sen, N., Paul, B.D., Gadalla, M.M., Mustafa, A.K., Sen, T., Xu, R., Kim, S., Snyder, S.H., 2012. Hydrogen sulfide-linked sulfhydration of NF-kappaB mediates its antiapoptotic actions. Mol. Cell 45, 13–24.
Shaul, Y.D., Seger, R., 2007. The MEK/ERK cascade: from signaling specificity to diverse functions. Biochim. Biophys. Acta 1773, 1213–1226.
Shibuya, N., Koike, S., Tanaka, M., Ishigami-Yuasa, M., Kimura, Y., Ogasawara, Y., Fukui, K., Nagahara, N., Kimura, H., 2013. A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells. Nat. Commun. 4, 1366.
Singh, S., Padovani, D., Leslie, R.A., Chiku, T., Banerjee, R., 2009. Relative contributions of cystathionine beta-synthase and gamma-cystathionase to H2S biogenesis via alternative trans-sulfuration reactions. J. Biol. Chem. 284, 22457–22466.
Smith, L., Kruszyna, H., Smith, R.P., 1977. The effect of methemoglobin on the inhibition of cytochrome c oxidase by cyanide, sulfide or azide. Biochem. Pharmacol. 26, 2247–2250.
Smith, R.P., Gosselin, R.E., 1979. Hydrogen sulfide poisoning. J. Occup. Med. 21, 93–97.
Snyder, J.W., Safir, E.F., Summerville, G.P., Middleberg, R.A., 1995. Occupational fatality and persistent neurological sequelae after mass exposure to hydrogen sulfide. Am. J. Emerg. Med. 13, 199–203.
Sommer, O., Aug, R.L., Schmidt, A.J., Heiser, P., Schulz, E., Vedder, H., Clement, H.W., 2018. Hydrogen sulfide affects radical formation in the Hippocampus of LPS treated rats and the effect of antipsychotics on hydrogen sulfide forming enzymes in human

cell lines. Front. Psychiatry 9, 501.
Soundarapandian, M.M., Wu, D., Zhong, X., Petralia, R.S., Peng, L., Tu, W., Lu, Y., 2007. Expression of functional Kir6.1 channels regulates glutamate release at CA3 synapses in generation of epileptic form of seizures. J. Neurochem. 103, 1982–1988.
Starkov, A.A., 1997. Mild" uncoupling of mitochondria. Biosci. Rep. 17, 273–279.
Stefanatos, R., Sanz, A., 2018. The role of mitochondrial ROS in the aging brain. FEBS Lett. 592, 743–758.
Stein, A., Bailey, S.M., 2013. Redox biology of hydrogen sulfide: implications for physiology, pathophysiology, and pharmacology. Redox Biol 1, 32–39.
Stipanuk, M.H., Beck, P.W., 1982. Characterization of the enzymic capacity for cysteine desulphhydration in liver and kidney of the rat. Biochem. J. 206, 267–277.
Sun, X.L., Zeng, X.N., Zhou, F., Dai, C.P., Ding, J.H., Hu, G., 2008. KATP channel openers facilitate glutamate uptake by GluTs in rat primary cultured astrocytes. Neuropsychopharmacology 33, 1336–1342.
Suzuki, M., Nelson, A.D., Eickstaedt, J.B., Wallace, K., Wright, L.S., Svendsen, C.N., 2006. Glutamate enhances proliferation and neurogenesis in human neural progenitor cell cultures derived from the fetal cortex. Eur. J. Neurosci. 24, 645–653.
Tan, S., Schubert, D., Maher, P., 2001. Oxytosis: a novel form of programmed cell death. Curr. Top. Med. Chem. 1, 497–506.
Tang, X.Q., Chen, R.Q., Ren, Y.K., Soldato, P.D., Sparatore, A., Zhuang, Y.Y., Fang, H.R., Wang, C.Y., 2011. ACS6, a Hydrogen sulfide-donating derivative of sildenafil, inhibits homocysteine-induced apoptosis by preservation of mitochondrial function. Med. Gas Res. 1, 20.
Tang, X.Q., Shen, X.T., Huang, Y.E., Ren, Y.K., Chen, R.Q., Hu, B., He, J.Q., Yin, W.L., Xu, J.H., Jiang, Z.S., 2010. Hydrogen sulfide antagonizes homocysteine-induced neurotoxicity in PC12 cells. Neurosci. Res. 68, 241–249.
Trotti, D., Danbolt, N.C., Volterra, A., 1998. Glutamate transporters are oxidant-vulnerable: a molecular link between oxidative and excitotoxic neurodegeneration? Trends Pharmacol. Sci. 19, 328–334.
Tsugane, M., Nagai, Y., Kimura, Y., Oka, J., Kimura, H., 2007. Differentiated astrocytes acquire sensitivity to hydrogen sulfide that is diminished by the transformation into reactive astrocytes. Antioxidants Redox Signal. 9, 257–269.
Tvedt, B., Skyberg, K., Aaserud, O., Hobbesland, A., Mathiesen, T., 1991. Brain damage caused by hydrogen sulfide: a follow-up study of six patients. Am. J. Ind. Med. 20, 91–101.
Tyagi, N., Moshal, K.S., Sen, U., Vacek, T.P., Kumar, M., Hughes Jr., W.M., Kundu, S., Tyagi, S.C., 2009. H2S protects against methionine-induced oxidative stress in brain endothelial cells. Antioxidants Redox Signal. 11, 25–33.
Wang, F., Zhang, C., Qu, X., Cheng, S., Xian, Y., 2018. Cationic cyanine chromophore-assembled upconversion nanoparticles for sensing and imaging H2S in living cells and zebrafish. Biosens. Bioelectron. 126, 96–101.
Wang, J.F., Li, Y., Song, J.N., Pang, H.G., 2014a. Role of hydrogen sulfide in secondary neuronal injury. Neurochem. Int. 64, 37–47.
Wang, Y., Jia, J., Ao, G., Hu, L., Liu, H., Xiao, Y., Du, H., Alkayed, N.J., Liu, C.F., Cheng, J., 2014b. Hydrogen sulfide protects blood-brain barrier integrity following cerebral ischemia. J. Neurochem. 129, 827–838.
Whiteman, M., Armstrong, J.S., Chu, S.H., Jia-Ling, S., Wong, B.S., Cheung, N.S., Halliwell, B., Moore, P.K., 2004. The novel neuromodulator hydrogen sulfide: an endogenous peroxynitrite 'scavenger'? J. Neurochem. 90, 765–768.
Whiteman, M., Cheung, N.S., Zhu, Y.Z., Chu, S.H., Siau, J.L., Wong, B.S., Armstrong, J.S., Moore, P.K., 2005. Hydrogen sulphide: a novel inhibitor of hypochlorous acid-mediated oxidative damage in the brain? Biochem. Biophys. Res. Commun. 326, 794–798.
Wintner, E.A., Deckwerth, T.L., Langston, W., Bengtsson, A., Leviten, D., Hill, P., Insko, M.A., Dumpit, R., VandenEkart, E., Toombs, C.F., Szabo, C., 2010. A monobromobimane-based assay to measure the pharmacokinetic profile of reactive sulphide species in blood. Br. J. Pharmacol. 160, 941–957.
Woods, J.J., Cao, J., Lippert, A.R., Wilson, J.J., 2018. Characterization and biological activity of a hydrogen sulfide-releasing red light-activated Ruthenium(II) complex. J. Am. Chem. Soc. 140, 12383–12387.
Xiao, F., Zhang, P., Chen, A.H., Wang, C.Y., Zou, W., Gu, H.F., Tang, X.Q., 2016. Hydrogen sulfide inhibits MPP(+)-induced aldehyde stress and endoplasmic reticulum stress in PC12 cells: involving upregulation of BDNF. Exp. Cell Res. 348, 106–114.
Xie, L., Hu, L.F., Teo, X.Q., Tiong, C.X., Tazzari, V., Sparatore, A., Del Soldato, P., Dawe, G.S., Bian, J.S., 2013. Therapeutic effect of hydrogen sulfide-releasing L-Dopa derivative ACS84 on 6-OHDA-induced Parkinson's disease rat model. PLoS One 8, e60200.
Xie, Z.Z., Shi, M.M., Xie, L., Wu, Z.Y., Li, G., Hua, F., Bian, J.S., 2014. Sulfhydration of p66Shc at cysteine59 mediates the antioxidant effect of hydrogen sulfide. Antioxidants Redox Signal. 21, 2531–2542.
Xiong, K., Liao, H., Long, L., Ding, Y., Huang, J., Yan, J., 2016. Necroptosis contributes to methamphetamine-induced cytotoxicity in rat cortical neurons. Toxicol. Vitro 35, 163–168.
Xiong, K., Long, L., Zhang, X., Qu, H., Deng, H., Ding, Y., Cai, J., Wang, S., Wang, M., Liao, L., Huang, J., Yi, C.X., Yan, J., 2017. Overview of long non-coding RNA and mRNA expression in response to methamphetamine treatment in vitro. Toxicol. Vitro 44, 1–10.
Yang, G., Zhao, K., Ju, Y., Mani, S., Cao, Q., Puukila, S., Khaper, N., Wu, L., Wang, R., 2013. Hydrogen sulfide protects against cellular senescence via S-sulfhydration of Keap1 and activation of Nrf2. Antioxidants Redox Signal. 18, 1906–1919.
Yang, X., Wang, Y., Li, Q., Zhong, Y., Chen, L., Du, Y., He, J., Liao, L., Xiong, K., Yi, C.X., Yan, J., 2018. The main molecular mechanisms underlying methamphetamine- induced neurotoxicity and implications for pharmacological treatment. Front. Mol. Neurosci. 11, 186.
Yin, J., Tu, C., Zhao, J., Ou, D., Chen, G., Liu, Y., Xiao, X., 2013. Exogenous hydrogen sulfide protects against global cerebral ischemia/reperfusion injury via its anti-oxidative, anti-inflammatory and anti-apoptotic effects in rats. Brain Res. 1491, 188–196.
Yin, W.L., Yin, W.G., Huang, B.S., Wu, L.X., 2017. Neuroprotective effects of lentivirus-mediated cystathionine-beta-synthase overexpression against 6-OHDA-induced Parkinson's disease rats. Neurosci. Lett. 657, 45–52.
Yong, Q.C., Choo, C.H., Tan, B.H., Low, C.M., Bian, J.S., 2010. Effect of hydrogen sulfide on intracellular calcium homeostasis in neuronal cells. Neurochem. Int. 56, 508–515.
Yuan, Y.Q., Wang, Y.L., Yuan, B.S., Yuan, X., Hou, X.O., Bian, J.S., Liu, C.F., Hu, L.F., 2018. Impaired CBS-H2S signaling axis contributes to MPTP-induced neurodegeneration in a mouse model of Parkinson's disease. Brain Behav. Immun. 67, 77–90.
Zawar, C., Plant, T.D., Schirra, C., Konnerth, A., Neumcke, B., 1999. Cell-type specific expression of ATP-sensitive potassium channels in the rat hippocampus. J. Physiol. 514 (Pt 2), 327–341.
Zhang, J.Y., Ding, Y.P., Wang, Z., Kong, Y., Gao, R., Chen, G., 2017. Hydrogen sulfide therapy in brain diseases: from bench to bedside. Med. Gas Res. 7, 113–119.
Zhang, M., Shan, H., Wang, T., Liu, W., Wang, Y., Wang, L., Zhang, L., Chang, P., Dong, W., Chen, X., Tao, L., 2013. Dynamic change of hydrogen sulfide after traumatic brain injury and its effect in mice. Neurochem. Res. 38, 714–725.
Zhang, X., Bian, J.S., 2014. Hydrogen sulfide: a neuromodulator and neuroprotectant in the central nervous system. ACS Chem. Neurosci. 5, 876–883.
Zhang, Y.P., Cai, J., Shields, L.B., Liu, N., Xu, X.M., Shields, C.B., 2014. Traumatic brain injury using mouse models. Transl. Stroke Res. 5, 454–471.