# Brain, Learning, and Memory: Role of $H_2S$ in Neurodegenerative Diseases

B.V. Nagpure and Jin-Song Bian

## Contents



**Abstract**

For more than 300 years, the toxicity of hydrogen sulfide ($H_2S$) has been known to mankind. However, this point of view is changing as an increased interest was

B.V. Nagpure • J.-S. Bian (✉)
Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore
e-mail: phcbjs@nus.edu.sg



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observed in $H_2S$ biology in the last two decades. The scientific community has succeeded to unravel many important physiological and pathological effects of $H_2S$ on mammalian body systems. Thus, $H_2S$ is now referred to as a third endogenous gaseous mediator along with nitric oxide and carbon monoxide. Acting as a neuromodulator, $H_2S$ facilitates long-term potentiation and regulates intracellular calcium levels, which are important processes in learning and memory. Aberrant endogenous production and metabolism of $H_2S$ are implicated in pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). Various $H_2S$ donors have shown beneficial therapeutic effects in neurodegenerative disease models by targeting hallmark pathological events (e.g., amyloid-β production in AD and neuroinflammation in PD). The results obtained from many in vivo studies clearly show that $H_2S$ not only prevents neuronal and synaptic deterioration but also improves deficits in memory, cognition, and learning. The anti-inflammatory, antioxidant, and anti-apoptotic effects of $H_2S$ underlie its neuroprotective properties. In this chapter, we will overview the current understanding of $H_2S$ in context of neurodegenerative diseases, with special emphasis on its corrective effects on impaired learning, memory, and cognition.

**Keywords**
Hydrogen sulfide • Neurodegeneration • Brain • Memory • Learning • Neuroinflammation

## Abbreviation

| | |
|---|---|
| 3-MST | 3-Mercaptopyruvate sulfurtransferase |
| Aβ | Amyloid-β |
| AD | Alzheimer's disease |
| APP | Amyloid precursor protein |
| CAT | Cysteine aminotransferase |
| CBS | Cystathionine-β-synthase |
| CNS | Central nervous system |
| CSE | Cystathionine-γ-lyase |
| $H_2S$ | Hydrogen sulfide |
| $K_{ATP}$ | ATP-sensitive potassium channel |
| LTP | Long-term potentiation |
| mito$K_{ATP}$ | Mitochondrial $K_{ATP}$ channel |
| NaHS | Sodium hydrogen sulfide |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NMDA | *N*-methyl-D-aspartic acid |
| NSAIDs | Non-steroidal anti-inflammatory drugs |

| | |
|---|---|
| PD | Parkinson's disease |
| ROS | Reactive oxygen species |

## 1 Introduction

Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative diseases share a number of common aspects—old-age onset, hereditary or sporadic appearance, and the aggregation and deposition of misfolded proteins. These diseases show overlapping spectrum of clinical signs and symptoms in their advance stages. In 2005, 24.2 million people worldwide had dementia, which is one of the most common sign of AD. The developed world i.e., North America and Western Europe showed the highest prevalence of dementia. It is estimated that these parts of the world along with China will be home to around 55 % of total affected population worldwide by 2040 (Reitz et al. 2011). The prevalence of dementia grows with age. The extensive Delphi consensus study done by Ferri et al. revealed the growth from 1 % in 60–64 years age group to about 30 % in those of >85 years age group (Ferri et al. 2005). The incidence rate of AD and other dementias also increase exponentially with the age, mirroring the prevalence rate. The worst affected is the seventh and eighth decade of life (Reitz et al. 2011). PD is the second most common neurodegenerative disorder, with incidence rate rising sharply after the age of 60. The prevalence of PD in people over age of 50 is feared to be doubled to approximately nine million by 2030 in the world's most populated and industrialized countries. Placing a great burden on caregivers, AD, PD, and other neurodegenerative diseases are costing dearly to today's society

In recent decades, the scientific community has witnessed the rise of a whole new class of gaseous biological mediators in mammalian cells. These are simple gas molecules, which are lipid soluble and hence freely membrane permeable reaching intracellular organelle. After the seminal discovery of physiological effects of nitric oxide (NO) on blood vessels, carbon monoxide (CO) and hydrogen sulfide ($H_2S$) have been recently recognized as two more "gasotransmitters." The physiological role of $H_2S$ was discovered by a Japanese group of scientists led by Kimura in 1996. In their pioneering study, the novel neuromodulator role of $H_2S$ was transpired (Abe and Kimura 1996). Since then its possible roles in other body systems have been investigated worldwide. In mammalian central nervous system (CNS), its prominent effects include modulation of neurotransmission and long-term potentiation (LTP) (Abe and Kimura 1996) and induction of neuroprotection (Hu et al. 2011) from myriad of pathogenic agents. In mammalian cardiovascular system (CVS), its protective effects are deeply studied (Pan et al. 2006; Hu et al. 2008; Liu et al. 2012; Polhemus et al. 2014). The induction of relaxation (Lee et al. 2007; Yang et al. 2008) and constriction (Lim et al. 2008; Kohn et al. 2012) in various types of blood vessels is also documented (d'Emmanuele di Villa Bianca et al. 2011). The opposite effects of $H_2S$ on systemic and localized inflammation have been observed in various mammalian tissues (Hegde and Bhatia

2011; Whiteman and Winyard 2011). In this book chapter, we will discuss the well-accepted and latest findings pertaining to neurophysiological and neuropharmacological effects of $H_2S$.

## 2 $H_2S$

### 2.1 Physical and Chemical Properties

At room temperature and ambient pressure, $H_2S$ exists in a colorless gaseous form. The smell is pungent with distinctive rotten-egg odor. It is readily water soluble due to its weak acidic nature. Its solubility was measured to be 80 mM at 37 °C as equilibrium between $H_2S$, $HS^-$, and $S^{2-}$. The acid dissociation constant ($pK_a$) values of the first and second dissociation steps are recorded as 7.0 and >12.0, respectively (Vorobets et al. 2002; Kabil and Banerjee 2010; Mark et al. 2011). Thus, at physiological pH of 7.4 $H_2S$ exists majorly as $HS^-$ moiety along with minor presence of free $H_2S$ in its dissociated form. The minute amounts of sulfide anions ($S^{2-}$) can also be detected. Even with the advent of various methods of $H_2S$ measurement, it is almost impossible to determine the active form of $H_2S$ ($H_2S$, $HS^-$, or $S^{2-}$) present in the biological system. Hence the all-encompassing term of $H_2S$ is now used to refer the total sulfide content present in the solution (i.e., $H_2S + HS^- + S^{2-}$) (Zhao et al. 2014).

### 2.2 Biosynthesis in Mammalian CNS

In mammalian tissues, $H_2S$ is biosynthesized from amino acid cysteine (Cys) and homocysteine (Hcy), which are recognized as the principle substrates for its endogenous production. They are acted upon by three different enzymes, namely cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfur transferase (3-MST) (Hu et al. 2011). Expressions of these enzymes are variable in different tissues. The study of this variation is important as the modulation of endogenous production of $H_2S$ can be achieved by targeting each enzyme separately or concurrently.

CBS, a pyridoxal-5′-phosphate (PLP)-dependent enzyme, is abundantly expressed in brain and is the key source of $H_2S$ there (Abe and Kimura 1996). The levels of CBS expression vary according to the stages of development. While the levels are low during embryonic brain, they increase notably from the late prenatal to the early postnatal period. After adulthood is reached, its level declines again (Enokido et al. 2005). Initially, the neuronal localization of CBS was demonstrated in major areas of brain including the hippocampus and the cerebellum (Robert et al. 2003). However, further study by Enokido et al. and Lee et al. revealed that $H_2S$ is preferentially expressed in radial glia/astrocyte lineage of developing mouse brain (Enokido et al. 2005; Lee et al. 2009). In support of these findings, CBS has been found to be elevated in reactive astrocytes (Kimura and Kimura 2004). CBS initiates the *trans*-sulfuration pathway by catalyzing

β-replacement of serine by Hcy to generate cystathionine and water. Furthermore, serine replacement by Cys as a substrate results into production of cystathionine and $H_2S$. Besides above-mentioned *trans*-sulfuration pathway, CBS also catalyzes condensation reactions between two molecules of Cys and β-replacement of Cys by water to produces $H_2S$ (Kabil and Banerjee 2014). The reaction replacing Hcy by Cys yields maximum generation (~96 %) of $H_2S$ in vitro. Whereas the minor share of 1–3 % is contributed by condensation reactions between two molecules of Cys (Singh et al. 2009).

CSE is yet another PLP-dependent enzyme, which mediates a reaction between thiocysteine and a thiol compound R-SH to generate $H_2S$ (Kimura 2011). The substrate thiocysteine is generated from L-cystine which in turn is produced by two L-cysteine molecules (Yamanishi and Tuboi 1981). Expression of CSE is rather widely distributed among peripheral tissues including liver, pancreas, uterus, and intestine (Kimura 2011). The activity of CSE in the human brain is 100 folds higher than mouse brain and it plays an important role in CNS physiology (Diwakar and Ravindranath 2007). CSE is a rate-limiting enzyme during the generation of Cys from methionine in *trans*-sulfuration pathway. The availability of Cys is an essential factor in glutathione (GSH) synthesis, which in turn is needed for mitochondrial function preservation to maintain redox homeostasis in cells. Thus CSE offers neuroprotection against oxidative stress by maintaining GSH and protein thiol homeostasis (Diwakar and Ravindranath 2007). Under physiologic conditions, CSE generates $H_2S$ mainly from Cys. However under hyperhomocysteinemic (abnormally high level of homocysteine in the blood) conditions, Hcy (γ-elimination) becomes its major substrate taking over Cys. This alteration might be responsible for elevated production of $H_2S$ in severe hyperhomocysteinemic conditions (Singh et al. 2009). Hence, it is probable that CSE becomes a major enzyme to produce $H_2S$ in conditions like hyperhomocysteinemia (Hu et al. 2011), which incidentally is a common feature of neurodegenerative diseases including AD and PD.

The third enzyme, 3-mercaptopyruvate sulfotransferase (3-MST), was identified in the neurons. The research group detected the significant presence of $H_2S$ in the brain homogenate preparation of $CBS^{-/-}$ mice (Shibuya et al. 2009). Kimura further observed that 3-MST acts together with cysteine aminotransferase (CAT) to generate $H_2S$ from Cys in the presence of α-ketoglutarate (Kimura et al. 2010). However, it is suggested that 3-MST is unable to produce $H_2S$ in normal physiological conditions as they exert their activities at higher alkaline pH level (Shibuya et al. 2009). Furthermore, it requires endogenous reducing substances such as thioredoxin and dihydrolipoic acid (DHLA) for the production of $H_2S$ (Kimura 2014). Aspartate can also act as a substrate for CAT, competitively binding to it and attenuating $H_2S$ synthesis (Guo et al. 2012).

Recently, Shibuya et al. discovered the additional pathway for $H_2S$ biosynthesis in mammalian cells. 3-MST along with D-amino acid oxidase (DAO) produces $H_2S$ from D-cysteine by the interaction of mitochondria and peroxisomes. It was evident that this D-cysteine-dependent pathway operates predominantly in the cerebellum and the kidney. The protective effects of D-cysteine were observed against oxidative

stress in cerebellar neurons and against ischemia-reperfusion injury in the kidney (Shibuya and Kimura 2013).

### 2.3 Storage and Metabolism

Although endogenous $H_2S$ can be synthesized and released immediately, the storage forms of $H_2S$ are also known. Acid-labile sulfur is primarily contained in iron-sulfur center of mitochondrial enzymes and can release $H_2S$ only in acidic pH of 5.4. Due to higher instability of iron-sulfur complexes, the release of $H_2S$ is readily achieved. Bound sulfane sulfur, which is localized in cytoplasm, consists of divalent sulfur bond (e.g., persulfide form). It releases $H_2S$ under reducing conditions of pH 8.4 (Ishigami et al. 2009). It is possible that $H_2S$ produced by 3-MST/CAT enzymatic pathway is stored in the bound sulfane sulfur form. The decreased amount of bound sulfane sulfur has been detected in cells without 3-MST/CAT compared to the cells with 3-MST/CAT (Shibuya et al. 2009).

$H_2S$ is catabolized in mammalian cells though various pathways. The major mechanism is through its mitochondrial oxidation in different tissues (Hildebrandt and Grieshaber 2008). In a reaction catalyzed by quinone oxidoreductase enzyme, $H_2S$ is converted into persulfides. Persulfides are, in turn, oxidized in sulfite and thiosulfite. In physiological normoxic conditions, the thiosulfite is further metabolized into excretable form of sulfate. $H_2S$ catabolism by quinone oxidoreductase enzyme seems to be universal in mammalian tissues, with possible exception of the brain (Mikami et al. 2011). $H_2S$ can also be methylated to produce methane thiol by the action of enzyme thiol-*S*-methyltransferase. Non-mitochondrial heme proteins such as hemoglobin and myoglobin also catabolize intracellular $H_2S$ by oxidation (Berzofsky et al. 1971; Stein and Bailey 2013). To a weaker extent, $H_2S$ can also interact with reactive oxygen and nitrogen species. It is interesting to know that the presence of oxygen ($O_2$) is a very influential factor in deciding the fate of cellular $H_2S$ as $O_2$ is capable of spontaneous oxidization of $H_2S$ (van Kampen and Zijlstra 1983; Stein and Bailey 2013). The intracellular concentration of $H_2S$ is kept firmly in low range, owing to the highly efficient nature of above-mentioned mechanisms.

## 3 Protective Roles of $H_2S$ in CNS

The molecular basis of protective effects of $H_2S$ in CNS during neurodegenerative diseases has received a considerable attention in recent years. This section summarizes the major protective effects of $H_2S$ in CNS with brief discussion about underlying molecular mechanism (Fig. 1).

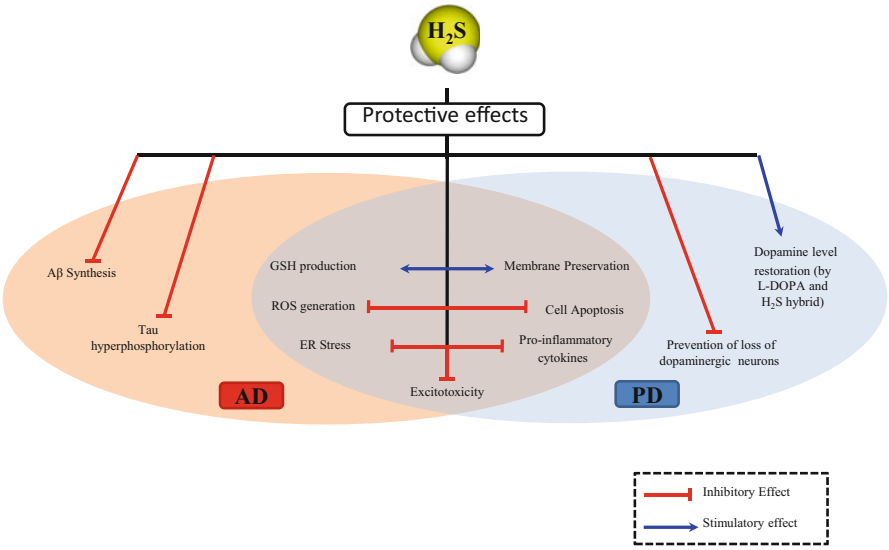


**Fig. 1** The various targets of $H_2S$ for its neuroprotective effects in the neurodegenerative diseases. The hallmark events in AD pathology i.e., Aβ generation and tau hyperphosphorylation are downregulated by $H_2S$. $H_2S$ donors and hybrids produce positive therapeutic effects in PD pathology as well. Apart from reducing loss of neurons in substantia nigra of striatum, it also restores dopamine levels. $H_2S$ elevates the intracellular levels of glutathione (GSH) while preserving membrane integrity, thus making neurons less susceptible to cellular injury. $H_2S$ is also shown to prevent excessive cellular apoptosis, lower oxidative stress, reduce neuroinflammation by several pro-inflammatory cytokines, and prevent cells from excitotoxicity caused by aberrant neurotransmitter release from neurons and astrocytes

## 3.1 Anti-Inflammation

Neuroinflammation is strongly implicated in the pathologies of all major neurodegenerative diseases. The non-neuronal cells like microglia, astrocytes, and oligodendrocytes constitute the microenvironment under which normal neuronal functions are kept smoothly running. However, in case of any pathological or toxic insult, their over/chronic activation can initiate many unwanted and potentially neurotoxic cascades.

The pioneering work of Hu et al. revealed the anti-inflammatory properties of $H_2S$ in lipopolysaccharide (LPS)-induced neuroinflammation in both primary cultured microglia and immortalized murine BV-2 microglial cells (Hu et al. 2007). In support of above findings, other studies also demonstrated the anti-inflammatory effects of $H_2S$-releasing NSAIDs in various neurodegenerative disease models. Although there is a lot to be done in order to completely reveal the underlying mechanisms of anti-inflammatory effect of $H_2S$, above-mentioned and other studies implicated inhibition of nuclear factor-kappa B (NF-κB) and MAPK signaling cascades in the observed effects. Additionally, in an interesting study analyzing the neuroprotective effects of *S*-propargyl-cysteine (a novel $H_2S$-modulating agent),

its inhibitory effects on tumor necrosis factor (TNF)-α and TNF-α receptor 1 (TNFR1) were demonstrated (Gong et al. 2011). Earlier this year, Zhao et al. shed some light upon a previously unrecognized mechanism underlying $H_2S$ suppression of neuroinflammation. They found that $H_2S$ polarized microglia to an anti-inflammatory (M2) phenotype by activating calmodulin-dependent protein kinase kinase β (CaMKKβ)-dependent AMP-activated protein kinase (AMPK) (Zhou et al. 2014). By suppressing neuroinflammation, $H_2S$ imparts improvement in learning and spatial memory in various animal models of AD (Xuan et al. 2012; He et al. 2014).

## 3.2 Anti-Oxidation

The brain is highly prone to oxidative stress than other organs in mammalian body (Chance et al. 1979). Accounting for relatively small fraction of body weight (2 %), it is constantly supplied with large amount of total body oxygen consumption (20 %) and total body glucose (25 %) in order to maintain high metabolic turnover (Uttara et al. 2009). During the mitochondrial generation of ATP via oxidative pathway, huge amount of ROS and hydrogen peroxide ($H_2O_2$) are generated. Furthermore, the biochemical structure of neurons makes them particularly vulnerable to ROS. The double bonds present in abundant unsaturated fatty acids are easily susceptible to peroxidation (Butterfield et al. 2002). To worsen the conditions, brain is not equipped with high antioxidant activity. Additionally, the higher concentration of iron and vitamin C in various regions of brain leads to increased interaction between $O_2$ and metal ions, culminating in ROS generation (Floyd and Carney 1992).

Oxidative stress caused by overproduction of ROS is detrimental and one of the etiological factors of many neurodegenerative diseases. Kimura et al. found that $H_2S$ protects primary neurons from oxidative glutamate toxicity (oxytosis) caused by glutamate. $H_2S$ elevated antioxidant GSH levels by enhancing the activity of gamma-glutamylcysteine synthetase and upregulating cystine transport. The upregulation of gamma-glutamylcysteine synthetase activity facilitates the redistribution of GSH into mitochondria, thus protecting cells against oxidative stress damage (Kimura and Kimura 2004). Later, the same group also discovered that $H_2S$ protects immortalized mouse hippocampal cells from oxytosis by activating ATP-dependent $K^+$ ($K_{ATP}$) and $Cl^-$ channels (Kimura et al. 2006). A study conducted by Lu et al. demonstrated that $H_2S$ protects astrocytes via enhancing glutamate uptake function of glutamate transporter-1 and elevating GSH production. This phenomenon prevents excessive accumulation of glutamate in synaptic clefts protecting neurons from excitotoxicity (Lu et al. 2008). Besides these, $H_2S$ has been show to downregulate peroxynitrite-mediated tyrosine nitration and inactivation of alpha1-antiproteinase inhibiting peroxynitrite-induced cytotoxicity, intracellular protein nitration, and protein oxidation in human neuroblastoma SH-SY5Y cells (Whiteman et al. 2004).

### 3.3 Anti-Apoptosis

Apart from antioxidant effects, $H_2S$ is also known to possess anti-apoptotic properties conferring neuroprotection. Hu and colleagues discovered that $H_2S$ inhibits apoptosis induced by rotenone (a toxin used to establish PD model) by preserving mitochondrial functions in human neuroblastoma cell line (SH-SY5Y). They observed that $H_2S$ regulated the mito$K_{ATP}$ channel and thus impeded the apoptosis cascade (prevention of mitochondrial membrane potential (MMP) dissipation, cytochrome c release, and caspase-9/3 activation) (Hu et al. 2009). The anti-apoptotic effect was supported by other studies as well. Zhang et al. found out that $H_2S$ attenuated neuronal injury induced by vascular dementia via inhibiting apoptosis in rats (Zhang et al. 2009). In yet another study, $H_2S$ imparted the cytoprotective effect to PC12 cells against amyloid β (25–35)-induced apoptosis (Tang et al. 2008).

## 4 $H_2S$ in Neurodegenerative Diseases

### 4.1 AD

AD is the most common neurodegenerative disease in today's society (Reitz et al. 2011). Classically, AD pathology is characterized by aggregation and deposition of Aβ plaques along with hyperphosphorylated tau in the brain (Goedert and Spillantini 2006).

More and more evidences are coming into light depicting a certain relevance of endogenous $H_2S$ generation and AD pathology. In the very first study of its kind, Morrison et al. showed that concentration of *S*-adenosylmethionine, a CBS activator, was notably depleted in brains of AD patients (Morrison et al. 1996). It was later found out that any interference in *trans*-sulfuration pathway (please refer to Sect. 2.3 of this chapter) results in both elevation in total serum Hcy (Clarke et al. 1998) and depletion in $H_2S$ production (Dwyer et al. 2004) in AD patients. It should also be noted that Hcy neurotoxicity itself inhibits CBS, reducing $H_2S$ production (Tang et al. 2011). Furthermore, an extensive clinical study conducted by Liu et al. has proven the direct correlation between severity of AD and $H_2S$ (Liu et al. 2008).

Recently, many studies have shown that $H_2S$ affects amyloidogenesis in the brain. The downregulated generation of Aβ was observed in primary neuron culture (Zhu et al. 2014), SH-SY5Y neuroblastoma cell line (Nagpure and Bian 2014), and APP/PS1 transgenic mice (He et al. 2014). Aβ is synthesized by sequential enzymatic cleavage of amyloid precursor protein (APP). Besides suppressing the expression of APP (Nagpure and Bian 2014), $H_2S$ has also been reported to inhibit the activities and expressions of the cleaving enzymes, BACE1 (Zhang et al. 2011) and γ-secretase (Nagpure and Bian 2014). In an interesting study investigating the effects of $H_2S$-rich Tabiano's spa-water on three experimental models of AD, Giuliani et al. found the lowered phosphorylation of tau protein at Thr181,

Ser396, and Ser202. In this particular study they also observed anti-amyloidogenic effects of $H_2S$ in AD mouse model harboring human transgenes APPSwe, PS1M146V, and tauP301L (Giuliani et al. 2013). The therapeutic strategy of tau manipulation is of great interest. Many studies have revealed that heat-shock proteins (Hsps), the molecular chaperone families, are involved in prevention of tau aggregation and tau degradation (Thompson et al. 2012; Voss et al. 2012). As $H_2S$ is known to elevate the expression of hsp90 (Xie et al. 2012), it is possible that $H_2S$ could be used as a tau aggregation inhibitor to maintain intracellular microtubule infrastructure

$H_2S$ targets multiple processes underlying AD pathology (Fig. 2) while exerting its neuroprotective effect. Hence $H_2S$ can be of potential therapeutic value in treatment of AD.

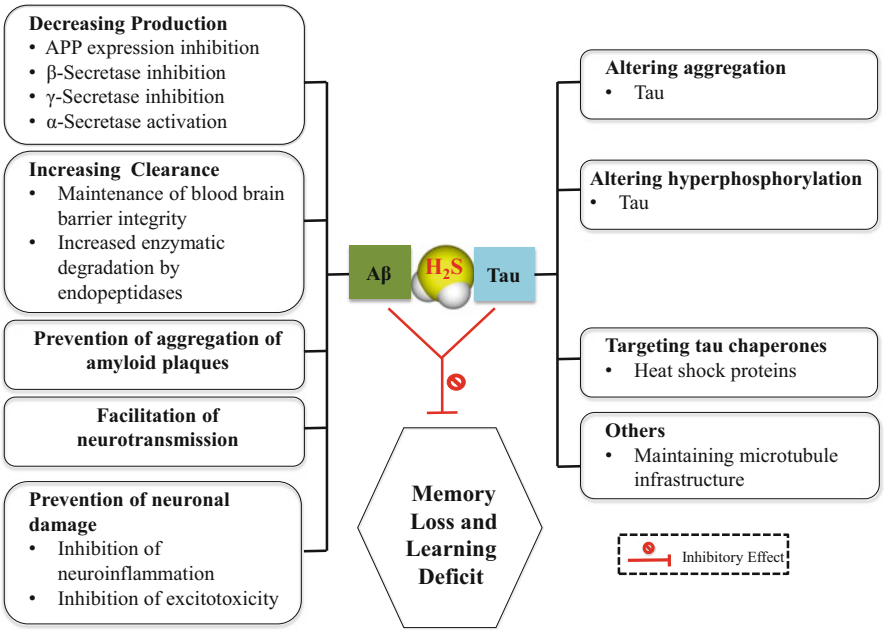


**Fig. 2** Effect of $H_2S$ on Aβ and tau aggregation and its potential role in prevention of memory loss and learning disabilities. $H_2S$ inhibits aggregation of amyloid protein by decreasing the amyloid burden and enhancing its clearance. $H_2S$ facilitates neurotransmission by acting as a neuromodulator. It also inhibits the production of several pro-inflammatory cytokines, maintaining the microenvironment in which neurons can function properly. By preventing hyperphosphorylation of tau proteins and inhibiting tau chaperons (Hsps), $H_2S$ can inhibit its aggregation into neurofibrillary tangles and preserve intracellular microtubule infrastructure

## 4.2 Vascular Dementia

Vascular dementia (VD), a heterogeneous group of brain disorders in which cognitive impairment is attributable to cerebrovascular pathologies, is responsible for at least 20 % of cases of dementia, being second only to AD (Gorelick et al. 2011; Iadecola 2013). Zhang et al. suggest that $H_2S$ could protect the brain against VD injury induced by cerebral ischemia reperfusion through inhibiting the apoptosis in the hippocampus. They found that NaHS-treated rats had a greater ratio of Bcl-2 (anti-apoptotic) over Bax (pro-apoptotic) with increased Bcl-2 expression and decreased Bax expression in the hippocampus (Zhang et al. 2009). It is generally believed that inflammation (Malaguarnera et al. 2006; Liu et al. 2007), oxidative stress (Liu et al. 2007), and vascular factors (Brown et al. 2007; Stephan and Brayne 2008) play important roles in the VD pathology. As discussed earlier in this chapter, $H_2S$ possesses potent anti-inflammatory (Hu et al. 2007) and anti-oxidative action (Kimura and Kimura 2004). Hence, it appears that $H_2S$ may protect against VD injury by targeting multiple signaling pathways and events.

## 4.3 PD

PD is the second most common neurodegenerative disease histopathologically characterized by progressive degeneration of dopaminergic neurons in substantia nigra of midbrain.

Many studies indicate that hyperhomocysteinemia is common in the patients of PD (O'Suilleabhain et al. 2004; Zoccolella et al. 2010). Various in vivo experiments in PD animal models detected reduced levels of $H_2S$ in substantia nigra and striatum regions of the brain. These findings suggest that impaired endogenous production of $H_2S$ has a substantial effect on pathogenesis and progression of PD. Furthermore, the administration of exogenous $H_2S$ has shown protective effects against underlying pathologic mechanisms. The study conducted by Yin et al. demonstrated that NaHS, a fast $H_2S$ donor, protected PC12 cells from cytotoxicity and apoptosis induced by MPP+, the active metabolite of MPTP. They found that $H_2S$ inhibited the loss of MMP and the accumulation of intracellular ROS (Yin et al. 2009). Recently, Xie et al. evaluated the therapeutic effects of ACS 84, a $H_2S$-releasing L-DOPA derivative, in a 6-OHDA-induced PD model (Xie et al. 2013). In this study, they observed that ACS84 not only attenuated 6-OHDA-induced cell injury and ROS production but also downregulated antioxidant enzyme expression. These results bolster the initial findings of Calvert and colleagues (Calvert et al. 2009) about upregulation of endogenous antioxidants by $H_2S$ via stimulation of nuclear-factor-E2-related (Nrf2)-dependent signaling pathway. Previously, it was shown that pretreatment with NaHS could suppress rotenone-induced cellular injury and apoptotic cell death in human neuroblastoma SH-SY5Y cells via regulation of mito$K_{ATP}$ channel/p38- and JNK-MAPK pathway (Hu et al. 2009). In yet another study using neurotoxin 6-OHDA to induce PD

model, $H_2S$ was shown to inhibit cell injury by stimulating prosurvival PKC/PI3K/Akt pathway (Tiong et al. 2010).

These findings in vitro studies were supported by the observations done in animal models of PD. Hu et al. found out that the systemic administration of NaHS dramatically reversed the progression of movement dysfunction, loss of tyrosine-hydroxylase (TH)-positive neurons in the striatum, and the elevated malondialdehyde level in injured striatum caused by 6-OHDA or rotenone (Hu et al. 2010). Inhaled $H_2S$ also prevented the MPTP-induced movement disorder and the degeneration of TH-containing neurons by upregulating heme oxygenase-1 and glutamate-cysteine ligase (Kida et al. 2011). The anti-inflammatory, antioxidant, and neuroprotective properties shown by new $H_2S$ releasing hybrids are encouraging, thus making them ideal candidates for PD treatment. ACS 84, a well-known L-DOPA hybrid, has been effective in reducing the release of pro-inflammatory cytokines and NO from stimulated microglia and astrocytes (Lee et al. 2010). Besides relieving from inflammation, $H_2S$-releasing L-DOPA hybrids also restore the depleted dopamine levels by inhibiting mono-amine oxidase B activity (Sparatore et al. 2011).

These findings highlight the potential therapeutic benefit of $H_2S$ in PD which can be achieved either by the administration of exogenous $H_2S$ or the modulation of endogenous $H_2S$ production.

## 5 Learning and Memory

The life-long thoughts, behavior, and actions of humans are mostly controlled by two processes occurring in CNS: learning and memory. The intrinsic cellular mechanisms are different for learning (procurement), consolidation, and evocation of memories (Kandel 2001). Notably, the modifications of synaptic connectivity, in terms of number and structures of synapses, are probably the underlying mechanisms for learning and memory. The ability of synaptic plasticity of neurons relies heavily on many intracellular secondary signaling pathways. Therefore, modulation of synthesis of proteins involved in activation and/or deactivation of signal transduction pathways in CNS plays a key role in the processes of learning and memory (Milner et al. 1998).

### 5.1 Endogenous $H_2S$ Levels: Relation with Learning and Memory

As mentioned earlier, $H_2S$ is generated endogenously in brain, including hippocampus. It is a small but an important region primarily associated with learning and memory functions. The intracellular concentrations of a CBS activator, *S*-adenosylmethionine (SAM), were found to be decreased in AD brains than those in the normal brains (Morrison et al. 1996). In an extensive clinical study conducted in many patients of AD and VD, the plasma $H_2S$ levels were demonstrated to be significantly lower than the normal controls (Liu et al. 2008). In accordance, Eto

et al. showed that the levels of $H_2S$ are drastically declined in the brains of AD patients compared with those of the age-matched normal individuals (Eto et al. 2002). A recent work characterized the levels of $H_2S$ at various time points through the development and progression of AD in double-transgenic APP/PS1 mice. This research group observed the decreased levels of $H_2S$ and protein expression of CBS in the cortex and hippocampus of 9- and 12-month-old AD mice (He et al. 2014). Thus, the plasma $H_2S$ concentration is directly correlated with the severity of memory-related symptoms of AD

## 5.2 Effect of $H_2S$ on Glutamatergic Neurotransmission

The interaction of $H_2S$ with the glutamatergic neurotransmission is well established. Kimura et al. found that $H_2S$ enhances the responses of NMDA receptors to the neurotransmitter glutamate in neurons (Abe and Kimura 1996). According to the previously published studies, $H_2S$ protects brain cells from death due to elevated glutamate levels in synapses. The underlying mechanism is via enhancing glutamate uptake function by glutamate transporters (Lu et al. 2008). It is well known that $H_2S$ attenuates the development of opioid dependence and alleviates heroin withdrawal symptoms in animals. The neural mechanism involved in these effects is closely related to inhibition of cAMP/PKA pathway (Jiang et al. 2012; Yang et al. 2013). Although this is the case, the modulation of the glutamatergic system can also be involved since presynaptic glutamate synaptic transmission by NMDA receptors is regulated directly by μ-opioid receptors (Garzon et al. 2012). Thus, these results signify the importance of $H_2S$ in modulating adaptations in the brain glutamatergic system involved in synaptic plasticity.

## 5.3 Role of $H_2S$ in Intracellular Calcium ($[Ca^{2+}]i$) Regulation

Many research groups have evaluated possible mechanisms by which $H_2S$ modulates learning and memory processes. The effect of $H_2S$ on $[Ca^{2+}]i$ homeostasis deserves a special mention here. $[Ca^{2+}]i$ is critical for normal neuron-glia communication and regulation of synaptic plasticity. It has been found that $H_2S$ is capable of regulating $[Ca^{2+}]i$ in all important brain cell types, namely neurons (Yong et al. 2010), microglia (Lee et al. 2006), and astrocytes (Nagai et al. 2004). LTP is considered as a major cellular mechanism underlying the learning and memory functions. Kimura et al. discovered that the physiological concentrations of $H_2S$ selectively enhance NMDA receptor-mediated currents and facilitate the induction of hippocampal LTP (Abe and Kimura 1996). L-type calcium channels contribute to LTP and fear memory formation (Bauer et al. 2002). Furthermore, they are essential in both the acquisition and retrieval of long-term recognition memory (Seoane et al. 2009). $H_2S$ activates L-type calcium channels and NMDA receptors on plasma membrane (Lee et al. 2006). Yong et al. discovered that the

action of $H_2S$ on $[Ca^{2+}]i$ can be suppressed by using inhibitors of PKA, phospholipase C (PLC), and protein kinase C (PKC), suggesting the role of PKA and PLC/PKC pathways in the regulatory effect of $H_2S$ on $[Ca^{2+}]i$ (Yong et al. 2010) and possibly on functions of learning and memory. Voltage-gated $Ca_V2.1$ (P/Q-type) $Ca^{2+}$ channels are essential in modulation of processes such as neurotransmitter release and synaptic plasticity. It was found that context-associated memory retrieval was dependent on these particular $Ca^{2+}$ channels (Chen et al. 2012). Mallmann et al. observed deficits in spatial learning and reference memory, reduced recognition memory in the forebrain-specific $Ca_V2.1$ knockout mice (Mallmann et al. 2013). Interestingly these channels are also believed to be involved in AD pathology as Aβ downregulates $Ca_V2.1$ channels, thus blocking $Ca^{2+}$ current (Nimmrich et al. 2008; Nimmrich and Ebert 2009). Furthermore, Gangarossa suggested the potential functional involvement of these specific $Ca^{2+}$ channels in many brain disorders as the physiological activity of these specific $Ca^{2+}$ channels is required for affective and cognitive behaviors (Gangarossa et al. 2014). $H_2S$ can modulate the activity of voltage-gated $Ca^{2+}$ channels. A recent study conducted by Sekiguchi et al. demonstrated that the function of these channels is tonically enhanced by endogenous $H_2S$ synthesized by CSE in HEK293 cells transfected with Cav3.2, and that exogenous $H_2S$ is capable of enhancing Cav3.2 function when endogenous $H_2S$ production by CSE is inhibited (Sekiguchi et al. 2014).

## 5.4 Neuroinflammation and Other Factors

Neuroinflammation involves elevated production of myriad of pro-inflammatory cytokines, ROS, and activation of apoptotic pathways. These events lead to neurodegeneration as they negatively impact the functions of neurons, which affect the processes of learning and memory. In various behavior studies, it has been seen that the $H_2S$ reverses neuroinflammatory changes, ultimately repairing the cognitive and memory impairments.

In the initial studies done in rat models of neuroinflammation, exogenous administration of $H_2S$ in the form of NaHS (Gong et al. 2010) or *S*-propargyl-cysteine (SPRC) (Gong et al. 2011) ameliorated LPS-induced cognitive impairment as evaluated in the Morris water maze test. Shortly afterwards, Tang et al. demonstrated that the disturbances in endogenous $H_2S$ generation played a pivotal role in formaldehyde-induced deficits in memory and cognition in animals (Tang et al. 2013). These results were confirmation of the findings of other study in which the neurotoxic effects of Hcy were investigated. Elevated plasma level of Hcy is a known risk factor for AD. The spatial memory acquisition and spatial learning as evaluated by probe trial and hidden-platform acquisition tests, respectively, showed that Hcy decreases spatial learning ability and memory of rats. They also employed novel object recognition test to study short-term, declarative memory and attention. Hcy, by decreasing endogenous production of $H_2S$, significantly decreased the discrimination index of rats in novel object recognition test highlighting the unsuccessful retention of memory of familiar objects (Tang

et al. 2011). Furthermore, the intraperitoneal administration of $H_2S$ attenuated the spatial memory impairment in Aβ rat model of AD (Xuan et al. 2012). In continuation of their previous study, Xuan et al. demonstrated that the application of exogenous $H_2S$ resulted in improved spatial learning and memory acquisition in double-transgenic APP/PS1 mice, an established animal model of AD (He et al. 2014)

## 6 Toxicity of $H_2S$

Although $H_2S$ is produced endogenously in the brain and plays important biological functions, one should bear in mind that long-term treatment of neurodegenerative diseases may potentially cause brain $H_2S$ accumulation and therefore neurotoxicity. Previous studies have shown that the exposure-response curve of $H_2S$ is steep, and thus concentration of inhaled gas is more important compared to the duration of exposure (Prior et al. 1988; Guidotti 1996). The approximate concentrations (exposure levels) of inhaled $H_2S$ for the major toxicological effects are given in Fig. 3. The toxidrome (i.e., a set of symptoms and signs associated with a particular poison) of $H_2S$ is often considered as one of the most unusual and reliable toxidromes (Wang 1989; Milby and Baselt 1999). It is characterized by the "knockdown" (acute central neurotoxicity), pulmonary edema, conjunctivitis, and odor perception followed by respiratory paralysis (Guidotti 2010). Acute toxicity leading to reversible unconsciousness caused by $H_2S$ inhalation is called as "knockdown" (Guidotti 1996). Although knockdowns can be fatal in the cases of prolonged high-concentration exposure (about 500–1000 ppm), the transient exposure is often reversible and apparently complete functionally (Burnett et al. 1977). Pulmonary edema is a well-recognized effect of acute $H_2S$ toxicity. As $H_2S$ has relatively low solubility, it penetrates deeply into respiratory track, causing alveolar injury culminating in acute pulmonary edema (Guidotti 2010). The conjunctivitis caused by prolonged low-concentration exposure (about 20 ppm) (Lambert et al. 2006) is peculiarly associated with reversible chromatic distortion and visual changes. These symptoms are sometimes accompanied by blepharospasm and photophobia (Tansy et al. 1981; Milby and Baselt 1999). $H_2S$ is an odorous gas at low concentration (0.01–0.3 ppm). As the concentration increases, however, the victims start to experience olfactory fatigue. It is a sensory adaptation where the victims get accustomed to strong odor. At around 100 ppm concentration, $H_2S$ paralyzes the olfactory mechanism, preventing perception of any smell. This phenomenon removes the primary warning sign of $H_2S$ exposure (Ronk and White 1985; Turner et al. 1990).

The primary mechanism underlying $H_2S$ toxicity is the inhibition of mitochondrial respiratory chain by $HS^-$ (a hydrogen sulfide ion). $HS^-$ binds to ferric iron ($Fe^{3+}$) of cytochrome oxidase C. It culminates into sulfmethemoglobinemia, lactic acidosis, and hypoxia (Sastre et al. 2013). $H_2S$ is not completely oxidized by brain, making it most vulnerable for the toxic effects. Initially, this pattern seemed identical to that observed in case of cyanide (HCN) poisoning (Dorman et al. 2002).

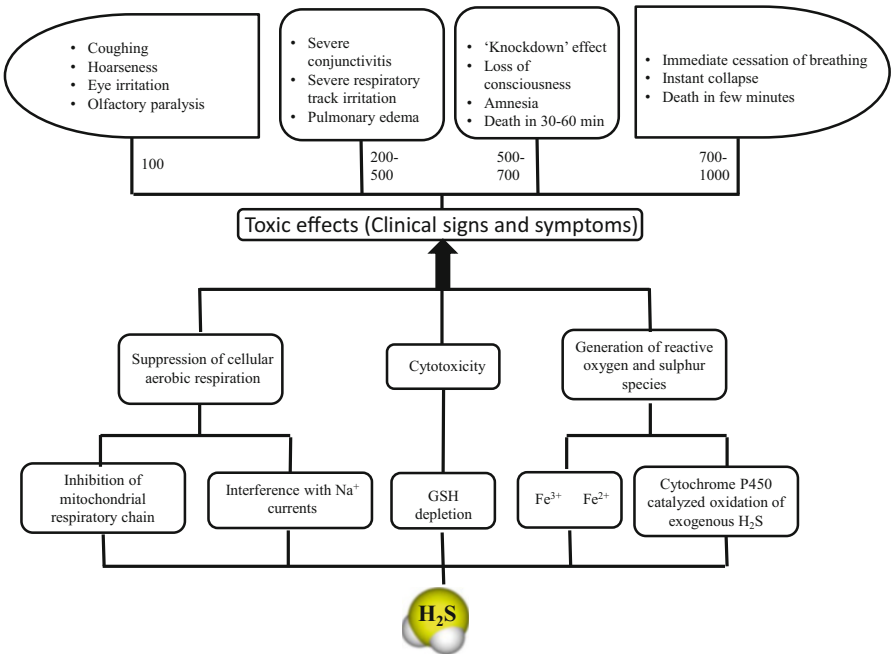


**Fig. 3** Toxicity of $H_2S$. The spectrum of toxic effects of $H_2S$ spans from mild irritation of eyes and respiratory tract to immediate deaths. The severity of symptoms depends on the exposure levels as depicted in the figure. The "toxidrome" of $H_2S$ is often considered as fairly constant and reliable. The underlying molecular mechanisms for toxicity are varied. Along with suppression of cellular aerobic respiration, excessive generation of reactive molecules is proposed as primary mechanisms. The depletion of cytoprotective GSH also makes cells vulnerable for cellular injury

However, the anomalies began to appear when methemoglobin treatment did not yield effective results in cases of $H_2S$ poisonings, despite its successful use in HCN poisoning (Truong et al. 2006). Hence, many other underlying mechanisms were proposed. Warenycia et al. demonstrated that $H_2S$ interferes with sodium currents by abolishing sodium channel function, which might be responsible for depletion of cellular respiration in $H_2S$ poisoning (Warenycia et al. 1989). $H_2S$ was also found responsible for reduction of bound form of iron (ferric, $Fe^{3+}$) to free ferrous ($Fe^{2+}$) form. This along with cytochrome P450-catalyzed oxidation of the exogenous $H_2S$ compound resulted into reactive sulfur and oxygen species generation. The concurrent depletion of GSH made neuronal cells more susceptible to neurotoxicity (Truong et al. 2006).

## 7 Concluding Remarks

The prevalence and morbidity of neurodegenerative diseases are increasing at rapid pace across the globe. Despite the investigations studying the therapeutic effects of $H_2S$ are still in their infancy, plentiful evidence has proven a protective role for this gasotransmitter in the pathology of neurodegenerative diseases. However, our present knowledge on neuroprotection offered by $H_2S$ mainly comes from cell and animal studies with the use of $H_2S$ donors and inhibitors of endogenous $H_2S$. Whether the therapeutic effects of these donors and inhibitors in "bench" studies can be transferred to "bedside" clinical studies needs to be explored. Additionally, more information about drug safety and toxicity due to long-term $H_2S$-based therapeutic approaches is desirable. The development of $H_2S$-releasing drug with a sustained and controlled release is necessary due to non-physiological rapid generation of $H_2S$ by most $H_2S$ donors. Thorough understanding of these problems will enable us to study underlying mechanisms still deeper, and formulate $H_2S$-based therapeutic interventions to treat neurodegenerative diseases.

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