



Review

Protective Roles of Hydrogen Sulfide in Alzheimer's Disease and Traumatic Brain Injury

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Abstract: The gaseous signaling molecule hydrogen sulfide (H₂S) critically modulates a plethora of physiological processes across evolutionary boundaries. These include responses to stress and other neuromodulatory effects that are typically dysregulated in aging, disease, and injury. H₂S has a particularly prominent role in modulating neuronal health and survival under both normal and pathologic conditions. Although toxic and even fatal at very high concentrations, emerging evidence has also revealed a pronounced neuroprotective role for lower doses of endogenously generated or exogenously administered H₂S. Unlike traditional neurotransmitters, H₂S is a gas and, therefore, is unable to be stored in vesicles for targeted delivery. Instead, it exerts its physiologic effects through the persulfidation/sulphydration of target proteins on reactive cysteine residues. Here, we review the latest discoveries on the neuroprotective roles of H₂S in Alzheimer's disease (AD) and traumatic brain injury, which is one the greatest risk factors for AD.

Keywords: transsulfuration; cysteine; hydrogen sulfide; Alzheimer's disease; Huntington's disease; traumatic brain injury; mitochondria; neuroprotection; learning and memory; dementia

1. Introduction

The mere mention of hydrogen sulfide (H₂S) conjures up images of rotten eggs and sewers. H₂S is a colorless, but not odorless, gas with the smell of rotten eggs and potent toxicity at high concentrations. In 1713, the Italian physician Bernardino Ramazzini first described H₂S toxicity when he reported eye inflammation in workers who cleaned “privies and cesspits” (Ramazzini B. De Morbis Artificum Diatriba. Mutinae (Modena). Antonii Capponi, 1700 [1]). It was later discovered that H₂S can be produced by both bacteria and eukaryotes and that the transsulfuration pathway mediates the interconversion of homocysteine and cysteine via the intermediate cystathionine [2,3]. This was followed by further biochemical characterization of the mammalian enzymes involved in H₂S synthesis by several independent research groups [4–7].

Traditionally studied in readily accessible peripheral organs such as the liver, investigation of H₂S in the brain gained momentum when Warenycia and colleagues observed that the inhalation of H₂S by rats increased brain sulfides in direct proportion to the dose of gas inhaled and also mortality [8]. These investigators further revealed the presence of endogenous sulfides in normal brains without the inhalation of H₂S, suggesting for the first time a normal physiologic role for H₂S in the brain. Additionally, around that same time, elevated sulfide levels were observed in the brain of two fatal cases of H₂S poisoning, further generating recognition and interest in the role of H₂S in the brain [9]. Taken together, the detection of sulfides in the brain spurred detailed studies that ultimately forged a new field of research into this ancient signaling molecule [10].

Initial studies on H₂S predominantly revolved around its toxic effects in mammals [11–13], most notably with respect to mitochondrial bioenergetics [14,15]. Indeed, at high concentrations, H₂S inhibits cytochrome c oxidase and uncouples oxidative phosphorylation, which decreases adenosine triphosphate (ATP) production [16,17]. At lower concentrations, however, H₂S exerts stimulatory and protective effects on mitochondria [18–20]. For example, H₂S stimulates mitochondrial bioenergetics in multiple ways, including enhancing mitochondrial biogenesis and promoting mitophagy of damaged mitochondria [18]. Depending on the method and condition used, H₂S levels can range anywhere from nanomolar levels to micromolar levels, with physiologic levels of H₂S in the nanomolar range (reviewed in [21]). There is a dire need for specific and sensitive probes that can be utilized to detect and measure H₂S in vivo. Diminished H₂S production has been observed in several neurodegenerative diseases, including Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer's disease (AD). On the other hand, elevated H₂S is also deleterious. For instance, the triplicated gene for cystathionine β -synthase (CBS) on chromosome 21 in Down syndrome increases H₂S levels throughout the body, which suppresses complex IV of the mitochondrial electron transport chain [22–24]. This article focuses on the neuroprotective roles of H₂S in vivo in the brain and its protective efficacy in both AD and traumatic brain injury (TBI), one of the leading risks factors for AD [25].

2. Biosynthesis of H₂S in the Brain

H₂S is generated in vivo in the brain by three enzymes: cystathionine γ -lyase (CSE), CBS, and 3-mercaptopyruvate sulfur transferase (3-MST) through a coordinated and highly regulated process known as the transsulfuration pathway [7,26–29] (Figure 1). Notably, the expression of the biosynthetic enzymes for H₂S is spatially compartmentalized. Specifically, CSE is exclusively localized to neurons, CBS is expressed in Bergmann glia and astrocytes [30,31], and 3-MST has also been localized to neurons [32]. All three enzymes utilize cysteine directly or indirectly to produce H₂S. 3-MST acts on 3-mercaptopyruvate (3-MP) produced by cysteine aminotransferase (CAT) to produce H₂S. In the absence of CAT, 3-MST cannot produce H₂S unless 3-MP is present. Apart from these pathways, H₂S can also be generated from the acid labile pool, iron–sulfur protein clusters, and the sulfane sulfur pool in the presence of endogenous reductants [33,34]. Higher levels of bound sulfur are found in the brain, with free H₂S being maintained at low levels under basal conditions. H₂S is also released from bound sulfur in homogenates of neurons and astrocytes under alkaline conditions, akin to what occurs in vivo when high extracellular concentrations of K⁺ ions are released by neuronal excitation [34]. The significance of the spatial compartmentalization of CSE, 3-MST, and CBS in the brain is not clear, and these enzymes may have cell-type-specific roles that are yet to be identified. It is increasingly evident that astrocytes have important signaling roles, ranging from immune signaling, synaptic plasticity, and metabolic functions to providing a support system for neurons [35–37]. The role of CBS in these processes is yet to be elucidated. Additionally, of the three H₂S-generating enzymes, CSE is highly inducible, whereas CBS is constitutively expressed [27]. CBS can be regulated at the post-translational level by S-adenosyl methionine (SAM), an allosteric modulator [38]. Levels of SAM are decreased in the cerebrospinal fluid and brain tissue of AD patients, which could lead to a decrease in H₂S levels [39,40].

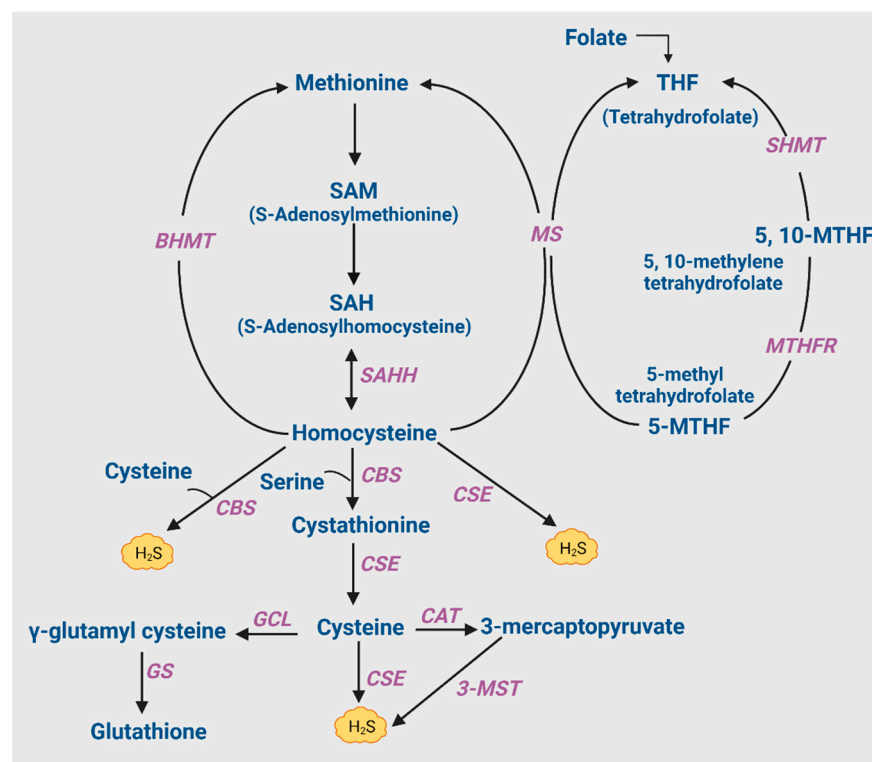


Figure 1. The transsulfuration and transmethylation pathways. Transsulfuration involves transfer of sulfur from homocysteine to cysteine. Homocysteine is generated from dietary methionine via S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH). SAH is converted to homocysteine by S-adenosylhomocysteine hydrolase (SAHH). Homocysteine is then used either for generation of H₂S via the transsulfuration pathway or moved into the transmethylation pathway to generate methionine. With respect to the transsulfuration pathway, cystathionine β-synthase (CBS) converts homocysteine to H₂S or condenses homocysteine with serine to form cystathionine, which is then converted to cysteine by cystathionine γ-lyase (CSE). Cysteine is directly utilized by CSE to form H₂S or alternatively converted to 3-mercaptopyruvate by cysteine aminotransferase (CAT). 3-mercaptopyruvate sulfurtransferase (3-MST) then converts 3-MST to H₂S. Cysteine can also be utilized to produce glutathione (GSH) by the sequential actions of glutamyl cysteine ligase (GCL) and GSH synthase (GS). The other pathway for homocysteine involves the regeneration of methionine via the transmethylation pathway. Methylation of homocysteine may occur either through a folate-independent or dependent pathway. In the folate-dependent pathway shown here, the vitamin B₁₂-dependent enzyme methionine synthase (MS) converts homocysteine to methionine and tetrahydrofolate (THF), utilizing 5-methyltetrahydrofolate (5-MTHF) as the methyl donor. Next, serine hydroxymethyltransferase (SHMT) converts THF to 5,10-methylenetetrahydrofolate (5,10-MTHF), utilizing serine and vitamin B₆. 5,10-MTHF is reduced to 5-MTHF by 5,10-methylenetetrahydrofolate reductase (MTHFR), remethylating another molecule of homocysteine in the process [29].

3. H₂S Signaling in Cognitive Functions

One of the earliest studies on the neuromodulator action of H₂S in the central nervous system, conducted by Kimura and associates in 1996, showed that H₂S acted on N-methyl D-aspartate (NMDA) receptors to modulate long-term potentiation and neurotransmission [10]. The same group also reported that H₂S diminished oxidative stress in neurons [41], which was later attributed to the restoration of glutathione (GSH) levels and the stabilization of the mitochondria [42]. Oxidative stress plays a central role in pathogenesis of several neurodegenerative diseases, and thus restoring dysregulated H₂S metabolism in these conditions was proposed to be beneficial [43]. However, it is important to note that H₂S exhibits a bell-shaped dose response curve, with lower concentrations being generally beneficial and higher doses being toxic. The importance of this equilibrium

is underscored by the tight regulation of endogenous H₂S synthesis. Here, we review the current understanding of the role of H₂S in two major forms of neuropsychiatric disease characterized by cognitive impairment: AD and TBI.

3.1. Alzheimer's Disease

Alzheimer's disease (AD), a multifactorial neurodegenerative condition characterized by the progressive loss of cognitive function and memory, is the leading worldwide cause of dementia [44,45]. Indeed, approximately 6.5 million Americans aged 65 and older are living with Alzheimer's dementia today [46]. The neuropathological hallmarks of Alzheimer's disease classically include the deposition of neurofibrillary tangles and paired helical fragments comprising the microtubule associated protein tau as well as the accumulation of plaques composed of A β peptides [47,48]. However, several lines of evidence also reveal that cognitively normal individuals often have deposits of amyloid plaques, and efforts to treat AD through addressing these two major forms of pathology have not yet succeeded [49,50]. The utility and safety of amyloid-based approaches has also recently been called into question by the Alves et al., whose meta-analysis of the published literature has shown that these therapeutic approaches may compromise long-term brain health by accelerating brain atrophy [51].

Notably, several studies have shown that the suboptimal or excessive levels of metabolites or cofactors of the transsulfuration pathway are also linked to dementia and cognitive deficits, pointing towards another possible therapeutic target for AD (Figure 1). For example, as described below, hyperhomocysteinemia has been linked to dementia.

3.1.1. Hyperhomocysteinemia and Its Causes

Homocysteine is formed from S-adenosyl homocysteine by S-adenosylhomocysteine hydrolase (SAHH), and hyperhomocysteinemia has been established as an independent risk factor for dementia and cardiovascular diseases. Homocysteine is utilized as a substrate for both CSE and CBS to produce H₂S. While CBS utilizes a combination of cysteine and homocysteine to produce H₂S, CSE utilizes homocysteine alone to generate the gasotransmitter [52,53]. A subset of patients displaying homocysteinemia exhibited diminished CBS activity and substantial cardiovascular disability [54]. Thus, both elevated homocysteine levels and decreased H₂S levels mediated vascular complications observed in subjects with impaired CBS activity [55]. Several studies have also shown that levels of homocysteine correlated with the severity of AD [56,57], and increased serum homocysteine was generally observed by the time people reached their nineties [58–61]. Elevated homocysteine levels additionally occur in TBI, one of the greatest risk factors for AD. Homocysteine can elicit toxicity in multiple ways, including the aberrant processing of the amyloid precursor protein (APP), overactivation of the NMDA receptor, DNA damage, and oxidative stress [29].

As described above, homocysteine resides at the intersection of the transsulfuration and transmethylation pathways, where it is either converted to cysteine via cystathionine or remethylated to methionine (Figure 1). Hyperhomocysteinemia may arise due to several reasons, including decreased expression or activity of the enzymes methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS), CBS, or CSE. MTHFR acts on 5,10-methylenetetrahydrofolate to produce 5-methyltetrahydrofolate, the methyl donor for remethylation of homocysteine to form methionine by MS. Notably, mutations in the *MTHFR* gene, which decrease the activity of the protein, have been linked to AD [62]. Along similar lines, mutations in the *CTH* gene are also associated with AD [63,64]. Decreased levels of folate, vitamin B₁₂ (a cofactor for MS), or S-adenosyl methionine (SAM) also lead to hyperhomocysteinemia. SAM is a methyl donor generated from S-adenosylhomocysteine (SAH), which also serves as a cofactor for CBS activity [38]. SAM levels are decreased in AD, which may compromise the levels of cystathionine formed from homocysteine by CBS as well as H₂S production because CBS utilizes homocysteine along with cysteine to produce H₂S [39,40,53]. The administration of SAM to the APP/Presenilin-1 (PS1) mouse

model of AD and to cultured astrocytes conferred cellular protection and stimulated the transsulfuration pathway [65]. Similarly, in both an A β intrahippocampal injection rat model and cultured SH-SY5Y cells, SAM enhanced GSH levels and prevented inflammatory changes and oxidative stress [66].

3.1.2. Cysteine and GSH Metabolism

GSH, a tripeptide of glycine, glutamate, and cysteine, is one of the most abundant antioxidants in cells and tissues [67]. Among its many roles, GSH serves as a cofactor for several enzymes, modulates redox balance in cells, and provides a reservoir for glutamatergic neurotransmission [68]. The availability of cysteine is the rate limiting step for the synthesis of GSH, and, therefore, any alterations in cysteine may compromise GSH metabolism and elevate oxidative stress [69]. Aging, the biggest risk factor for developing AD, has also been associated with declining cysteine levels, and, as such, it has been designated as a “cysteine deficiency syndrome” [70]. Dysregulated cysteine metabolism has been observed in AD as well [71,72]. Cysteine levels are also regulated by the activity of its transporters, which exhibit suboptimal activity in several models of AD. Furthermore, soluble A β oligomers inhibit both basal and insulin-like growth factor-1 (IGF-1)-stimulated cysteine uptake through the neuronal cysteine transporter, the excitatory amino acid transporter 3 (EAAT3/EAAC1) [73]. Another study reported an increase in detergent-insoluble EAAC1 in the hippocampus of AD patients compared to normal subjects [74].

Along with declining cysteine levels, GSH is also significantly diminished in mouse models of AD prior to amyloid- β deposition, with the magnitude of the decrease in GSH correlating exponentially with the magnitude of increased intraneuronal A β accumulation [75]. Decreased GSH and antioxidant enzymes have also been linked to disease progression in AD [76]. While one meta-analysis of studies of postmortem tissues from subjects with mild cognitive impairment (MCI) and AD did not detect significant changes in GSH [77], it is important to note that the postmortem preservation of metabolites is notoriously variable. By contrast, recent magnetic resonance spectroscopy (MRS) studies have revealed significant depletion of brain GSH in MCI and AD, including the highly affected hippocampal brain region [78–81]. GSH depletion may also compromise the activity of GSH-requiring enzymes, such as glyoxalase 1 and 2 (GLO1 and 2), which are dysregulated in AD [82]. GLO1 and GLO2 are a part of the glyoxalase system that prevents glycation reactions mediated by alpha-ketoaldehydes such as methylglyoxal and glyoxal [83].

3.1.3. H₂S and AD

Although disrupted H₂S balance in AD was reported several decades ago, the molecular mechanisms are only beginning to be understood [29]. Diminished brain H₂S levels in AD were first observed in 2002 and correlated to decreased CBS activity [84]. Decreased H₂S was also observed in the plasma of AD patients and correlated with severity of disease [85]. The same study also observed an increase in homocysteine levels. Diminished H₂S that correlated with brain energy levels in the APP/PS1 mouse model of AD was additionally demonstrated using a fluorescent probe that simultaneously measured ATP [86]. In addition, decreased CSE levels have been observed in different models of AD, as described below [72,87].

Initial studies investigating the neuroprotective role of H₂S in AD involved the administration of H₂S donors, which exerted protective effects in several AD models. In a rat model involving the hippocampal injection of A β 1-40, for example, the fast release H₂S donor sodium hydrosulfide (NaHS) prevented neuroinflammation by suppressing the increase in cytokines, such as Tumor necrosis factor alpha (TNF- α), interleukin 1-beta (IL-1 β), IL-6, and pro-inflammatory cyclooxygenase-2 (COX-2) [88]. NaHS also prevented amyloid- β -induced toxicity in microglial cultures, reduced inflammation, preserved mitochondrial function [89], and prevented A β -induced toxicity in PC12 cells [90,91]. Furthermore, NaHS prevented spatial memory impairment and neuroinflammation in an amyloid-based rat model of AD [92]. A separate study utilizing NaHS and Tabiano’s spa-water (rich in sulfur

compounds) ameliorated behavioral deficits in three experimental models of AD [93]. H₂S donors were also tested in a *C. elegans* model of AD and shown to reduce A β aggregation, increase levels of acetylcholine, and reduce oxidative stress [94]. Another study reported that dietary methionine restriction in APP/PS1 mice ameliorated neurodegeneration, improved cognition, and increased H₂S production [95]. Several studies have also reported on the beneficial effects of natural products or plant-based foods that are rich sources of H₂S, including garlic [96]. In 2007, for example, it was demonstrated that the garlic-derived compounds diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) all release H₂S, with diallyl trisulfide (DATS) showing the greatest activity [97,98]. S-allylcysteine (SAC), another garlic compound, also increases H₂S by increasing expression of CSE [99,100]. After these findings, garlic extracts and their endogenous sulfur containing compounds were tested and found to be efficacious in models of AD [101–106]. A summary of beneficial effects of H₂S in models of AD is shown below in Table 1.

Table 1. Neuroprotective effects of hydrogen sulfide.

H ₂ S Donor/ Boosting Agent	System	Effect	Ref.
NaHS	β (A β 25-35)-treated PC12 cells	Prevented β (A β 25-35)-induced cytotoxicity and apoptosis by reducing the loss of MMP and attenuating the increase in intracellular ROS.	[90]
NaHS	PC12 cells	Decreased beta secretase-1 (BACE-1) levels and A β 1-42 release. Increased phosphorylation of Akt. Attenuated A β 1-40-induced lactate dehydrogenase (LDH) release and expression of growth arrest DNA damage (GADD 153). Inhibited release of nitric oxide, induction of inducible nitric oxide synthase (iNOS), and expression of tumor necrosis factor α (TNF- α) and cyclooxygenase 2 (COX-2).	[91]
NaHS	A β 1-40-induced toxicity in BV-2 microglial cells	Ameliorated learning and memory deficits. Suppressed A β (1-40)-induced apoptosis in the hippocampal CA1 region. Diminished hippocampal inflammation, astrogliosis, and microgliosis.	[89]
NaHS	Rat Amyloid β (A β 1-40)-injection model	Improved spatial memory. Decreased expression of BACE1, PS1, and amyloidogenic C99 fragment. Increased expression of ADAM17 and nonamyloidogenic C83 fragment.	[92]
NaHS	APP/PS1 mouse model of AD	Increased hippocampal H ₂ S levels, intracellular ATP, and mitochondrial COX IV activity. Improved hippocampus-dependent contextual fear memory and novel object recognition. Decreased A β accumulation in mitochondria.	[107]
NaHS	APP/PS1 mouse model of AD	Inhibited γ -secretase activity and decreases mitochondrial A β production in neurons. Prevented neuronal loss, apoptosis, and activation of pro-caspase-3. Decreased expression of phosphodiesterase 5 (PDE-5) in the hippocampus.	[108]
NaHS	APP/PS1 mouse model of AD	Upregulated expression of peroxisome proliferator-activated receptor (PPAR)- α and PPAR- γ . Prevented A β 25-35-decrease in I κ B- α degradation and increase in nuclear factor- κ B (NF- κ B) p65 phosphorylation levels.	[109]
NaHS	Rat amyloid β (A β 25-35)-injection model		[110]

Table 1. Cont.

H ₂ S Donor/ Boosting Agent	System	Effect	Ref.
NaHS	Primary hippocampal neuronal culture from C57/BL6 mice at P0-P1	Reduced A β -induced apoptosis. Decreased release of cytochrome C into the cytosol and caspase-3 activity. Decreased translocation of the phosphatase and tensin homologs deleted on chromosome 10 (PTEN) from the cytosol to the mitochondria. Increased p-AKT/AKT levels in PI3K-dependent manner.	[111]
NaHS	APP/PS1 mouse model of AD	Mitigated cognitive deficits. Decreased the number of senile plaques, A β 1-40 and A β 1-42 levels, neuronal loss, beta-amyloid precursor (APP), and BACE1. Increased CBS and 3MST. Augmented antioxidant effects through induction of nuclear factor erythroid-2-related factor 2 (Nrf2), heme oxygenase-1(HO-1), and glutathione S-transferase (GST).	[112]
Memit (Derived from memantine by replacing the free amine group with an isothiocyanate moiety)	A β oligomers-induced damage in human neurons and rat	Decreased A β (1-42)-induced aggregation and A β oligomer-induced damage in human neurons and rat microglial cells. Increased neuroprotective autophagy.	[113]
H ₂ S releasing peptide conjugates	<i>C. elegans</i>	Reduced A β 1-42 amyloid deposits and ROS.	[94]
Sulfanagen	APP/PS1 mouse model of AD	Increased acetylcholine levels. Stimulated 3-MST and prevented neuropathology. Decreased A β accumulation. Improved cognitive function. Restored synapse ultrastructure. Alleviated mitochondrial dysfunction by enhancing mitochondrial biogenesis in male mice. Balanced the redox status and activated cystathionine- β -synthase (CBS)/ H ₂ S pathway.	[114]
Methionine restriction	APP/PS1 mouse model of AD	Improved spatial memory. Increased H ₂ S production.	[95]
Naringin	Rat Amyloid β (A β)-injection model	Reduced inflammation. Decreased oxidative stress, apoptosis, and histopathological alterations.	[115]
NaHS	LPS-induced AD-like cognitive deficits in Wistar albino rats	Ameliorated BBB disruption, impaired cerebral blood flow (CBF), and diminished synaptic function.	[116]
NaHS in combination with the NMDA-receptor antagonist, MK801	Homocysteine (intracerebral injection)-induced AD-like neurodegeneration	Reduced neuronal death in A β 1-42 treated primary hippocampal neuronal culture and increased neurite length. Increased plasma H ₂ S and decreased anxiety-like behavior and cognitive deficits in 3xTg-AD mice. Reduced amyloid deposits and hyperphosphorylation of Tau. Decreased inflammatory responses, oxidative stress, and gliosis in 3xTg-AD mice.	[117]
NaHS	Mouse primary hippocampal neurons (E16–18), 3xTg-AD mouse model of AD	Prevented learning and memory deficits. Reduced size of amyloid β plaques. Decreased activity of c-jun N-terminal kinases, extracellular signal-regulated kinases, and p38.	[118]
NaHS, sulfurous water	3xTg-AD mouse model of AD	Improved learning and memory deficits in all three models. Decreased amyloid deposits in the rat models of AD. The spa-water decreased oxidative and nitrosative stress, MAPK activation, inflammation, and apoptosis in 3xTg-AD mice.	[119]
NaHS, Tabiano's spa-water	Rat A β 1-40 injection model of AD, Streptozotocin-induced AD, 3xTg-AD mouse model of AD	Improved motor and cognitive function in 3xTg-AD mice. Increased overall sulphydration. Inhibited Tau phosphorylation by sulphydrating glycogen synthase kinase (GSK3 β) and inhibiting its activity.	[93]
Na-GYY4137	3xTg-AD mouse model of AD		[72]

Persulfidation, AD, and Aging

One of the modes by which H_2S signals is through post-translational modification, termed sulfhydration or persulfidation, which both refer to the same chemical reaction in which the thiol group of cysteine is converted to an $-SSH$ or persulfide group [52,120,121]. Here, H_2S cannot directly modify an $-SH$ group, and the main mechanisms by which persulfides are generated are by reactions of H_2S with oxidized cysteines or disulfides or by reactions of cysteine residues with sulfide radicals, polysulfides, and other persulfides [121,122]. Persulfidation is a reversible modification regulated by the endogenous thioredoxin/thioredoxin reductase system [123–125]. Notably, persulfidation and H_2S signaling are compromised in several age-related neurodegenerative diseases, including AD, HD, PD, and spinocerebellar ataxia (SCA) [126–129].

Although there are numerous studies on the beneficial effects of H_2S in AD, analysis of persulfidation (the major mode by which the gaseous molecule signals) in AD is scarce. More recently, the status of persulfidation has been studied directly in AD (Figure 2). For example, overall persulfidation is decreased in mouse models of AD as well as postmortem samples from human AD subjects [72]. Notably, persulfidation of Glycogen synthase kinase-3 β (GSK-3 β), the major kinase that phosphorylates Tau, is decreased in AD. Administration of Na-GYY4137 to the 3xTg-AD model of AD rectified the persulfidation deficits and prevented motor and cognitive decline [29,72]. Suboptimal persulfidation was also observed in the APP/PS1 mouse model of AD, where decreased expression of CSE was observed, in addition to the human hippocampal and cortex samples [87]. This study also demonstrated a role for the autophagy-related activating factor 6 (ATF6) in expression of CSE. Stereotaxic injection of lentiviral particles encoding CTH into the ventricular system of the brain rescued spatial memory deficits in *Atf6* CKO/APP/PS1 mice. The transport of ATF6 from the endoplasmic reticulum to the Golgi apparatus under ER stress is mediated by the Soluble NSF attachment protein (α SNAP)/SNAP receptor (SNARE) pathway. Persulfidation of α SNAP is also decreased in ATF6 knockout mice, which may indicate a role in AD.

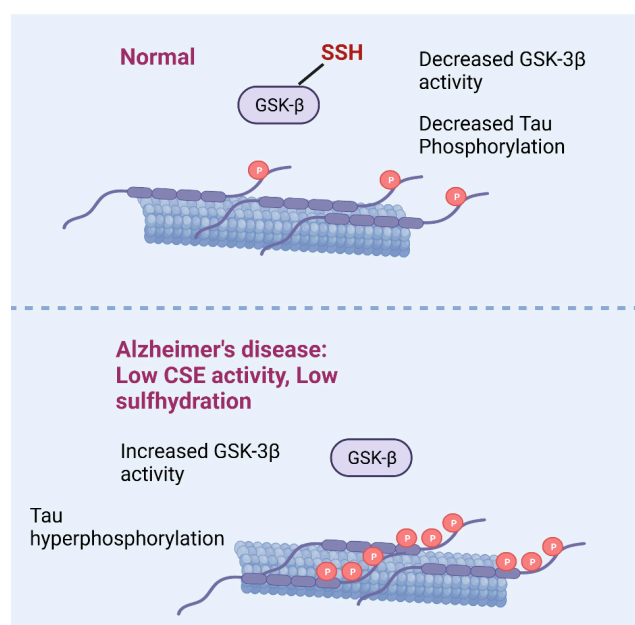


Figure 2. Disruption of H_2S signaling in Alzheimer's disease (AD). During normal conditions, glycogen synthase kinase-3 β (GSK-3 β) is sulfhydrated, which inhibits its catalytic activity and prevents hyper-phosphorylation of Tau (Top panel). In AD, decreased CSE activity leads to lower sulfhydration of GSK-3 β , which leads to elevated phosphorylation of Tau.

Lastly, aging is the biggest risk factor for developing AD, and diminished persulfidation is also ubiquitously observed across evolutionary boundaries during aging. Importantly, several of the proteins whose persulfidation levels are altered may modulate AD pathology and disease progression [122,130]. A systematic analysis of these targets is warranted to elucidate the links between persulfidation and AD. For instance, MTHFR, a key enzyme regulating intracellular homocysteine metabolism, is normally persulfidated, and decreased persulfidation of MTHFR promotes hyperhomocysteinemia, a risk factor for AD [131].

3.2. Traumatic Brain Injury

TBI and H₂S

Traumatic brain injury (TBI) is one of the most prevalent forms of neurodegenerative disease, and typically entails chronic and progressive neuropsychiatric impairment even after a single injury. This pathologic process is poorly understood, and, to date, there are no protective treatments for patients. It is well-established that there is considerable overlap in pathology between TBI and AD [25], and H₂S is involved in various biological functions after TBI, including the response to oxidative stress in the brain. Due to the brain's voracious need for the constant generation of ATP, which generates free radicals as a by-product, and the brain's abundance of metal ions and phospholipids that generate additional oxidative products, the brain, even under normal circumstances, is constantly exposed to high levels of oxidative stress. This vulnerability is further exacerbated by TBI because of an increased energy requirement for self-repair processes after injury that ultimately leads to an inability to maintain mitochondrial membrane potential, resulting in complete energy failure and cell death. Early results in cellular models indicated protective efficacy of H₂S in this scenario. For example, H₂S generated by mitochondrial 3-MST directly reduced the generation of ROS and protected PC12 cells from apoptosis after severe oxidative stress [132]. In cultured neurons, H₂S promoted the neuronal production of GSH and the scavenging of oxygen free radicals, hydrogen peroxide, and lipid peroxides [42,133]. Thus, whether changes in brain H₂S might be involved in the pathophysiology of TBI, and whether supplemental H₂S might be neuroprotective in TBI, became an active area of investigation.

There is now substantial evidence in animal models that TBI decreases brain levels of H₂S and that exogenous supplementation of H₂S protects the brain after injury. In 2013, Zhang et al. observed that subjecting mice to the weight drop model of TBI acutely decreased levels of hippocampal and cortical CBS mRNA and protein, and this correlated with decreased levels of H₂S [134]. They additionally demonstrated that pretreatment with the H₂S donor NaHS partially reduced lesion volume after injury [134]. That same year, Jiang et al. showed the protective efficacy of NaHS in an additional model of TBI induced by controlled cortical impact (CCI) in rats [135]. Specifically, CCI acutely decreased brain H₂S, and the preservation of brain H₂S with NaHS treatment beginning before injury blocked brain edema, blood–brain barrier (BBB) impairment, and the acquisition of motor deficits. They also reported that NaHS-treated rats showed reduced TBI lesion volume and were protected from TBI-induced decreases in brain superoxide dismutase and choline acetyltransferase activity, as well as TBI-induced increases in the oxidative products 8-iso-prostaglandin F₂ alpha and malondialdehyde, up to 72 h after injury [135].

These results were further bolstered when Zhang et al. extended their work in the weight drop model of TBI the following year, showing that NaHS pretreatment prevented cerebral edema and cognitive impairment in the Morris water maze after TBI, as well as cleavage of caspase-3, decreased Bcl-2, and elevated neuronal apoptosis [136]. Preserved cognition in the Morris water maze by NaHS pretreatment in rats exposed to CCI was also independently established by the Hajisoltani laboratory [137], and Xu et al. additionally demonstrated that NaHS-mediated modulation of the PI3K/Akt/mTOR signaling pathway after TBI in mice was associated with BBB protection, the inhibition of neuronal apoptosis, remyelination of axons, and preservation of mitochondrial function [138]. Evidence

for protective efficacy of H₂S in the CCI model of TBI was also demonstrated by Campolo et al., who showed that the administration of 2-(6-methoxynaphthalen-2-yl)-propionic acid 4-thiocarbamoyl-phenyl ester (ATB-346), a H₂S-releasing derivative of naproxen, attenuated TBI-induced brain edema, neuronal cell death, and motor impairment, while naproxen (which does not release H₂S) had no protective efficacy [139]. ATB-346 was also associated with significantly decreased expression of inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), tumor necrosis factor alpha (TNF α), and interleukin 1-beta (IL-1 β), as well as normalized levels of glial-derived neurotrophic factor (GDNF) and nerve growth factor (NGF), and increased levels of vascular endothelial growth factor (VEGF), after TBI [139]. While all of these changes would be considered likely beneficial to brain health in the setting of TBI, it is unclear whether any of these occur as a direct result of H₂S action or if this simply reflects the profile of a healthier brain by virtue of other upstream effects of H₂S. Interestingly, Zhang et al. have shown that increased expression of 3-MST in neurons occurs predominantly in those neurons that survive after TBI [140], implicating a regulated and direct protective role of endogenous H₂S after TBI. More recently, H₂S-mediated protection in TBI in rats has been linked to the modulation of glutamate-mediated oxidative stress via the p53/glutaminase2 pathway [141]. In addition, the Centurion laboratory recently reported that subchronic treatment with NaHS protected rats from hemodynamic and sympathetic nervous system impairments after TBI and also restored CSE and CBS expression in the brain [142]. It has also been demonstrated that subchronic NaHS after TBI in rats prevents hypertension, vascular impairment, and oxidative stress [143]. In conclusion, there are a myriad of central and peripheral beneficial effects of H₂S on TBI outcomes, although the precise mechanisms by which these protective effects occur are currently unknown (Figure 3).

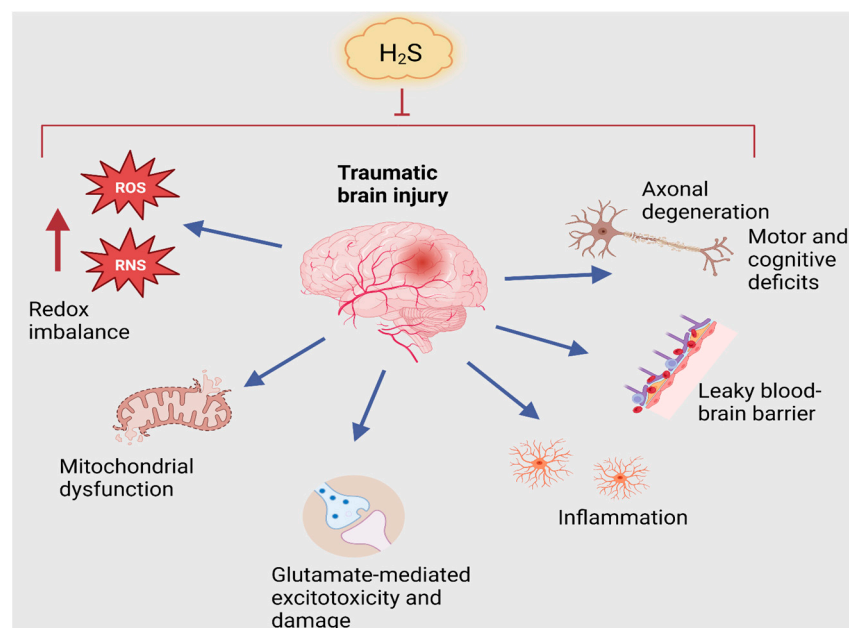


Figure 3. Neuroprotective effects of H₂S in traumatic brain injury (TBI). TBI impacts several physiological processes that lead to motor and cognitive deficits. TBI causes increases in reactive oxygen and nitrogen species (ROS and RNS), leading to oxidative and nitrosative stress and mitochondrial dysfunction. TBI also elicits glutamate-induced neurotoxicity and inflammation and causes a leaky blood–brain barrier. All of these processes influence each other and ultimately culminate in neurodegeneration.

4. Dysregulation of Iron Homeostasis in AD, TBI and Intersection with H₂S Signaling

Iron is a transition metal with important roles in the brain, ranging from being a component of iron–sulfur cluster proteins and heme proteins to participating in DNA synthesis

and neurotransmitter metabolism. However, the dysregulation of iron homeostasis can be deleterious, as ferrous iron (Fe^{2+}) reacts with H_2O_2 and produces $\bullet\text{OH}$ and HO_2 to oxidize lipids, proteins, and DNA [43]. Additionally, superoxide radicals ($\text{O}_2^{\bullet-}$) produced by mitochondria during respiration reduce Fe^{3+} to Fe^{2+} by the Haber–Weiss reaction [144]. The accumulation of iron in the brain is a common feature of aging, several neurodegenerative diseases, and TBI and is known to drive neuronal loss [145–149]. Specifically, disrupted iron metabolism and its aberrant redox cycling trigger ferroptosis, an iron-dependent cell death pathway that elicits lipid peroxidation and damage to cellular components in several neurodegenerative diseases, including AD [150–153]. Ferroptosis was described over a decade ago as a distinct form of cell death linked to aging, neurodegeneration, immune system dysfunction, and cancer [151,154]. It is well-established that ferroptosis is intimately linked to depletion of cysteine, a component of GSH in cells, and several studies have shown that cysteine/cystine deprivation can elicit this form of cell death. As cysteine serves as the substrate for generation of H_2S , the involvement of this gasotransmitter in ferroptosis has been explored. To date, H_2S donors have been shown to alleviate damage caused by ferroptosis in various contexts by activating cytoprotective signaling pathways [155–157]. The effect of H_2S on ferroptosis in the brain in the context of injury and neurodegeneration is yet to be systematically studied and could inform the development of novel therapeutics.

5. Therapeutic Opportunities

Although significant advances in the elucidation of signaling mediated by H_2S have been made, clinical translation has yet to follow. While there is abundant evidence of the neuroprotective efficacy of H_2S donors in rodents, *Drosophila*, and worm models, examples of translation to human disease are scarce. However, some H_2S -donating hybrid drugs have made it into clinical trials, including a phase 2B study that demonstrated a reduction in gastrointestinal toxicity of the hybrid H_2S -releasing analgesic/anti-inflammatory drug ATB-346, as compared to the non-steroidal anti-inflammatory drug (NSAID) naproxen that produces a similar inhibition of the inflammatory cyclooxygenase-2 (COX2) molecule. [158]. The safety and side-effects of these compounds are still being evaluated. Harnessing H_2S donors can prove challenging, as the timing and dose of the donors likely requires optimization. For example, numerous reports have demonstrated a biphasic dose–response curve for H_2S , with higher doses being toxic. An alternate approach involves the use of natural H_2S donors such as garlic extracts, which are rich in sulfur compounds that release H_2S and may be beneficial in cardiovascular disorders [97,98]. The use of such donors might also be considered in ameliorating symptoms of AD, TBI, and other neurodegenerative disorders involving diminished H_2S signaling. The opposite may be true of diseases involving elevated H_2S , such as Down syndrome, in which the trisomy of chromosome 21 leads to excess H_2S production due to an extra copy of CBS [23,24]. Thus, depending on the paucity or excess of H_2S , appropriate treatment strategies will need to be developed.

6. Conclusions

AD is a complex, multifactorial disease, with most cases arising sporadically. The susceptibility factors for developing AD are several, with aging and TBI being major risk factors. There are several commonalities between AD and TBI, including dysregulated gasotransmitter signaling. Accumulating evidence shows that deficiencies in the gaseous signaling molecule H_2S can drive pathology in AD and TBI and that the augmentation of H_2S levels affords therapeutic benefits in these conditions. Stimulating H_2S production or restoring the homeostasis of the various metabolites of the transsulfuration and transmethylation pathway that contribute to cysteine, GSH, or H_2S production may be beneficial for these or other related forms of neurodegenerative disease. H_2S is a gaseous molecule and cannot be stored in vesicles, unlike conventional neurotransmitters, but elicits effects through sulfhydration, which can be used as a marker for its action. Accurate measurement of the various forms and metabolites H_2S would further deepen our knowledge pertaining to the physiological relevance of this gaseous messenger molecule.

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Abbreviations

3-MST	3-mercaptopyruvate sulfurtransferase
AD	Alzheimer’s disease
APP	Amyloid precursor protein
ATB346	2-(6-methoxynaphthalen-2-yl)-propionic acid 4-thiocarbamoyl-phenyl ester
ATF6	Activating factor 6
BBB	Blood–brain barrier
CAT	Cysteine aminotransferase
CBF	Cerebral blood flow
CBS	Cystathionine β -synthase
CSE	Cystathionine γ -lyase
CCI	Controlled cortical impact
COX-2	Cyclo-oxygenase-2
DADS	Diallyl disulfide
DATS	Diallyl trisulfide
EAAT3/EAAC1	Excitatory amino acid transporter 3
GDNF	Glial-derived neurotrophic factor
GLO-1,2	Glyoxalase 1,2
GSH	Glutathione
GSK-3 β	Glycogen synthase kinase-3 β
HD	Huntington’s disease
iNOS	Inducible nitric oxide synthase
MCI	Mild cognitive impairment
MRS	Magnetic resonance spectroscopy
MTHFR	Methylenetetrahydrofolate reductase
NGF	Nerve growth factor
Nrf2	Nuclear factor erythroid-2-related factor 2
PD	Parkinson’s disease
PDE5	Phosphodiesterase 5
PS1	Presenilin-1
ROS	Reactive Oxygen Species
RNS	Reactive Nitrogen Species
SAC	S-allyl cysteine
SAHH	S-adenosylhomocysteine hydrolase

SAM	S-adenosyl methionine
SCA	Spinocerebellar ataxia
α -SNAP	α -soluble NSF attachment protein
SNARE	Soluble NSF attachment protein receptor
TNF- α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

References

- Ramazzini, B. De Morbis Artificum Diatriba. Mutinae (Modena). Antonii Capponi. In *Google Scholar*; 1700. Available online: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446785/> (accessed on 1 April 2023).
- du Vigneaud, V.; Loring, G.S.; Craft, H.A. The oxidation of the sulfur of homocystine, methionine, and S-methylcysteine in the animal body. *J. Biol. Chem.* **1934**, *105*, 481–488. [\[CrossRef\]](#)
- Binkley, F.; Du Vigneaud, V. The formation of cysteine from homocysteine and serine by liver tissue of rats. *J. Biol. Chem.* **1942**, *144*, 507–511. [\[CrossRef\]](#)
- Hanson, H.; Eisfeld, G. Intermediary sulfur metabolism. III. Formation of hydrogen sulfide from cystine and cysteine by the liver. *Z. Gesamte Inn. Med.* **1952**, *7*, 801–810. [\[PubMed\]](#)
- Chatagner, F.; Sauret-Ignazi, G. Role of transamination and pyridoxal phosphate in the enzymatic formation of hydrogen sulfide from cysteine by the rat liver under anaerobiosis. *Bull. Soc. Chim. Biol.* **1956**, *38*, 415–428.
- Ubuka, T.; Yuasa, S.; Ishimoto, Y.; Shimomura, M. Desulfuration of L-cysteine through transamination and transsulfuration in rat liver. *Physiol. Chem. Phys.* **1977**, *9*, 241–246.
- Stipanuk, M.H.; Beck, P.W. Characterization of the enzymic capacity for cysteine desulphhydration in liver and kidney of the rat. *Biochem. J.* **1982**, *206*, 267–277. [\[CrossRef\]](#)
- Warenycia, M.W.; Goodwin, L.R.; Benishin, C.G.; Reiffenstein, R.J.; Francom, D.M.; Taylor, J.D.; Dieken, F.P. Acute hydrogen sulfide poisoning. Demonstration of selective uptake of sulfide by the brainstem by measurement of brain sulfide levels. *Biochem. Pharmacol.* **1989**, *38*, 973–981. [\[CrossRef\]](#)
- Goodwin, L.R.; Francom, D.; Dieken, F.P.; Taylor, J.D.; Warenycia, M.W.; Reiffenstein, R.J.; Dowling, G. Determination of sulfide in brain tissue by gas dialysis/ion chromatography: Postmortem studies and two case reports. *J. Anal. Toxicol.* **1989**, *13*, 105–109. [\[CrossRef\]](#)
- Abe, K.; Kimura, H. The possible role of hydrogen sulfide as an endogenous neuromodulator. *J. Neurosci.* **1996**, *16*, 1066–1071. [\[CrossRef\]](#)
- Wang, R. Physiological implications of hydrogen sulfide: A whiff exploration that blossomed. *Physiol. Rev.* **2012**, *92*, 791–896. [\[CrossRef\]](#) [\[PubMed\]](#)
- Haouzi, P.; Sonobe, T.; Judenherc-Haouzi, A. Hydrogen sulfide intoxication induced brain injury and methylene blue. *Neurobiol. Dis.* **2020**, *133*, 104474. [\[CrossRef\]](#)
- Reiffenstein, R.J.; Hulbert, W.C.; Roth, S.H. Toxicology of hydrogen sulfide. *Annu. Rev. Pharmacol. Toxicol.* **1992**, *32*, 109–134. [\[CrossRef\]](#)
- Nicholls, P.; Kim, J.K. Sulphide as an inhibitor and electron donor for the cytochrome c oxidase system. *Can. J. Biochem.* **1982**, *60*, 613–623. [\[CrossRef\]](#) [\[PubMed\]](#)
- Blackstone, E.; Morrison, M.; Roth, M.B. H₂S induces a suspended animation-like state in mice. *Science* **2005**, *308*, 518. [\[CrossRef\]](#)
- Nicholls, P.; Marshall, D.C.; Cooper, C.E.; Wilson, M.T. Sulfide inhibition of and metabolism by cytochrome c oxidase. *Biochem. Soc. Trans.* **2013**, *41*, 1312–1316. [\[CrossRef\]](#) [\[PubMed\]](#)
- Collman, J.P.; Ghosh, S.; Dey, A.; Decreau, R.A. Using a functional enzyme model to understand the chemistry behind hydrogen sulfide induced hibernation. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 22090–22095. [\[CrossRef\]](#)
- Paul, B.D.; Snyder, S.H.; Kashfi, K. Effects of hydrogen sulfide on mitochondrial function and cellular bioenergetics. *Redox Biol.* **2021**, *38*, 101772. [\[CrossRef\]](#) [\[PubMed\]](#)
- Modis, K.; Bos, E.M.; Calzia, E.; van Goor, H.; Coletta, C.; Papapetropoulos, A.; Hellmich, M.R.; Radermacher, P.; Bouillaud, F.; Szabo, C. Regulation of mitochondrial bioenergetic function by hydrogen sulfide. Part II. Pathophysiological and therapeutic aspects. *Br. J. Pharmacol.* **2014**, *171*, 2123–2146. [\[CrossRef\]](#)
- Szabo, C.; Ransy, C.; Modis, K.; Andriamihaja, M.; Murghes, B.; Coletta, C.; Olah, G.; Yanagi, K.; Bouillaud, F. Regulation of mitochondrial bioenergetic function by hydrogen sulfide. Part I. Biochemical and physiological mechanisms. *Br. J. Pharmacol.* **2014**, *171*, 2099–2122. [\[CrossRef\]](#)
- Cirino, G.; Szabo, C.; Papapetropoulos, A. Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs. *Physiol. Rev.* **2023**, *103*, 31–276. [\[CrossRef\]](#) [\[PubMed\]](#)
- Panagaki, T.; Randi, E.B.; Augsburger, F.; Szabo, C. Overproduction of H(2)S, generated by CBS, inhibits mitochondrial Complex IV and suppresses oxidative phosphorylation in Down syndrome. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 18769–18771. [\[CrossRef\]](#) [\[PubMed\]](#)
- Ichinohe, A.; Kanaumi, T.; Takashima, S.; Enokido, Y.; Nagai, Y.; Kimura, H. Cystathionine beta-synthase is enriched in the brains of Down's patients. *Biochem. Biophys. Res. Commun.* **2005**, *338*, 1547–1550. [\[CrossRef\]](#)

24. Szabo, C. The re-emerging pathophysiological role of the cystathionine-beta-synthase—Hydrogen sulfide system in Down syndrome. *FEBS J.* **2020**, *287*, 3150–3160. [\[CrossRef\]](#)
25. Barker, S.; Paul, B.D.; Pieper, A.A. Increased risk of aging-related neurodegenerative disease after traumatic brain injury. *biomedicines* **2023**, *11*, 1154. [\[CrossRef\]](#)
26. Paul, B.D.; Snyder, S.H. Modes of physiologic H₂S signaling in the brain and peripheral tissues. *Antioxid. Redox Signal.* **2015**, *22*, 411–423. [\[CrossRef\]](#)
27. Sbodio, J.I.; Snyder, S.H.; Paul, B.D. Regulators of the transsulfuration pathway. *Br. J. Pharmacol.* **2019**, *176*, 583–593. [\[CrossRef\]](#)
28. Paul, B.D.; Snyder, S.H. Gasotransmitter hydrogen sulfide signaling in neuronal health and disease. *Biochem. Pharmacol.* **2018**, *149*, 101–109. [\[CrossRef\]](#)
29. Paul, B.D. Neuroprotective Roles of the Reverse Transsulfuration Pathway in Alzheimer's Disease. *Front Aging Neurosci* **2021**, *13*, 659402. [\[CrossRef\]](#)
30. Morikawa, T.; Kajimura, M.; Nakamura, T.; Hishiki, T.; Nakanishi, T.; Yukutake, Y.; Nagahata, Y.; Ishikawa, M.; Hattori, K.; Takenouchi, T.; et al. Hypoxic regulation of the cerebral microcirculation is mediated by a carbon monoxide-sensitive hydrogen sulfide pathway. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1293–1298. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Enokido, Y.; Suzuki, E.; Iwasawa, K.; Namekata, K.; Okazawa, H.; Kimura, H. Cystathionine beta-synthase, a key enzyme for homocysteine metabolism, is preferentially expressed in the radial glia/astrocyte lineage of developing mouse CNS. *FASEB J.* **2005**, *19*, 1854–1856. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Shibuya, N.; Tanaka, M.; Yoshida, M.; Ogasawara, Y.; Togawa, T.; Ishii, K.; Kimura, H. 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. *Antioxid. Redox Signal.* **2009**, *11*, 703–714. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Shen, X.; Peter, E.A.; Bir, S.; Wang, R.; Kevil, C.G. Analytical measurement of discrete hydrogen sulfide pools in biological specimens. *Free Radic. Biol. Med.* **2012**, *52*, 2276–2283. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Ishigami, M.; Hiraki, K.; Umemura, K.; Ogasawara, Y.; Ishii, K.; Kimura, H. A source of hydrogen sulfide and a mechanism of its release in the brain. *Antioxid. Redox Signal.* **2009**, *11*, 205–214. [\[CrossRef\]](#)
35. Khaspekov, L.G.; Frumkina, L.E. Molecular Mechanisms of Astrocyte Involvement in Synaptogenesis and Brain Synaptic Plasticity. *Biochemistry* **2023**, *88*, 502–514. [\[CrossRef\]](#)
36. Farizatto, K.L.G.; Baldwin, K.T. Astrocyte-synapse interactions during brain development. *Curr. Opin. Neurobiol.* **2023**, *80*, 102704. [\[CrossRef\]](#)
37. Jorgacevski, J.; Potokar, M. Immune Functions of Astrocytes in Viral Neuroinfections. *Int. J. Mol. Sci.* **2023**, *24*, 3514. [\[CrossRef\]](#)
38. Finkelstein, J.D.; Kyle, W.E.; Martin, J.L.; Pick, A.M. Activation of cystathionine synthase by adenosylmethionine and adenosylethionine. *Biochem. Biophys. Res. Commun.* **1975**, *66*, 81–87. [\[CrossRef\]](#)
39. Morrison, L.D.; Smith, D.D.; Kish, S.J. Brain S-adenosylmethionine levels are severely decreased in Alzheimer's disease. *J. Neurochem.* **1996**, *67*, 1328–1331. [\[CrossRef\]](#)
40. Linnebank, M.; Popp, J.; Smulders, Y.; Smith, D.; Semmler, A.; Farkas, M.; Kulic, L.; Cvetanovska, G.; Blom, H.; Stoffel-Wagner, B.; et al. S-adenosylmethionine is decreased in the cerebrospinal fluid of patients with Alzheimer's disease. *Neurodegener. Dis.* **2010**, *7*, 373–378. [\[CrossRef\]](#)
41. Kimura, H.; Shibuya, N.; Kimura, Y. Hydrogen sulfide is a signaling molecule and a cytoprotectant. *Antioxid. Redox Signal.* **2012**, *17*, 45–57. [\[CrossRef\]](#)
42. Kimura, Y.; Goto, Y.; Kimura, H. Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. *Antioxid. Redox Signal.* **2010**, *12*, 1–13. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Sbodio, J.I.; Snyder, S.H.; Paul, B.D. Redox Mechanisms in Neurodegeneration: From Disease Outcomes to Therapeutic Opportunities. *Antioxid. Redox Signal.* **2019**, *30*, 1450–1499. [\[CrossRef\]](#)
44. Masters, C.L.; Bateman, R.; Blennow, K.; Rowe, C.C.; Sperling, R.A.; Cummings, J.L. Alzheimer's disease. *Nat. Rev. Dis. Primers* **2015**, *1*, 15056. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Lane, C.A.; Hardy, J.; Schott, J.M. Alzheimer's disease. *Eur. J. Neurol.* **2018**, *25*, 59–70. [\[CrossRef\]](#) [\[PubMed\]](#)
46. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* **2022**, *18*, 700–789. [\[CrossRef\]](#)
47. Braak, H.; Braak, E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol. Aging* **1995**, *16*, 271–278, discussion 278–284. [\[CrossRef\]](#)
48. Braak, H.; Braak, E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* **1991**, *82*, 239–259. [\[CrossRef\]](#)
49. Snitz, B.E.; Weissfeld, L.A.; Lopez, O.L.; Kuller, L.H.; Saxton, J.; Singhabahu, D.M.; Klunk, W.E.; Mathis, C.A.; Price, J.C.; Ives, D.G.; et al. Cognitive trajectories associated with beta-amyloid deposition in the oldest-old without dementia. *Neurology* **2013**, *80*, 1378–1384. [\[CrossRef\]](#)
50. Rentz, D.M.; Locascio, J.J.; Becker, J.A.; Moran, E.K.; Eng, E.; Buckner, R.L.; Sperling, R.A.; Johnson, K.A. Cognition, reserve, and amyloid deposition in normal aging. *Ann. Neurol.* **2010**, *67*, 353–364. [\[CrossRef\]](#)
51. Alves, F.; Kallinowski, P.; Ayton, S. Accelerated Brain Volume Loss Caused by Anti-beta-Amyloid Drugs: A Systematic Review and Meta-analysis. *Neurology* **2023**. [\[CrossRef\]](#)
52. Paul, B.D.; Snyder, S.H. H(2)S signalling through protein sulphydration and beyond. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 499–507. [\[CrossRef\]](#)
53. Chen, X.; Jhee, K.H.; Kruger, W.D. Production of the neuromodulator H₂S by cystathionine beta-synthase via the condensation of cysteine and homocysteine. *J. Biol. Chem.* **2004**, *279*, 52082–52086. [\[CrossRef\]](#)

54. Beard, R.S., Jr.; Bearden, S.E. Vascular complications of cystathionine beta-synthase deficiency: Future directions for homocysteine-to-hydrogen sulfide research. *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *300*, H13–H26. [\[CrossRef\]](#)
55. Sen, U.; Mishra, P.K.; Tyagi, N.; Tyagi, S.C. Homocysteine to hydrogen sulfide or hypertension. *Cell Biochem. Biophys.* **2010**, *57*, 49–58. [\[CrossRef\]](#)
56. Kitzlerova, E.; Fisar, Z.; Jirak, R.; Zverova, M.; Hroudova, J.; Benakova, H.; Raboch, J. Plasma homocysteine in Alzheimer's disease with or without co-morbid depressive symptoms. *Neuro Endocrinol. Lett.* **2014**, *35*, 42–49.
57. Farina, N.; Jerneren, F.; Turner, C.; Hart, K.; Tabet, N. Homocysteine concentrations in the cognitive progression of Alzheimer's disease. *Exp. Gerontol.* **2017**, *99*, 146–150. [\[CrossRef\]](#) [\[PubMed\]](#)
58. McCaddon, A.; Davies, G.; Hudson, P.; Tandy, S.; Cattell, H. Total serum homocysteine in senile dementia of Alzheimer type. *Int. J. Geriatr. Psychiatry* **1998**, *13*, 235–239. [\[CrossRef\]](#)
59. Smith, A.D.; Refsum, H.; Bottiglieri, T.; Fenech, M.; Hooshmand, B.; McCaddon, A.; Miller, J.W.; Rosenberg, I.H.; Obeid, R. Homocysteine and Dementia: An International Consensus Statement. *J. Alzheimers Dis.* **2018**, *62*, 561–570. [\[CrossRef\]](#)
60. Clarke, R.; Smith, A.D.; Jobst, K.A.; Refsum, H.; Sutton, L.; Ueland, P.M. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch. Neurol.* **1998**, *55*, 1449–1455. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Zhang, L.; Xie, X.; Sun, Y.; Zhou, F. Blood and CSF Homocysteine Levels in Alzheimer's Disease: A Meta-Analysis and Meta-Regression of Case-Control Studies. *Neuropsychiatr. Dis. Treat.* **2022**, *18*, 2391–2403. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Castro, R.; Rivera, I.; Ravasco, P.; Jakobs, C.; Blom, H.J.; Camilo, M.E.; de Almeida, I.T. 5,10-Methylenetetrahydrofolate reductase 677C→T and 1298A→C mutations are genetic determinants of elevated homocysteine. *QJM* **2003**, *96*, 297–303. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Wang, J.; Hegele, R.A. Genomic basis of cystathioninuria (MIM 219500) revealed by multiple mutations in cystathionine gamma-lyase (CTH). *Hum. Genet.* **2003**, *112*, 404–408. [\[CrossRef\]](#)
64. Wang, J.; Huff, A.M.; Spence, J.D.; Hegele, R.A. Single nucleotide polymorphism in CTH associated with variation in plasma homocysteine concentration. *Clin. Genet.* **2004**, *65*, 483–486. [\[CrossRef\]](#)
65. Wan, X.; Ma, B.; Wang, X.; Guo, C.; Sun, J.; Cui, J.; Li, L. S-Adenosylmethionine Alleviates Amyloid-beta-Induced Neural Injury by Enhancing Trans-Sulfuration Pathway Activity in Astrocytes. *J. Alzheimers Dis.* **2020**, *76*, 981–995. [\[CrossRef\]](#)
66. Li, Q.; Cui, J.; Fang, C.; Liu, M.; Min, G.; Li, L. S-Adenosylmethionine Attenuates Oxidative Stress and Neuroinflammation Induced by Amyloid-beta Through Modulation of Glutathione Metabolism. *J. Alzheimers Dis.* **2017**, *58*, 549–558. [\[CrossRef\]](#)
67. Forman, H.J.; Zhang, H.; Rinna, A. Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Mol. Aspects Med.* **2009**, *30*, 1–12. [\[CrossRef\]](#)
68. Sedlak, T.W.; Paul, B.D.; Parker, G.M.; Hester, L.D.; Snowman, A.M.; Taniguchi, Y.; Kamiya, A.; Snyder, S.H.; Sawa, A. The glutathione cycle shapes synaptic glutamate activity. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 2701–2706. [\[CrossRef\]](#)
69. Griffith, O.W. Biologic and pharmacologic regulation of mammalian glutathione synthesis. *Free. Radic. Biol. Med.* **1999**, *27*, 922–935. [\[CrossRef\]](#) [\[PubMed\]](#)
70. Droge, W. Oxidative stress and ageing: Is ageing a cysteine deficiency syndrome? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2005**, *360*, 2355–2372. [\[CrossRef\]](#)
71. Han, H.; Wang, F.; Chen, J.; Li, X.; Fu, G.; Zhou, J.; Zhou, D.; Wu, W.; Chen, H. Changes in Biothiol Levels Are Closely Associated with Alzheimer's Disease. *J. Alzheimers Dis.* **2021**, *82*, 527–540. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Giovinazzo, D.; Bursac, B.; Sbodio, J.I.; Nalluru, S.; Vignane, T.; Snowman, A.M.; Albacarys, L.M.; Sedlak, T.W.; Torregrossa, R.; Whiteman, M.; et al. Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulfhydrating GSK3beta and inhibiting Tau hyperphosphorylation. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2017225118. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Hodgson, N.; Trivedi, M.; Muratore, C.; Li, S.; Deth, R. Soluble oligomers of amyloid-beta cause changes in redox state, DNA methylation, and gene transcription by inhibiting EAAT3 mediated cysteine uptake. *J. Alzheimers Dis.* **2013**, *36*, 197–209. [\[CrossRef\]](#)
74. Duerson, K.; Woltjer, R.L.; Mookherjee, P.; Leverenz, J.B.; Montine, T.J.; Bird, T.D.; Pow, D.V.; Rauen, T.; Cook, D.G. Detergent-insoluble EAAC1/EAAT3 aberrantly accumulates in hippocampal neurons of Alzheimer's disease patients. *Brain Pathol.* **2009**, *19*, 267–278. [\[CrossRef\]](#)
75. Pontrello, C.G.; McWhirt, J.M.; Glabe, C.G.; Brewer, G.J. Age-Related Oxidative Redox and Metabolic Changes Precede Intraneuronal Amyloid-beta Accumulation and Plaque Deposition in a Transgenic Alzheimer's Disease Mouse Model. *J. Alzheimers Dis.* **2022**, *90*, 1501–1521. [\[CrossRef\]](#)
76. Ansari, M.A.; Scheff, S.W. Oxidative stress in the progression of Alzheimer disease in the frontal cortex. *J. Neuropathol. Exp. Neurol.* **2010**, *69*, 155–167. [\[CrossRef\]](#)
77. Zabel, M.; Nackenoff, A.; Kirsch, W.M.; Harrison, F.E.; Perry, G.; Schrag, M. Markers of oxidative damage to lipids, nucleic acids and proteins and antioxidant enzymes activities in Alzheimer's disease brain: A meta-analysis in human pathological specimens. *Free. Radic. Biol. Med.* **2018**, *115*, 351–360. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Mandal, P.K.; Saharan, S.; Tripathi, M.; Murari, G. Brain glutathione levels—a novel biomarker for mild cognitive impairment and Alzheimer's disease. *Biol. Psychiatry* **2015**, *78*, 702–710. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Shukla, D.; Mandal, P.K.; Mishra, R.; Punjabi, K.; Dwivedi, D.; Tripathi, M.; Badhautia, V. Hippocampal Glutathione Depletion and pH Increment in Alzheimer's Disease: An in vivo MRS Study. *J. Alzheimers Dis.* **2021**, *84*, 1139–1152. [\[CrossRef\]](#)

80. Chen, J.J.; Thiagarajah, M.; Song, J.; Chen, C.; Herrmann, N.; Gallagher, D.; Rapoport, M.J.; Black, S.E.; Ramirez, J.; Andreazza, A.C.; et al. Altered central and blood glutathione in Alzheimer's disease and mild cognitive impairment: A meta-analysis. *Alzheimers Res. Ther.* **2022**, *14*, 23. [\[CrossRef\]](#)
81. Dwivedi, D.; Megha, K.; Mishra, R.; Mandal, P.K. Glutathione in Brain: Overview of Its Conformations, Functions, Biochemical Characteristics, Quantitation and Potential Therapeutic Role in Brain Disorders. *Neurochem. Res.* **2020**, *45*, 1461–1480. [\[CrossRef\]](#)
82. Navarro, J.F.; Croteau, D.L.; Jurek, A.; Andrusivova, Z.; Yang, B.; Wang, Y.; Ogedegbe, B.; Riaz, T.; Stoen, M.; Desler, C.; et al. Spatial Transcriptomics Reveals Genes Associated with Dysregulated Mitochondrial Functions and Stress Signaling in Alzheimer Disease. *iScience* **2020**, *23*, 101556. [\[CrossRef\]](#)
83. Thornalley, P.J. Glyoxalase I—structure, function and a critical role in the enzymatic defence against glycation. *Biochem. Soc. Trans.* **2003**, *31*, 1343–1348. [\[CrossRef\]](#)
84. Eto, K.; Asada, T.; Arima, K.; Makifuchi, T.; Kimura, H. Brain hydrogen sulfide is severely decreased in Alzheimer's disease. *Biochem. Biophys. Res. Commun.* **2002**, *293*, 1485–1488. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Liu, X.Q.; Liu, X.Q.; Jiang, P.; Huang, H.; Yan, Y. Plasma levels of endogenous hydrogen sulfide and homocysteine in patients with Alzheimer's disease and vascular dementia and the significance thereof. *Zhonghua Yi Xue Za Zhi* **2008**, *88*, 2246–2249.
86. Sun, P.; Chen, H.C.; Lu, S.; Hai, J.; Guo, W.; Jing, Y.H.; Wang, B. Simultaneous Sensing of H(2)S and ATP with a Two-Photon Fluorescent Probe in Alzheimer's Disease: Toward Understanding Why H(2)S Regulates Glutamate-Induced ATP Dysregulation. *Anal. Chem.* **2022**, *94*, 11573–11581. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Zhang, J.Y.; Ma, S.; Liu, X.; Du, Y.; Zhu, X.; Liu, Y.; Wu, X. Activating transcription factor 6 regulates cystathionine to increase autophagy and restore memory in Alzheimer's disease model mice. *Biochem. Biophys. Res. Commun.* **2022**, *615*, 109–115. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Fan, H.; Guo, Y.; Liang, X.; Yuan, Y.; Qi, X.; Wang, M.; Ma, J.; Zhou, H. Hydrogen sulfide protects against amyloid beta-peptide induced neuronal injury via attenuating inflammatory responses in a rat model. *J. Biomed. Res.* **2013**, *27*, 296–304. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Liu, Y.Y.; Bian, J.S. Hydrogen sulfide protects amyloid-beta induced cell toxicity in microglia. *J. Alzheimers Dis.* **2010**, *22*, 1189–1200. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Tang, X.Q.; Yang, C.T.; Chen, J.; Yin, W.L.; Tian, S.W.; Hu, B.; Feng, J.Q.; Li, Y.J. Effect of hydrogen sulphide on beta-amyloid-induced damage in PC12 cells. *Clin. Exp. Pharmacol. Physiol.* **2008**, *35*, 180–186. [\[CrossRef\]](#)
91. Zhang, H.; Gao, Y.; Zhao, F.; Dai, Z.; Meng, T.; Tu, S.; Yan, Y. Hydrogen sulfide reduces mRNA and protein levels of beta-site amyloid precursor protein cleaving enzyme 1 in PC12 cells. *Neurochem. Int.* **2011**, *58*, 169–175. [\[CrossRef\]](#)
92. Xuan, A.; Long, D.; Li, J.; Ji, W.; Zhang, M.; Hong, L.; Liu, J. Hydrogen sulfide attenuates spatial memory impairment and hippocampal neuroinflammation in beta-amyloid rat model of Alzheimer's disease. *J. Neuroinflammation* **2012**, *9*, 202. [\[CrossRef\]](#)
93. Giuliani, D.; Ottani, A.; Zaffe, D.; Galantucci, M.; Strinati, F.; Lodi, R.; Guarini, S. Hydrogen sulfide slows down progression of experimental Alzheimer's disease by targeting multiple pathophysiological mechanisms. *Neurobiol. Learn. Mem.* **2013**, *104*, 82–91. [\[CrossRef\]](#)
94. Ali, R.; Hameed, R.; Chauhan, D.; Sen, S.; Wahajuddin, M.; Nazir, A.; Verma, S. Multiple Actions of H(2)S-Releasing Peptides in Human beta-Amyloid Expressing C. elegans. *ACS Chem. Neurosci.* **2022**, *13*, 3378–3388. [\[CrossRef\]](#)
95. Xi, Y.; Zhang, Y.; Zhou, Y.; Liu, Q.; Chen, X.; Liu, X.; Grune, T.; Shi, L.; Hou, M.; Liu, Z. Effects of methionine intake on cognitive function in mild cognitive impairment patients and APP/PS1 Alzheimer's Disease model mice: Role of the cystathionine-beta-synthase/H(2)S pathway. *Redox Biol.* **2023**, *59*, 102595. [\[CrossRef\]](#)
96. Rose, P.; Moore, P.K.; Zhu, Y.Z. Garlic and Gaseous Mediators. *Trends Pharmacol. Sci.* **2018**, *39*, 624–634. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Benavides, G.A.; Squadrito, G.L.; Mills, R.W.; Patel, H.D.; Isbell, T.S.; Patel, R.P.; Darley-Usmar, V.M.; Doeller, J.E.; Kraus, D.W. Hydrogen sulfide mediates the vasoactivity of garlic. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17977–17982. [\[CrossRef\]](#)
98. Liang, D.; Wu, H.; Wong, M.W.; Huang, D. Diallyl Trisulfide Is a Fast H2S Donor, but Diallyl Disulfide Is a Slow One: The Reaction Pathways and Intermediates of Glutathione with Polysulfides. *Org. Lett.* **2015**, *17*, 4196–4199. [\[CrossRef\]](#)
99. Chuah, S.C.; Moore, P.K.; Zhu, Y.Z. S-allylcysteine mediates cardioprotection in an acute myocardial infarction rat model via a hydrogen sulfide-mediated pathway. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *293*, H2693–H2701. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Ghazimoradi, M.M.; Ghoushi, E.; Ghobadi Pour, M.; Karimi Ahmadabadi, H.; Rafieian-Kopaei, M. A review on garlic as a supplement for Alzheimer's disease: A mechanistic insight in its direct and indirect effects. *Curr. Pharm. Des.* **2023**, *29*, 519–526. [\[CrossRef\]](#)
101. Ray, B.; Chauhan, N.B.; Lahiri, D.K. The “aged garlic extract” (AGE) and one of its active ingredients S-allyl-L-cysteine (SAC) as potential preventive and therapeutic agents for Alzheimer's disease (AD). *Curr. Med. Chem.* **2011**, *18*, 3306–3313. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Chauhan, N.B. Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. *J. Ethnopharmacol.* **2006**, *108*, 385–394. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Tedeschi, P.; Nigro, M.; Travagli, A.; Catani, M.; Cavazzini, A.; Merighi, S.; Gessi, S. Therapeutic Potential of Allicin and Aged Garlic Extract in Alzheimer's Disease. *Int. J. Mol. Sci.* **2022**, *23*, 6950. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Griffin, B.; Selassie, M.; Gwebu, E.T. Effect of Aged Garlic Extract on the Cytotoxicity of Alzheimer beta-Amyloid Peptide in Neuronal PC12 Cells. *Nutr. Neurosci.* **2000**, *3*, 139–142. [\[CrossRef\]](#)

105. Gupta, V.B.; Indi, S.S.; Rao, K.S. Garlic extract exhibits anti-amyloidogenic activity on amyloid-beta fibrillogenesis: Relevance to Alzheimer's disease. *Phytother. Res.* **2009**, *23*, 111–115. [\[CrossRef\]](#)
106. Luo, J.F.; Dong, Y.; Chen, J.Y.; Lu, J.H. The effect and underlying mechanisms of garlic extract against cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis of experimental animal studies. *J. Ethnopharmacol.* **2021**, *280*, 114423. [\[CrossRef\]](#)
107. He, X.L.; Yan, N.; Zhang, H.; Qi, Y.W.; Zhu, L.J.; Liu, M.J.; Yan, Y. Hydrogen sulfide improves spatial memory impairment and decreases production of Aβ in APP/PS1 transgenic mice. *Neurochem. Int.* **2014**, *67*, 1–8. [\[CrossRef\]](#)
108. Yang, Y.J.; Zhao, Y.; Yu, B.; Xu, G.G.; Wang, W.; Zhan, J.Q.; Tang, Z.Y.; Wang, T.; Wei, B. GluN2B-containing NMDA receptors contribute to the beneficial effects of hydrogen sulfide on cognitive and synaptic plasticity deficits in APP/PS1 transgenic mice. *Neuroscience* **2016**, *335*, 170–183. [\[CrossRef\]](#)
109. Zhao, F.L.; Qiao, P.F.; Yan, N.; Gao, D.; Liu, M.J.; Yan, Y. Hydrogen Sulfide Selectively Inhibits gamma-Secretase Activity and Decreases Mitochondrial Aβ Production in Neurons from APP/PS1 Transgenic Mice. *Neurochem. Res.* **2016**, *41*, 1145–1159. [\[CrossRef\]](#)
110. Li, X.H.; Deng, Y.Y.; Li, F.; Shi, J.S.; Gong, Q.H. Neuroprotective effects of sodium hydrosulfide against beta-amyloid-induced neurotoxicity. *Int. J. Mol. Med.* **2016**, *38*, 1152–1160. [\[CrossRef\]](#)
111. Cui, W.; Zhang, Y.; Yang, C.; Sun, Y.; Zhang, M.; Wang, S. Hydrogen sulfide prevents Aβ-induced neuronal apoptosis by attenuating mitochondrial translocation of PTEN. *Neuroscience* **2016**, *325*, 165–174. [\[CrossRef\]](#)
112. Liu, Y.; Deng, Y.; Liu, H.; Yin, C.; Li, X.; Gong, Q. Hydrogen sulfide ameliorates learning memory impairment in APP/PS1 transgenic mice: A novel mechanism mediated by the activation of Nrf2. *Pharmacol. Biochem. Behav.* **2016**, *150–151*, 207–216. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Sestito, S.; Daniele, S.; Pietrobono, D.; Citi, V.; Bellusci, L.; Chiellini, G.; Calderone, V.; Martini, C.; Rapposelli, S. Memantine prodrug as a new agent for Alzheimer's Disease. *Sci. Rep.* **2019**, *9*, 4612. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Rao, S.P.; Xie, W.; Christopher Kwon, Y.I.; Juckel, N.; Xie, J.; Dronamraju, V.R.; Vince, R.; Lee, M.K.; More, S.S. Sulfanegen stimulates 3-mercaptopyruvate sulfurtransferase activity and ameliorates Alzheimer's disease pathology and oxidative stress in vivo. *Redox Biol.* **2022**, *57*, 102484. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Salehpour, M.; Ashabi, G.; Kashef, M.; Marashi, E.S.; Ghasemi, T. Aerobic Training with Naringin Supplementation Improved Spatial Cognition via H(2)S Signaling Pathway in Alzheimer's Disease Model Rats. *Exp. Aging Res.* **2022**, 1–14. [\[CrossRef\]](#)
116. Aboulhoda, B.E.; Rashed, L.A.; Ahmed, H.; Obaya, E.M.M.; Ibrahim, W.; Alkafass, M.A.L.; Abd El-Aal, S.A.; ShamsEldeen, A.M. Hydrogen sulfide and mesenchymal stem cells-extracted microvesicles attenuate LPS-induced Alzheimer's disease. *J. Cell. Physiol.* **2021**, *236*, 5994–6010. [\[CrossRef\]](#) [\[PubMed\]](#)
117. Kamat, P.K.; Kyles, P.; Kalani, A.; Tyagi, N. Hydrogen Sulfide Ameliorates Homocysteine-Induced Alzheimer's Disease-Like Pathology, Blood-Brain Barrier Disruption, and Synaptic Disorder. *Mol. Neurobiol.* **2016**, *53*, 2451–2467. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Huang, H.J.; Chen, S.L.; Hsieh-Li, H.M. Administration of NaHS Attenuates Footshock-Induced Pathologies and Emotional and Cognitive Dysfunction in Triple Transgenic Alzheimer's Mice. *Front. Behav. Neurosci.* **2015**, *9*, 312. [\[CrossRef\]](#)
119. Vandini, E.; Ottani, A.; Zaffe, D.; Calevro, A.; Canalini, F.; Cavallini, G.M.; Rossi, R.; Guarini, S.; Giuliani, D. Mechanisms of Hydrogen Sulfide against the Progression of Severe Alzheimer's Disease in Transgenic Mice at Different Ages. *Pharmacology* **2019**, *103*, 50–60. [\[CrossRef\]](#)
120. Mustafa, A.K.; Gadalla, M.M.; Sen, N.; Kim, S.; Mu, W.; Gazi, S.K.; Barrow, R.K.; Yang, G.; Wang, R.; Snyder, S.H. H₂S signals through protein S-sulfhydration. *Sci. Signal.* **2009**, *2*, ra72. [\[CrossRef\]](#)
121. Paul, B.D.; Snyder, S.H. H₂S: A Novel Gasotransmitter that Signals by Sulfhydration. *Trends Biochem. Sci.* **2015**, *40*, 687–700. [\[CrossRef\]](#)
122. Petrovic, D.; Kouroussis, E.; Vignane, T.; Filipovic, M.R. The Role of Protein Persulfidation in Brain Aging and Neurodegeneration. *Front. Aging Neurosci.* **2021**, *13*, 674135. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Doka, E.; Pader, I.; Biro, A.; Johansson, K.; Cheng, Q.; Ballago, K.; Prigge, J.R.; Pastor-Flores, D.; Dick, T.P.; Schmidt, E.E.; et al. A novel persulfide detection method reveals protein persulfide- and polysulfide-reducing functions of thioredoxin and glutathione systems. *Sci. Adv.* **2016**, *2*, e1500968. [\[CrossRef\]](#)
124. Krishnan, N.; Fu, C.; Pappin, D.J.; Tonks, N.K. H₂S-Induced sulfhydration of the phosphatase PTP1B and its role in the endoplasmic reticulum stress response. *Sci. Signal.* **2011**, *4*, ra86. [\[CrossRef\]](#)
125. Wedmann, R.; Onderka, C.; Wei, S.; Szijarto, I.A.; Miljkovic, J.L.; Mitrovic, A.; Lange, M.; Savitsky, S.; Yadav, P.K.; Torregrossa, R.; et al. Improved tag-switch method reveals that thioredoxin acts as depersulfidase and controls the intracellular levels of protein persulfidation. *Chem. Sci.* **2016**, *7*, 3414–3426. [\[CrossRef\]](#)
126. Vandiver, M.S.; Paul, B.D.; Xu, R.; Karuppagounder, S.; Rao, F.; Snowman, A.M.; Ko, H.S.; Lee, Y.I.; Dawson, V.L.; Dawson, T.M.; et al. Sulfhydration mediates neuroprotective actions of parkin. *Nat. Commun.* **2013**, *4*, 1626. [\[CrossRef\]](#)
127. Paul, B.D.; Sbodio, J.I.; Snyder, S.H. Mutant Huntingtin Derails Cysteine Metabolism in Huntington's Disease at Both Transcriptional and Post-Translational Levels. *Antioxidants* **2022**, *11*, 1470. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Sbodio, J.I.; Snyder, S.H.; Paul, B.D. Golgi stress response reprograms cysteine metabolism to confer cytoprotection in Huntington's disease. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 780–785. [\[CrossRef\]](#)

129. Snijder, P.M.; Baratashvili, M.; Grzeschik, N.A.; Leuvenink, H.G.D.; Kuipers, L.; Huitema, S.; Schaap, O.; Giepmans, B.N.G.; Kuipers, J.; Miljkovic, J.L.; et al. Overexpression of Cystathionine gamma-Lyase Suppresses Detrimental Effects of Spinocerebellar Ataxia Type 3. *Mol. Med.* **2016**, *21*, 758–768. [\[CrossRef\]](#) [\[PubMed\]](#)
130. Zivanovic, J.; Kouroussis, E.; Kohl, J.B.; Adhikari, B.; Bursac, B.; Schott-Roux, S.; Petrovic, D.; Miljkovic, J.L.; Thomas-Lopez, D.; Jung, Y.; et al. Selective Persulfide Detection Reveals Evolutionarily Conserved Antiaging Effects of S-Sulfhydration. *Cell Metab.* **2019**, *30*, 1152–1170.e1113. [\[CrossRef\]](#)
131. Ji, D.; Luo, C.; Liu, J.; Cao, Y.; Wu, J.; Yan, W.; Xue, K.; Chai, J.; Zhu, X.; Wu, Y.; et al. Insufficient S-Sulfhydration of Methylenetetrahydrofolate Reductase Contributes to the Progress of Hyperhomocysteinemia. *Antioxid. Redox Signal.* **2022**, *36*, 1–14. [\[CrossRef\]](#)
132. Yin, W.L.; He, J.Q.; Hu, B.; Jiang, Z.S.; Tang, X.Q. Hydrogen sulfide inhibits MPP⁺-induced apoptosis in PC12 cells. *Life Sci.* **2009**, *85*, 269–275. [\[CrossRef\]](#)
133. Kimura, Y.; Kimura, H. Hydrogen sulfide protects neurons from oxidative stress. *FASEB J.* **2004**, *18*, 1165–1167. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Zhang, M.; Shan, H.; Wang, T.; Liu, W.; Wang, Y.; Wang, L.; Zhang, L.; Chang, P.; Dong, W.; Chen, X.; et al. Dynamic change of hydrogen sulfide after traumatic brain injury and its effect in mice. *Neurochem. Res.* **2013**, *38*, 714–725. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Jiang, X.; Huang, Y.; Lin, W.; Gao, D.; Fei, Z. 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.* **2013**, *184*, e27–e35. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Zhang, M.; Shan, H.; Chang, P.; Wang, T.; Dong, W.; Chen, X.; Tao, L. Hydrogen sulfide offers neuroprotection on traumatic brain injury in parallel with reduced apoptosis and autophagy in mice. *PLoS ONE* **2014**, *9*, e87241. [\[CrossRef\]](#)
137. Karimi, S.A.; Hosseinmardi, N.; Janahmadi, M.; Sayyah, M.; Hajisoltani, R. The protective effect of hydrogen sulfide (H₂S) on traumatic brain injury (TBI) induced memory deficits in rats. *Brain Res. Bull.* **2017**, *134*, 177–182. [\[CrossRef\]](#)
138. Xu, K.; Wu, F.; Xu, K.; Li, Z.; Wei, X.; Lu, Q.; Jiang, T.; Wu, F.; Xu, X.; Xiao, J.; et al. NaHS restores mitochondrial function and inhibits autophagy by activating the PI3K/Akt/mTOR signalling pathway to improve functional recovery after traumatic brain injury. *Chem. Biol. Interact.* **2018**, *286*, 96–105. [\[CrossRef\]](#)
139. Campolo, M.; Esposito, E.; Ahmad, A.; Di Paola, R.; Paterniti, I.; Cordaro, M.; Bruschetta, G.; Wallace, J.L.; Cuzzocrea, S. Hydrogen sulfide-releasing cyclooxygenase inhibitor ATB-346 enhances motor function and reduces cortical lesion volume following traumatic brain injury in mice. *J. Neuroinflamm.* **2014**, *11*, 196. [\[CrossRef\]](#)
140. Zhang, M.; Shan, H.; Chang, P.; Ma, L.; Chu, Y.; Shen, X.; Wu, Q.; Wang, Z.; Luo, C.; Wang, T.; et al. Upregulation of 3-MST Relates to Neuronal Autophagy After Traumatic Brain Injury in Mice. *Cell. Mol. Neurobiol.* **2017**, *37*, 291–302. [\[CrossRef\]](#)
141. Sun, J.; Li, X.; Gu, X.; Du, H.; Zhang, G.; Wu, J.; Wang, F. Neuroprotective effect of hydrogen sulfide against glutamate-induced oxidative stress is mediated via the p53/glutaminase 2 pathway after traumatic brain injury. *Aging* **2021**, *13*, 7180–7189. [\[CrossRef\]](#)
142. Huerta de la Cruz, S.; Rocha, L.; Santiago-Castaneda, C.; Sanchez-Lopez, A.; Pinedo-Rodriguez, A.D.; Medina-Terol, G.J.; Centurion, D. Hydrogen Sulfide Subchronic Treatment Improves Hypertension Induced by Traumatic Brain Injury in Rats through Vasopressor Sympathetic Outflow Inhibition. *J. Neurotrauma* **2022**, *39*, 181–195. [\[CrossRef\]](#)
143. Lopez-Preza, F.I.; Huerta de la Cruz, S.; Santiago-Castaneda, C.; Silva-Velasco, D.L.; Beltran-Ornelas, J.H.; Tapia-Martinez, J.; Sanchez-Lopez, A.; Rocha, L.; Centurion, D. Hydrogen sulfide prevents the vascular dysfunction induced by severe traumatic brain injury in rats by reducing reactive oxygen species and modulating eNOS and H₂S-synthesizing enzyme expression. *Life Sci.* **2023**, *312*, 121218. [\[CrossRef\]](#)
144. Kehrer, J.P. The Haber-Weiss reaction and mechanisms of toxicity. *Toxicology* **2000**, *149*, 43–50. [\[CrossRef\]](#)
145. Lin, Q.; Shahid, S.; Hone-Blanchet, A.; Huang, S.; Wu, J.; Bisht, A.; Loring, D.; Goldstein, F.; Levey, A.; Crosson, B.; et al. Magnetic resonance evidence of increased iron content in subcortical brain regions in asymptomatic Alzheimer’s disease. *Hum. Brain Mapp.* **2023**. [\[CrossRef\]](#) [\[PubMed\]](#)
146. Kenkhuis, B.; Bush, A.I.; Ayton, S. How iron can drive neurodegeneration. *Trends Neurosci.* **2023**, *46*, 333–335. [\[CrossRef\]](#)
147. Mahoney-Sanchez, L.; Bouchaoui, H.; Ayton, S.; Devos, D.; Duce, J.A.; Devedjian, J.C. Ferroptosis and its potential role in the pathophysiology of Parkinson’s Disease. *Prog. Neurobiol.* **2021**, *196*, 101890. [\[CrossRef\]](#)
148. Robicsek, S.A.; Bhattacharya, A.; Rabai, F.; Shukla, K.; Dore, S. Blood-Related Toxicity after Traumatic Brain Injury: Potential Targets for Neuroprotection. *Mol. Neurobiol.* **2020**, *57*, 159–178. [\[CrossRef\]](#)
149. Nisenbaum, E.J.; Novikov, D.S.; Lui, Y.W. The presence and role of iron in mild traumatic brain injury: An imaging perspective. *J. Neurotrauma* **2014**, *31*, 301–307. [\[CrossRef\]](#) [\[PubMed\]](#)
150. Braughler, J.M.; Duncan, L.A.; Chase, R.L. The involvement of iron in lipid peroxidation. Importance of ferric to ferrous ratios in initiation. *J. Biol. Chem.* **1986**, *261*, 10282–10289. [\[CrossRef\]](#) [\[PubMed\]](#)
151. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell* **2012**, *149*, 1060–1072. [\[CrossRef\]](#)
152. Ashraf, A.; Jeandriens, J.; Parkes, H.G.; So, P.W. Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Alzheimer’s disease: Evidence of ferroptosis. *Redox Biol.* **2020**, *32*, 101494. [\[CrossRef\]](#) [\[PubMed\]](#)
153. Wu, Y.; Torabi, S.F.; Lake, R.J.; Hong, S.; Yu, Z.; Wu, P.; Yang, Z.; Nelson, K.; Guo, W.; Pawel, G.T.; et al. Simultaneous Fe²⁺/Fe³⁺ imaging shows Fe³⁺ over Fe²⁺ enrichment in Alzheimer’s disease mouse brain. *Sci. Adv.* **2023**, *9*, eade7622. [\[CrossRef\]](#) [\[PubMed\]](#)

154. Stockwell, B.R. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell* **2022**, *185*, 2401–2421. [[CrossRef](#)]
155. Wang, Y.; Ying, X.; Wang, Y.; Zou, Z.; Yuan, A.; Xiao, Z.; Geng, N.; Qiao, Z.; Li, W.; Lu, X.; et al. Hydrogen sulfide alleviates mitochondrial damage and ferroptosis by regulating OPA3-NFS1 axis in doxorubicin-induced cardiotoxicity. *Cell. Signal.* **2023**, *107*, 110655. [[CrossRef](#)]
156. Yu, Y.; Li, X.; Wu, X.; Li, X.; Wei, J.; Chen, X.; Sun, Z.; Zhang, Q. Sodium hydrosulfide inhibits hemin-induced ferroptosis and lipid peroxidation in BV2 cells via the CBS/H(2)S system. *Cell. Signal.* **2023**, *104*, 110594. [[CrossRef](#)] [[PubMed](#)]
157. Yu, M.; Wang, W.; Dang, J.; Liu, B.; Xu, J.; Li, J.; Liu, Y.; He, L.; Ying, Y.; Cai, J.; et al. Hydrogen sulfide protects retinal pigment epithelium cells against ferroptosis through the AMPK- and p62-dependent non-canonical NRF2-KEAP1 pathway. *Exp. Cell Res.* **2023**, *422*, 113436. [[CrossRef](#)]
158. Wallace, J.L.; Nagy, P.; Feener, T.D.; Allain, T.; Ditroi, T.; Vaughan, D.J.; Muscara, M.N.; de Nucci, G.; Buret, A.G. A proof-of-concept, Phase 2 clinical trial of the gastrointestinal safety of a hydrogen sulfide-releasing anti-inflammatory drug. *Br. J. Pharmacol.* **2020**, *177*, 769–777. [[CrossRef](#)]

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