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Hydrogen sulfide signaling in neurodegenerative diseases

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Abstract

The gaseous neurotransmitter hydrogen sulfide (H_2S) exerts neuroprotective efficacy in the brain via post-translational modification of cysteine residues by sulfhydration, also known as persulfidation. This process is comparable in biological impact to phosphorylation and mediates a variety of signaling events. Unlike conventional neurotransmitters, H_2S cannot be stored in vesicles due to its gaseous nature. Instead, it is either locally synthesized or released from

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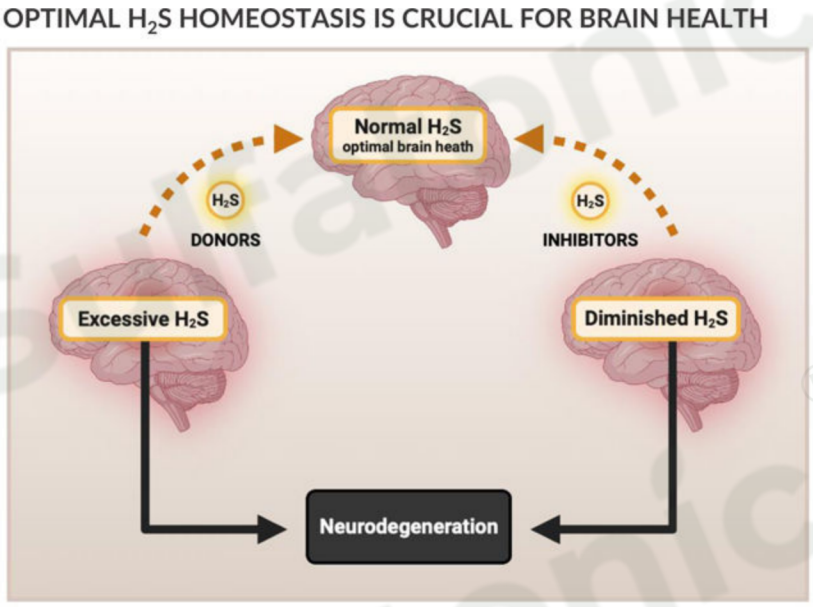
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endogenous stores. Sulfhydration affords both specific and general neuroprotective effects and is critically diminished in several neurodegenerative disorders. Conversely, some forms of neurodegenerative disease are linked to excessive cellular H_2S. Here, we review the signaling roles of H_2S across the spectrum of neurodegenerative diseases, including Huntington's disease, Parkinson's disease, Alzheimer's disease, Down syndrome, traumatic brain injury, the ataxias, and amyotrophic lateral sclerosis, as well as neurodegeneration generally associated with aging.

Graphical Abstract



Introduction

Eons ago in the Proterozoic oceans, early life on Earth flourished in an H_2S-rich environment, where the gas served as an energy substrate for various organisms (Olson & Straub, 2016). Notably, H2S was also detected within the famous "primordial soup" described by Miller in the electric discharge experiment (Parker et al., 2011). Later, with the planet-altering increase in ambient oxygen levels 2.33 billion years ago, termed the "great oxygenation event", evolution adapted by incorporating the chemical versatility of sulfur into multiple signaling pathways (Luo, Ono, Beukes, Wang, Xie & Summons, 2016). Thus, this non-respiratory gas has evolved to function alongside other gases, such as carbon monoxide (CO) and nitric oxide (NO), in all phyla.

Although H_2S is ubiquitously present across all organ systems, including the nervous system, to date its mechanistic roles have been predominantly studied in peripheral tissues. Furthermore, most studies of H_2S in the brain have been phenomenologically descriptive rather than mechanistic. Initial reports of H_2S in the brain focused on the deleterious effects of high exogenous doses, and the normal biological presence of H_2S in the brain was an unanticipated discovery in control brain tissue. This sparked rapidly growing interest

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in the role of H_2S in the central nervous system, particularly as it relates to various neurodegenerative conditions.

Biosynthesis, sources, and regulation of H_2S in mammals

Until its endogenous generation in mammalian systems was discovered, H_2S was regarded solely as a noxious molecule and environmental toxin (Clarke, 1953). It is now known, however, that H_2S is regularly physiologically generated by both enzymatic and non-enzymatic routes. At least three enzymes, cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (MPST) synthesize H_2S (Paul & Snyder, 2012; Stipanuk & Beck, 1982). Other sources of H_2S include the acid labile pool, the sulfane sulfur pool, and the microbiota (Ishigami, Hiraki, Umemura, Ogasawara, Ishii & Kimura, 2009; Shen, Carlstrom, Borniquel, Jadert, Kevil & Lundberg, 2013; Shen, Peter, Bir, Wang & Kevil, 2012). Dietary sources of H_2S include garlic, sulforaphane and isothiocyanates, quercetin, resveratrol, and other compounds (Benavides et al., 2007; Chuah, Moore & Zhu, 2007; El-Sayed, Shahin, Fahmy & Elshazly, 2021; Martelli, Citi, Testai, Brogi & Calderone, 2020; Yetik-Anacak, Dereli, Sevin, Ozzayim, Erac & Ahmed, 2015; Yetik-Anacak, Sevin, Ozzayim, Dereli & Ahmed, 2016). Another mode of non-enzymatic production of H_2S involves iron and vitamin B6 (Yang et al., 2019). These sources of H_2S are summarized in Figure 1A.

Endogenous enzymatic synthesis of H_2S is tightly coordinated by the transsulfuration pathway (Figure 1A). Here, dietary methionine provides sulfur, which is converted via S-adenosyl methionine (SAM) and S-adenosylhomocysteine to homocysteine. Homocysteine is then condensed with serine to produce cystathionine by CBS, which in turn is converted to cysteine (cys) by CSE. CSE is the only mammalian enzyme that synthesizes cysteine, and $CSE^{-/-}$ mice display cysteine and glutathione (GSH) depletion, weight loss, myopathy, and premature death (Ishigami, Hiraki, Umemura, Ogasawara, Ishii & Kimura, 2009; Mani, Yang & Wang, 2011). Because CSE activity does not begin until after birth, preterm infants and fetuses are dependent entirely on dietary cysteine (Gaull, Sturman & Raiha, 1972; Sturman, Gaull & Raiha, 1970; Vina et al., 1995). Similarly, HIV depletes CSE, such that AIDS patients may also become dependent on diet-derived cysteine (Martin, Sastre, de la Asuncion, Pallardo & Vina, 2001). Thus, cysteine is classified as a semi-essential amino acid because it is both endogenously synthesized and exogenously obtained from the diet. Importantly, cysteine serves as a precursor for several sulfur containing molecules, such as glutathione, lanthionine, homolanthionine, coenzyme A, iron sulfur cluster proteins, and H_2S (Paul, Sbodio & Snyder, 2018; Sbodio, Snyder & Paul, 2019). Notably, although cysteine is one of the rarest amino acids and comprises only 2% of the human proteome, it is highly versatile and undergoes the largest number of post-translational modifications of all amino acids, underscoring its important biological role (Miseta & Csutora, 2000; Sbodio, Snyder & Paul, 2019).

Whereas CSE utilizes either cysteine or homocysteine alone to produce H_2S, CBS utilizes a combination of these two molecules to efficiently produce the gas (Chen, Jhee & Kruger, 2004; Filipovic, Zivanovic, Alvarez & Banerjee, 2018; Paul & Snyder, 2012). CSE is highly expressed in the liver and kidney, with lower levels in the brain (Ishii et al., 2004). Among

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the three enzymes that produce H_2S in the brain, CSE is highly inducible and enriched in neurons. CSE is also induced by several forms of stress, such as endoplasmic reticulum stress, Golgi stress, oxidative stress, mitochondrial stress, inflammation, and starvation (Hine et al., 2015; Martin et al., 2007; Sbodio, Snyder & Paul, 2016; Sbodio, Snyder & Paul, 2018; Sen et al., 2012; Zivanovic et al., 2019). CBS and MPST, on the other hand, are less readily inducible, with CBS being regulated through its heme center by other gaseous molecules such as NO and CO, or by allosteric modulation by SAM (Finkelstein, Kyle, Martin & Pick, 1975; Morikawa et al., 2012; Singh, Madzelan & Banerjee, 2007). CBS is also regulated in response to nuclear hormones, such as testosterone and estradiol, glucocorticoids, and the nuclear hormone receptor ligand 1,25-dihydroxyvitamin D3, as well as hypoxia (Lechuga, Bilg, Patel, Nguyen, Qi & Chen, 2019; Ratnam, Maclean, Jacobs, Brosnan, Kraus & Brosnan, 2002; Takano et al., 2014; Vitvitsky, Prudova, Stabler, Dayal, Lentz & Banerjee, 2007). In neurons, glutamate decreases CBS expression in an NO-dependent manner (Wang & Yang, 2016). Similarly, MPST is induced under certain conditions, including hypoxia, shear stress and exposure to fatty acids (Huang, Chen, Chen, Wang, Hsieh & Wang, 2015; Li et al., 2018; Tao, Wang, Sun & Zhu, 2017). Interestingly, optimal enzymatic activity of MPST requires endogenous reductants, such as thioredoxin and dihydrolipoic acid, while CSE and CBS do not (Mikami, Shibuya, Kimura, Nagahara, Ogasawara & Kimura, 2011). Finally, the activity of these three enzymes is also modulated at post-translational levels.

Signaling by H_2S

H_2S exerts its cellular effects through multiple mechanisms. For example, its role in mitochondrial metabolism has been intensely researched since 1986 when it was discovered that oxidized mitochondrial H_2S produces ATP through oxidative phosphorylation in *Solemya reidi*, a gutless clam that lives in sulfide-enriched waters (Powell & Somero, 1986). Two decades later, H_2S was demonstrated as the first inorganic donor for energy metabolism by mitochondria at low micromolar concentrations (Goubern, Andriamihaja, Nubel, Blachier & Bouillaud, 2007). Specifically, it was established that H_2S directly donates electrons to the mitochondrial electron transport chain (ETC), via either sulfide quinone oxidoreductase (SQR) or complex IV (cytochrome c oxidase) (Goubern, Andriamihaja, Nubel, Blachier & Bouillaud, 2007; Lagoutte, Mimoun, Andriamihaja, Chaumontet, Blachier & Bouillaud, 2010; Nicholls & Kim, 1982; Paul, Snyder & Kashfi, 2021; Vitvitsky et al., 2018).

The physiological effects of H_2S follow a bell shaped, or biphasic, dose-response curve. For example, lower doses of H_2S are beneficial to mitochondria, whereas higher doses are harmful. One of the earliest recognized effects of H_2S on energy metabolism involved induction of suspended animation in mice, which was caused by H_2S-mediated inhibition of complex IV of the ETC via binding the copper center of cytochrome c oxidase (Blackstone, Morrison & Roth, 2005; Hill, Woon, Nicholls, Peterson, Greenwood & Thomson, 1984; Modis et al., 2014; Nicholls, Marshall, Cooper & Wilson, 2013). In addition to binding metal centers involving iron and copper, H_2S is now known to signal prolifically via the posttranslational modification of proteins designated as sulfhydration, also known as persulfidation, wherein thiol groups on cysteine residues are converted to SSH groups, also known as persulfides (Filipovic, 2015; Mustafa et al., 2009; Paul & Snyder, 2012; Paul &

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Snyder, 2015). Notably, H_2S cannot directly modify –SH groups, and several mechanisms are involved in this modification (Figure 1B). These include nucleophilic attack of sulfide on oxidized cysteine residues such as cysteine sulfenic acids (Cys-SOH) or cysteine disulfides (–S–S–), reactions between oxidized sulfides such as polysulfides and cysteine thiols, or reaction of hydrogen disulfide (H_2S_2) with a cysteine thiol (Paul & Snyder, 2015). Cysteine sulfhydration is substantially more prevalent than cysteine S-nitrosylation, with about 25 percent of liver proteins sulfhydrated (Mustafa et al., 2009). Most frequently, sulfhydration of a cysteine residue increases its nucleophilicity, whereas S-nitrosylation decreases it. Reciprocity of function of sulfhydration and S-nitrosylation has been observed in several cases, as discussed in later sections.

Physiologic roles of H_2S in the brain

H_2S participates in multiple processes in the central nervous system, and one of its earliest reported roles involved modulation of amino acid neurotransmitters in H_2S intoxication (Kombian, Warenycia, Mele & Reiffenstein, 1988). Shortly thereafter, the unexpected presence of endogenous H_2S in the brain was discovered when other investigators who were studying a rat toxicological model of exogenously administered H_2S were surprised to find baseline levels of H_2S in the brains of control mice (Warenycia et al., 1989). Further analysis revealed that increased H_2S in the brain was associated with increased levels of dopamine, epinephrine, norepinephrine, and 5-hydroxytryptamine, as well as inhibition of monoamine oxidase, the enzyme that metabolizes catecholamines (Warenycia, Smith, Blashko, Kombian & Reiffenstein, 1989). The effect of H_2S was further examined when Abe and Kimura studied its role in N-methyl D-aspartate (NMDA) receptor-mediated long-term potentiation (LTP), confirming its physiologic function as a neuromodulator (Abe & Kimura, 1996). The NMDA receptor ion channel is regulated by glutamate and coagonists (glycine, D-serine, or D-cysteine), and modulates memory and synaptic plasticity (Lee et al., 2014). H_2S by itself does not cause LTP, but rather augments LTP at active NMDA-receptor synapses. Subsequent studies using various model systems further established the supporting role of H_2S in cognitive functions mediated by NMDA receptors, which included increased sulfhydration of NMDA receptor subunits (Li et al., 2017; Tu, Li, Li & Wang, 2016; Xu, Liu, Li & Zhang, 2015). These reports prompted detailed studies of the localization of H_2S-generating enzymes in the brain, and it is now well-established that CSE is localized to neurons, CBS is preferentially expressed in Bergman glia and astrocytes (Enokido, Suzuki, Iwasawa, Namekata, Okazawa & Kimura, 2005; Linden et al., 2008; Morikawa et al., 2012), and MPST is present in both neurons and astrocytes (Kimura et al., 2015; Shibuya et al., 2009).

H_2S is also important in maintenance of redox balance in the brain. Although it is not directly a strong reducing agent, H_2S indirectly elicits potent antioxidant effects. For example, H_2S mitigates oxidative stress by stimulating cystine uptake into neurons by both the cysteine transporter and the cystine/glutamate antiporter, which boosts synthesis of the antioxidant glutathione (Kimura, Goto & Kimura, 2010; Kimura & Kimura, 2004). These studies were the first to show that H_2S protected against oxytosis, a form of glutamate-induced cell death that intersects with ferroptosis, which is iron-mediated cell death discussed in later sections. H_2S also scavenges peroxynitrite radicals (Whiteman et

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al., 2004). Importantly, redox imbalance related to dysregulated H_2S has been observed in several neurodegenerative diseases, as described below.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant condition triggered by pathologic expansion of polyglutamine-encoding repeats in the huntingtin gene (1993). HD profoundly affects the corpus striatum of the brain, leading to cognitive deficits and impaired motor function characterized by chorea and involuntary movements (Bates et al., 2015). Mutant huntingtin (mHtt) aggregates and impacts almost all cellular and physiologic processes, including transcription, translation, mitochondrial function, redox balance, nucleocytoplasmic transport, autophagy, stress response, nutrient signaling, and DNA repair (Ahmed et al., 2015; Cha, 2000; Grima et al., 2017; Morozko et al., 2021; Paul, 2022; Paul, Sbodio & Snyder, 2022; Paul & Snyder, 2019; Pryor et al., 2014; Sbodio, Snyder & Paul, 2016; Sbodio, Snyder & Paul, 2018). H_2S modulates several of these processes and multiple lines of evidence indicate a role for disrupted cysteine metabolism in HD. For example, early studies using yeast two-hybrid analysis identified CBS as a huntingtin-interacting protein, but its effects on activity of CBS were not determined (Boutell, Wood, Harper & Jones, 1998). In addition, normal functioning and trafficking of the transporters for cysteine (excitatory amino acid transporter 1: EAAC1) and cystine (xCT/system x_c^-) are compromised in HD (Frederick et al., 2014; Li et al., 2010). CSE and cysteine are also dysregulated in HD, with drastic depletion in cell culture and mouse models of HD, as well as human HD (Paul et al., 2014; Paul & Snyder, 2014). Furthermore, this depletion is accompanied by decreased H_2S production and sulfhydration, along with elevated oxidative stress (Paul et al., 2014; Sbodio, Snyder & Paul, 2016; Zivanovic et al., 2019). Decreased CSE in HD originates with mHtt-mediated sequestration of specificity protein 1 (SP1), the transcription factor that regulates CSE expression. Notably, overexpressing SP1 in cell culture models of HD restores normal CSE expression (Li et al., 2016; Paul et al., 2014). Furthermore, mHtt derails not only basal expression of CSE, but also stress-responsive transcriptional regulation of CSE by activating transcription factor 4 (ATF4) (the master regulator for amino acid homeostasis), leading to cysteine deficit in HD cells (Paul, 2022; Sbodio, Snyder & Paul, 2016) (Figure 2). Elevated oxidative stress in HD cells is partially responsible for the lack of inducibility of ATF4 during oxidative stress (Sbodio, Snyder & Paul, 2016). Strikingly, supplementing the diet of HD mice with cysteine rescues their motor symptoms, mitigates neuropathology, and improves survival (Paul et al., 2014). Later studies also uncovered another layer of regulation at the post-translational level, in which mHtt binds both CSE and CBS and inhibits their catalytic activity (Paul, Sbodio & Snyder, 2022). Thus, cysteine metabolism is impaired at multiple levels by mHtt (Figure 2). Stimulating transsulfuration with agents that upregulate CSE expression, such as the Golgi stressor monensin at low doses, also rescues ATF4 and CSE expression, H_2S production, and sulfhydration, and decreases oxidative stress (Sbodio, Snyder & Paul, 2018; Zivanovic et al., 2019) Taken together, these studies demonstrate a neuroprotective role of the transsulfuration pathway and H_2S in HD.

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Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease and principally affects dopaminergic neurons of the substantia nigra. Symptoms of PD include motor dysfunction characterized by resting tremors, instability, rigidity, and bradykinesia, neuropsychiatric symptoms of cognitive impairment, depression, and anxiety, and other changes involving sleep disorders, olfactory impairment, and gastrointestinal tract disturbances. A molecular hallmark of PD is misfolding and aggregation of α-synuclein, a component of Lewy bodies (Spillantini, Schmidt, Lee, Trojanowski, Jakes & Goedert, 1997). Links between H_2S and PD were first implicated in a study that analyzed cognitive and motor functions in residents of Rotorua in New Zealand, which is known for its 'rotten egg' smell due to high ambient levels of H_2S emitted from geothermal vents. Specifically, residents living in areas with a higher level of the gas scored better on the finger tapping test, a component of the PD Motor Rating Scale examination tests (Cakmak, 2017). Our laboratory has also shown that H_2S signaling is disrupted in PD, leading to impaired sulfhydration. Interestingly, there is a concomitant increase in S-nitrosylation. Specifically, sulfhydration of the E3-ubiquitin ligase parkin is reduced, which impairs the normal clearance of toxic, misfolded proteins in PD (Vandiver et al., 2013). The major target of sulfhydration on parkin is Cys95, with Cys59 and Cys182 also being modified to some degree. Notably, biochemical analysis of postmortem PD patient striata revealed a decrease in sulfhydration and increase in S-nitrosylation of parkin, resulting in parkin inactivation (Vandiver et al., 2013) (Figure 3). Parkin also mediates mitophagy, which clears damaged and dysfunctional mitochondria, and sulfhydration enhances mitophagy by stimulating the deubiquitinase ubiquitin specific peptidase 8 (USP8) that removes ubiquitin groups from parkin and facilitates its recruitment to damaged mitochondria (Sun et al., 2020). There have also been reports on the potential pathologic role of H_2S in PD through the gut bacterium *Desulfovibrio*, which produces excess H_2S, although this is debated (Nie et al., 2023). Regardless, overexpression of H_2S-producing enzymes or administration of H_2S donors are neuroprotective in animal models of PD, suggesting that carefully calibrated doses may offer therapeutic benefits to patients (Kida et al., 2011). Similarly, overexpression of CBS or use of H_2S donors in mouse models of PD affords neuroprotection (Cao, Cao, Ding & Bian, 2018; Jiang et al., 2022; Sarukhani, Haghdoost-Yazdi, Sarbazi Golezari, Babayan-Tazehkand, Dargahi & Rastgoo, 2018; Xue & Bian, 2015; Yin, Yin, Huang & Wu, 2017). Although there are numerous instances of the neuroprotective effects of H_2S, the underlying mechanisms are still unknown. A systematic study of endogenous H_2S levels and sulfhydration in PD would deepen our understanding of H_2S signaling in PD.

Alzheimer's disease

Alzheimer's disease (AD) is a complex, multifactorial neurodegenerative disease and the leading cause of dementia in the elderly, with about 413 million individuals on the AD continuum globally and 30 million exhibiting AD dementia (Gustavsson et al., 2023). The hippocampus and cortex are the main regions affected in AD, causing memory loss, cognitive deficits, and impaired executive functions (Lane, Hardy & Schott, 2018; Masters, Bateman, Blennow, Rowe, Sperling & Cummings, 2015). Risk factors for AD include age, genetics, traumatic brain injury and having a family history of AD (Barker, Paul & Pieper, 2023; Fratiglioni, Ahlbom, Viitanen & Winblad, 1993; Hebert, Korabek & Scott, 2006;

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Karch & Goate, 2015; Saunders et al., 1993). AD may either be familial or sporadic, with most AD cases being sporadic and familial cases constituting only 5% of the total (Karch & Goate, 2015). The classical neuropathological hallmarks of AD include deposition of amyloid-β peptides in plaques and accumulation of paired helical filaments and tangles composed of the microtubule binding protein tau (Glenner & Wong, 1984; Grundke-Iqbal, Iqbal, Quinlan, Tung, Zaidi & Wisniewski, 1986; Masters, Simms, Weinman, Multhaup, McDonald & Beyreuther, 1985).

Similar to several other neurodegenerative diseases, AD is associated with elevated oxidative stress and dysregulation of the transsulfuration pathway at multiple levels (Paul, 2021). For example, levels of H_2S are lower in the plasma of AD patients and correlate with severity of cognitive impairment (Liu, Liu, Jiang, Huang & Yan, 2008). Levels of SAM, the allosteric regulator of CBS, are also reduced in both the brain and cerebrospinal fluid of AD patients (Linnebank et al., 2010; Morrison, Smith & Kish, 1996). Furthermore, higher levels of homocysteine, a substrate for CSE and CBS, are found in AD and correlate with disease severity (Clarke, Smith, Jobst, Refsum, Sutton & Ueland, 1998; Farina, Jerneren, Turner, Hart & Tabet, 2017; Kitzlerova et al., 2014). Levels of Cys, and GSH are also decreased and homocysteine levels are increased in Aβ1–42-treated PC12 cells, the brain and hippocampus of APP/PS1 mice, and the serum of AD patients (Han et al., 2021). More recently, we showed that levels of overall sulfhydration are decreased in the 3xTg-AD mouse model of AD as well as in post-mortem human AD brain (Giovinazzo et al., 2021). We further showed that wild type tau, but not mutant P301L tau, interacts with CSE and stimulates its activity in 3xTg-AD mice. H_2S produced by CSE prevents pathological phosphorylation of tau by sulfhydrating glycogen synthase kinase-3β (GSK-3β) and inhibiting its catalytic activity (Giovinazzo et al., 2021). In AD, decreased sulfhydration of GSK-3β is observed and could contribute to hyper-phosphorylation and aggregation of tau (Figure 4). Diminished sulfhydration and activity of methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in transmethylation and homocysteine clearance, is also seen in a mouse model of hyperhomocysteinemia and could contribute to cognitive decline in AD (Ji et al., 2022).

In line with these studies, administration of H_2S donors alleviates cognitive decline and delays disease progression in mouse models of AD. Mechanistically, H_2S preserves several aspects of normal physiology and abrogates aberrant activity of enzymes involved in AD progression (Figure 5). For example, H_2S donors maintain mitochondrial function and cellular autophagy, activate the antioxidant stress response, modulate NMDA receptors, increase acetylcholine levels, inhibit oxidation of cysteine residues and oxidative stress, restore overall sulfhydration levels and specific activity of β-secretase 1 (BACE-1), and attenuate amyloid plaque deposition and neuroinflammation (Ali et al., 2022; Giovinazzo et al., 2021; Giuliani et al., 2013; Paul & Pieper, 2023; Sestito et al., 2019; Tang et al., 2008; Vandini et al., 2019; Xi et al., 2023; Zhang et al., 2011; Zivanovic et al., 2019).

Down syndrome

Down syndrome (DS), which is caused by a trisomy of chromosome 21, is the most common survivable autosomal aneuploidy and the leading cause of intellectual disability

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(Antonarakis, 2017; Antonarakis et al., 2020; Lejeune, Gautier & Turpin, 1959). As more than 200 protein-encoding genes reside on chromosome 21, DS manifests as multiple abnormalities across musculoskeletal, neurological, and cardiovascular systems. Notably, DS is also associated with early-onset AD (Antonarakis et al., 2020). CBS, the biosynthetic enzyme for H_2S in astrocytes, is localized to chromosome 21, and hence is triplicated in DS. In the early 2000s, it was demonstrated that DS patients exhibit high levels of circulating sulfhemoglobin, which is formed by reaction of H_2S with hemoglobin, as well as increased urinary excretion of thiosulfate, a degradation product of H_2S (Belardinelli, Chabli, Chadefaux-Vekemans & Kamoun, 2001; Kamoun, 2001; Kamoun, Belardinelli, Chabli, Lallouchi & Chadefaux-Vekemans, 2003). This prompted the hypothesis that CBS-generated excessive H_2S could be responsible for the neuropsychiatric manifestations of DS, such as mental retardation (Kamoun, 2001). This discovery spurred new research on the dual effects of H_2S in neurodegenerative diseases, raising awareness that there are "low H_2S diseases" and "high H_2S diseases," thereby revealing that both paucity and excess of H_2S are deleterious. CBS is also particularly overexpressed in astrocytes surrounding senile plaques in the brains of DS patients. With this finding, the pathophysiology of CBS in DS was linked to inhibition of mitochondrial bioenergetics, in which excess H_2S inhibits complex IV of the ETC. Notably, inhibiting or silencing CBS in fibroblasts derived from DS patients reverses mitochondrial dysfunction and restores mitochondrial electron transport, mitochondrial oxygen consumption, ATP generation, and cell proliferation (Panagaki, Randi, Augsburger & Szabo, 2019). The deleterious effect of elevated CBS in DS was further confirmed in a rat model of DS, in which excess H_2S elicits neurobehavioral defects accompanied by loss of gamma brain wave activity and decreased expression of multiple synaptic proteins, all of which are reversed by CBS inhibition (Panagaki et al., 2022). Independent studies further confirmed that CBS overexpression causes dysregulation of the neurotransmitters serotonin and dopamine, and is both necessary and sufficient to cause cognitive deficits in mouse models of DS (London et al., 2019; Marechal et al., 2019). More recently, increased expression and activity of MPST was observed in DS, which could further contribute to disease progression (Panagaki et al., 2022). (Figure 6).

Traumatic brain injury

Traumatic brain injury (TBI) is one of the most widespread neurodegenerative conditions and constitutes the most significant risk factor for developing AD, after aging and genetics. TBI impacts several physiologic processes, all of which are modulated by H_2S (Figure 7) (Pieper & Paul, 2023). Links between H_2S signaling and TBI were established when dysregulation of H_2S biosynthetic enzymes was observed in animal models and H_2S donors were found to confer neuroprotection. For instance, in the weight-drop model of TBI, decreased expression of CBS in the hippocampus and cortex correlates with decreased levels of H_2S, and pretreatment with sodium hydrogen sulfide (NaHS) reduces lesion volume after injury (Zhang et al., 2013). The neuroprotective action of H_2S in TBI was further confirmed in the controlled cortical impact (CCI) model in rats (Jiang, Huang, Lin, Gao & Fei, 2013). Specifically, decreased brain levels of H_2S are observed and pretreatment with NaHS blocks edema and blood-brain barrier (BBB) damage and reduces lesion volume. NaHS administration also prevents TBI-induced decreases in choline acetyltransferase and superoxide dismutase activity, and blocks TBI-induced increase in markers of oxidative

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damage, such as 8-iso-prostaglandin F2 alpha and malondialdehyde. NaHS pretreatment additionally prevents cognitive impairment in both TBI models (Karimi, Hosseinmardi, Janahmadi, Sayyah & Hajisoltani, 2017; Zhang et al., 2014). Later studies mechanistically implicated the PI3K/Akt/mTOR signaling pathway in the neuroprotective effects of NaHS on the BBB, remyelination of axons, and maintenance of mitochondrial functions (Xu et al., 2018). Another hybrid H_2S donor, 2-(6-methoxynapthalen-2-yl)-propionic acid 4-thiocarbamoyl-phenyl ester (ATB-346), a H_2S-releasing derivative of naproxen, prevents TBI-induced neuronal cell death, brain edema, and motor dysfunction, while naproxen (which does not release H_2S) does not (Campolo et al., 2014). This study also demonstrated that treatment with ATB346 decreases expression of the pro-inflammatory mediators, inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), tumor necrosis factor alpha (TNFα), and interleukin 1-beta (IL-1β). In addition, ATB-346 treatment normalizes levels of glial-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) and increases levels of vascular endothelial growth factor (VEGF) after TBI. Interestingly, Zhang et al have also shown an upregulation of MPST in neurons that survive after TBI (Zhang et al., 2017). Later studies linked protection by H_2S to regulation of glutamate-mediated oxidative stress via the p53/glutaminase-2 pathway (Sun et al., 2021). It has also been reported that subchronic treatment with NaHS prevents sympathetic nervous system and hemodynamic dysfunction after TBI, and restores expression of CSE and CBS in the brain (Huerta de la Cruz et al., 2022). H_2S also ameliorates TBI-induced iron-mediated cell death, known as ferroptosis, resulting in overall reduction in oxidative damage and lipid peroxidation throughout the brain (Paul & Pieper, 2023). Ferroptosis intersects extensively with oxytosis, a form of glutamate-mediated cell death discovered over 30 years ago, and some have proposed that ferroptosis and oxytosis are components of the same pathway and should be collectively termed oxytosis/ferroptosis (Maher, Currais & Schubert, 2020; Murphy, Miyamoto, Sastre, Schnaar & Coyle, 1989; Stockwell, 2022). Regardless, H_2S protects against these intersecting pathways of cell death, with protective efficacy involving stimulation of cystine uptake through the System Xc^- (Kimura, Goto & Kimura, 2010; Kimura & Kimura, 2004). In summary, H_2S ameliorates multiple behavioral and physiological abnormalities triggered by TBI, and much remains to be learned about this potential therapeutic approach (Figure 7).

H_2S and ataxias

The ataxia disorders are characterized by lack of muscle coordination with voluntary movement, and generally involve the cerebellum. Dysregulation of the transsulfuration pathway and H_2S metabolism have been reported in some forms of ataxia. For example, in spinocerebellar ataxia 3 (SCA3), an autosomal dominant disease caused by expansion of polyglutamine repeats in the ataxin-3 protein, CSE depletion and diminished sulfhydration are observed in both a *D. melanogaster* model as well as postmortem human disease tissue (Snijder et al., 2016). Notably, overexpression of CSE ameliorates neurodegeneration in the *D. melanogaster* model. H_2S metabolism is also compromised in the autosomal recessive ataxia known as ataxia telangiectasia. In addition to unsteady gait, this disease manifests as dilation of blood vessels termed telangiectases in the conjunctiva of the eye and facial skin (Savitsky et al., 1995). The disease is caused by a mutation in the ataxia-telangiectasia mutated (ATM) protein, which regulates cell cycle checkpoints, redox balance, and double-

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stranded DNA break repair. Importantly, ATM expression suppresses CBS and CSE protein expression, as well as CSE enzymatic activity (Islam, Shen, Pardue, Kevil & Shackelford, 2022). Expression of CSE is approximately four times lower in ATM cells and its enzymatic activity is roughly 40% lower with ATM expression. At this stage, further study on the role of sulfhydration in the ataxias is warranted.

H_2S in amyotrophic lateral sclerosis

ALS is a fatal neurodegenerative disease leading to selective degeneration of upper and lower motor neurons. The causes of ALS may be sporadic or familial, with about 20% of familial causes attributed to mutations in the Cu/Zn superoxide dismutase (SOD1) gene. The most studied mutation in this gene is the G93A mutation, a gain of function mutation that causes the mutant protein to aggregate, leading to loss of motor neurons (Gurney et al., 1994; Rosen et al., 1993). Elevated levels of H_2S have been observed in ALS (Davoli et al., 2015), and increased H_2S production has been attributed to CBS, with the G93A mouse model exhibiting increased H_2S production in tissues and spinal cord cultures possessing high intracellular Ca^{2+} levels. Elevated H_2S is also detected in cerebrospinal fluid of ALS patients. Interestingly, administering amino-oxyacetic acid, an inhibitor of CBS, decreases H_2S in cerebral tissues and increases survival of female but not male mice (Spalloni et al., 2019). Although much remains to be discovered about the potential role for H_2S in ALS, it appears that this represents another neurodegenerative condition associated with excessive production of H_2S.

H_2S and aging

Aging, a currently inevitable and irreversible process, is the biggest risk factor for developing neurodegeneration (Hou et al., 2019). Aging is complex and may be broadly defined as a functional decline over time. Originally, researchers defined nine molecular, cellular, and systemic hallmarks of aging: DNA instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. These have now been expanded to additionally include disabled macroautophagy, chronic inflammation, and dysbiosis (Lopez-Otin, Blasco, Partridge, Serrano & Kroemer, 2013; Lopez-Otin, Blasco, Partridge, Serrano & Kroemer, 2023). H_2S impacts almost all these hallmarks and plays a central role in delaying senescence and aging phenotypes (Figure 8) (de Cabo & Diaz-Ruiz, 2020; Zivanovic et al., 2019). Caloric restriction, which increases longevity in several species including worms, flies, yeast, and mammals, elevates H_2S via the reverse transsulfuration pathway (Hine et al., 2015). We proposed in 2012 that H_2S-mediated sulfhydration could be expected to protect proteins from irreversible oxidation on cysteine residues (Paul & Snyder, 2012). Now, protection of SH groups of cysteine residues by persulfidation has been verified in the case of phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and most recently in a landmark study by Filipovic and colleagues that showed evolutionary conservation of this phenomenon (Gao et al., 2015; Ohno, Okuda & Uehara, 2015; Zivanovic et al., 2019). Specifically, decreased sulfhydration is associated with a concomitant increase in cysteine oxidation in aging. Similarly, sulfhydration levels are also decreased over time in mice and rats (Zivanovic et al., 2019).

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Thus, H_2S production and sulfhydration may prevent oxidation of proteins and contribute to longevity, both at the level of protein half-life and overall life span of the organism. Accordingly, restoring H_2S metabolism may improve the healthspan and lifespan of people, including those afflicted with neurodegenerative diseases.

Intersections of sulfhydration and S-nitrosylation in neurodegeneration

NO and H_2S, which both modify cysteine residues, exhibit several similarities and differences in their mode of action and biosynthesis. In some cases, the same cysteine residue can be modified by either process. Like H_2S, NO is also synthesized by both canonical and non-canonical pathways (Kapil et al., 2020). Furthermore, both sulfhydration and S-nitrosylation can be reversed by endogenous reductants and associated enzymes, such as the thioredoxin/thioredoxin reductase system (Benhar, Forrester & Stamler, 2009; Doka et al., 2016; Krishnan, Fu, Pappin & Tonks, 2011). In terms of differences, only a very small fraction of the total amount of any given protein is S-nitrosylated, whereas 25–50% of most hepatic proteins are sulfhydrated (Jaffrey & Snyder, 2001; Mustafa et al., 2009). Transfer of s-nitrosothiol groups among proteins and molecules has been shown to be enzymatically regulated with target specificity (Jia et al., 2014; Kornberg et al., 2010; Nakamura, Oh, Zhang, Tannenbaum & Lipton, 2021; Seth, Hess, Hausladen, Wang, Wang & Stamler, 2018; Stomberski, Hess & Stamler, 2019; Stomberski et al., 2022), whereas a similar system has not been identified for sulfhydration. Moreover, sulfhydration and S-nitrosylation can have different effects on protein function. For example, GAPDH, a key regulatory enzyme of glycolysis and a modulator of gene transcription and cell death, is activated by sulfhydration and inhibited by S-nitrosylation on cysteine 150 (Mustafa et al., 2009; Sen et al., 2008). A later study reported that GAPDH was inhibited by sulfhydration on cysteine 156 (Jarosz et al., 2015). Similarly, the E3-ligase activity of parkin is increased by sulfhydration and decreased by S-nitrosylation (Chung et al., 2004; Vandiver et al., 2013). Along similar lines, the DNA-binding activity of the p65 subunit of nuclear factor κB (NF-κB) is enhanced by sulfhydration and impaired by S-nitrosylation (Sen et al., 2012). Lastly, aberrantly high S-nitroslylation is observed in human brain and proposed to be linked to female predominance of AD (Yang et al., 2022), whereas current evidence suggests that H_2S is likely to be generally protective in AD. However, it has been reported that homocysteine is elevated to a much larger extent in the plasma of female CSE knockout mice, constituting a risk factor for developing cardiovascular deficits and dementia (Yang et al., 2008). The complete scope of differential sulfhydration in males and females has not yet been determined. Another area of study that is gaining momentum is the interdependence of H_2S and NO, and their downstream signaling products (Coletta et al., 2012; Cortese-Krott, 2020; Zarenkiewicz et al., 2022). Thus, this is an exciting time in redox biology with much remaining to be discovered and applied with respect to the complementary and at times reciprocal modification of cysteines by H_2S and NO.

Concluding remarks

H_2S regulates diverse aspects of physiology, and its role in the brain is a growing area of active investigation. The levels of this gaseous messenger molecule are tightly controlled, and both excess and scarcity of H_2S are deleterious to the nervous system and can exacerbate neurodegeneration (Figure 9). Given the potential for new neuroprotective

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therapeutics, there is much interest in developing agents that modulate H_2S production in the brain, and in clarifying the range of levels of H_2S that are protective. The varying effects of H_2S reported in the literature can likely be attributed to the differing effects of H_2S at higher and lower doses. To effectively pursue these lines of investigation, the field needs to develop reagents that encompass both specificity and sensitivity in detecting the presence of H_2S *in vivo*. Meeting these needs are critical for future clinical trials involving H_2S donors. It is notable that S-nitrosylation is elevated in both AD and PD, whereas sulfhydration is decreased, leading to accumulation of misfolded proteins and neurotoxicity (Ghatak, Nakamura & Lipton, 2023; Giovinazzo et al., 2021; Nakamura, Oh, Zhang & Lipton, 2021; Nakamura, Oh, Zhang, Tannenbaum & Lipton, 2021; Vandiver et al., 2013). As S-nitrosylation regulates multiple signaling pathways leading to neurodegeneration, therapeutics aimed at targeting pathologic S-nitrosylation under conditions of excess NO production, while preserving the beneficial effects of NO, could also prove helpful. Indeed, it is conceivable that augmenting sulfhydration could help safely modulate S-nitrosylation. For example, dual action drugs that promote sulfhydration and target S-nitrosylation might exert beneficial effects in neurodegenerative conditions such as AD and PD, in which elevated S-nitrosylation and diminished sulfhydration are linked to the underlying pathology. In conclusion, this is an exciting time for the field of redox biology, with much remaining to be learned about the mechanisms and therapeutic potential of modulating cysteine biology. With respect to H_2S signaling, a chief challenge in the field will be to understand the biphasic response of the brain to low versus high levels of H_2S in ways that enable therapeutic restoration of the proper balance of this critical gas.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY(http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22: G-protein-coupled receptors (Alexander et al., 2021).

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Data availability statement

N/A-review

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Abbreviations:

MPST	3-mercaptopuruvate sulfurtransferase
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ATF4	Activating transcription factor 4
ATM	ataxia-telangiectasia mutated
BACE-1	β-secretase 1
BBB	blood-brain barrier
CBS	cystathionine β-synthase
CCI	control cortical impact
CO	carbon monoxide
Complex IV	cytochrome c oxidase
COX-2	cyclooxygenase 2
CSE	cystathionine γ-lyase
Cys	cysteine
Cys-SOH	cysteine sulfenic acids
DS	Down syndrome
EAAC1	excitatory amino acid transporter 1
ER	endoplasmic reticulum
ETC	electron transport chain
GDNF	glial-derived neurotrophic factor
GSH	glutathione
GSK-3β	glycogen synthase kinase-3β
H_2S	hydrogen sulfide
H_2S_2	hydrogen disulfide
HD	Huntington's disease
IL-1β	interleukin 1-beta
iNOS	inducible nitric oxide synthase
LTP	long-term potentiation

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MAO	monoamine oxidase
mHtt	mutant huntingtin
MTHFR	methylenetetrahydrofolate reductase
NGF	nerve growth factor
NMDA	n-methyl d-aspartate
NO	nitric oxide
O_2	oxygen
PD	Parkinson's disease
SAM	s-adenosyl methionine
SCA3	spinocerebellar ataxia 3
SP1	specificity protein 1
SQR	sulfide quinone oxidoreductase
–S–S–	cysteine disulfides
TBI	traumatic brain injury
TNFα	tumor necrosis factor alpha
USP8	ubiquitin specific peptidase 8
VEGF	vascular endothelial growth factor
Sx_c^-	system x_c^-

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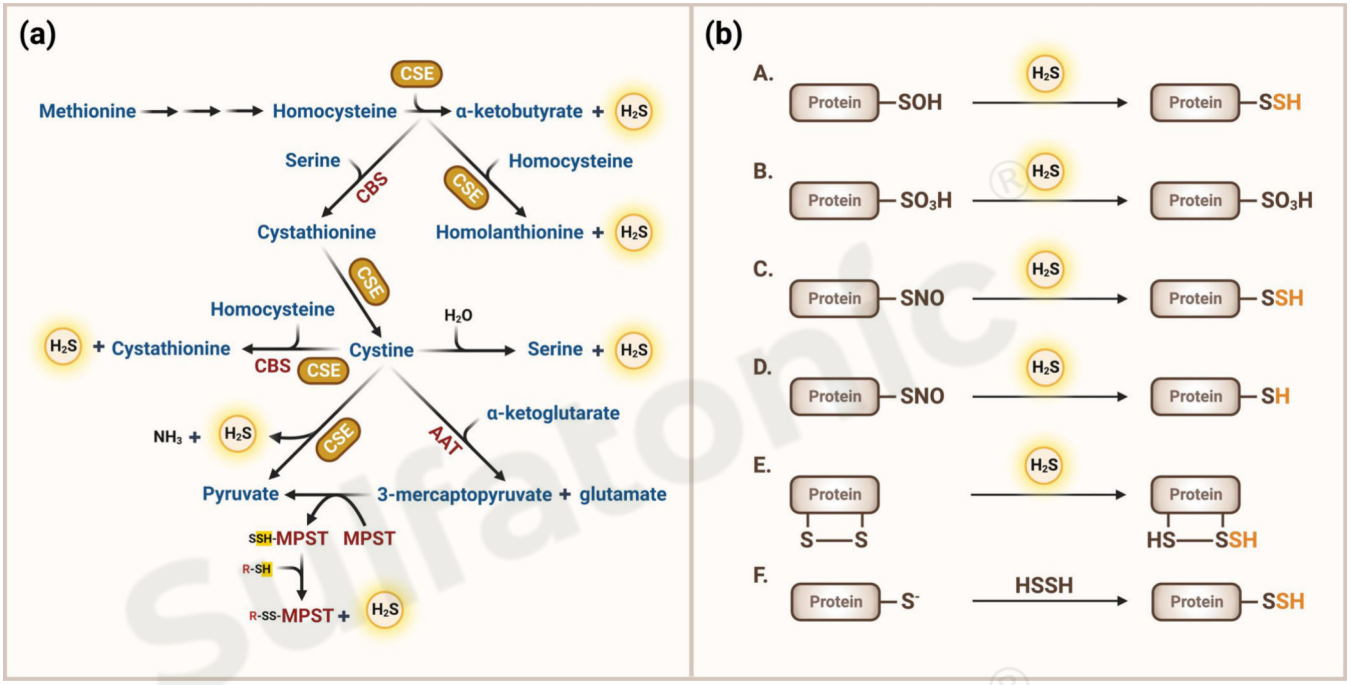


FIGURE 1.

The biochemistry of hydrogen sulfide (H_2S) production and signaling. (a) Major pathways of H_2S enzymatic synthesis are displayed. H_2S is predominantly produced by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (MPST). Homocysteine, derived from dietary methionine, is condensed with serine by CBS to form cystathionine, which is converted to cysteine by CSE. Cysteine is used as a substrate by both CBS and CSE to produce H_2S. A combination of homocysteine and cysteine is preferred by CBS to generate H_2S and cystathionine. Although the canonical function of CSE is biosynthesis of cysteine, CSE can also utilize Cys and homocysteine to produce H_2S. In the process, various sulfur-containing metabolites, such as α-ketobutyrate, cystathionine and homolanthionine are produced. 3-MST generates H_2S from 3-mercaptopyruvate, which is generated by Asp aminotransferase (AAT) and possesses Cys aminotransferase (CAT) activity. AAT forms 3-mercaptopyruvate and glutamate from cysteine and α-ketoglutarate. The sulfur of 3-mercaptopyruvate forms a covalent bond with the Cys residue in the active site of MPST (MST-SH) to produce a persulfide (MPST-SSH) and pyruvate. The persulfide then releases H_2S in the presence of an endogenous reductant (R-SH), which generates the corresponding disulfide (MPST-SSR) and H_2S. (b) Sulfhydration/persulfidation consists of various reactions that generate H_2S. H_2S does not directly react with –SH groups of cysteine residues, but may readily react with oxidized cysteine residues, as depicted.

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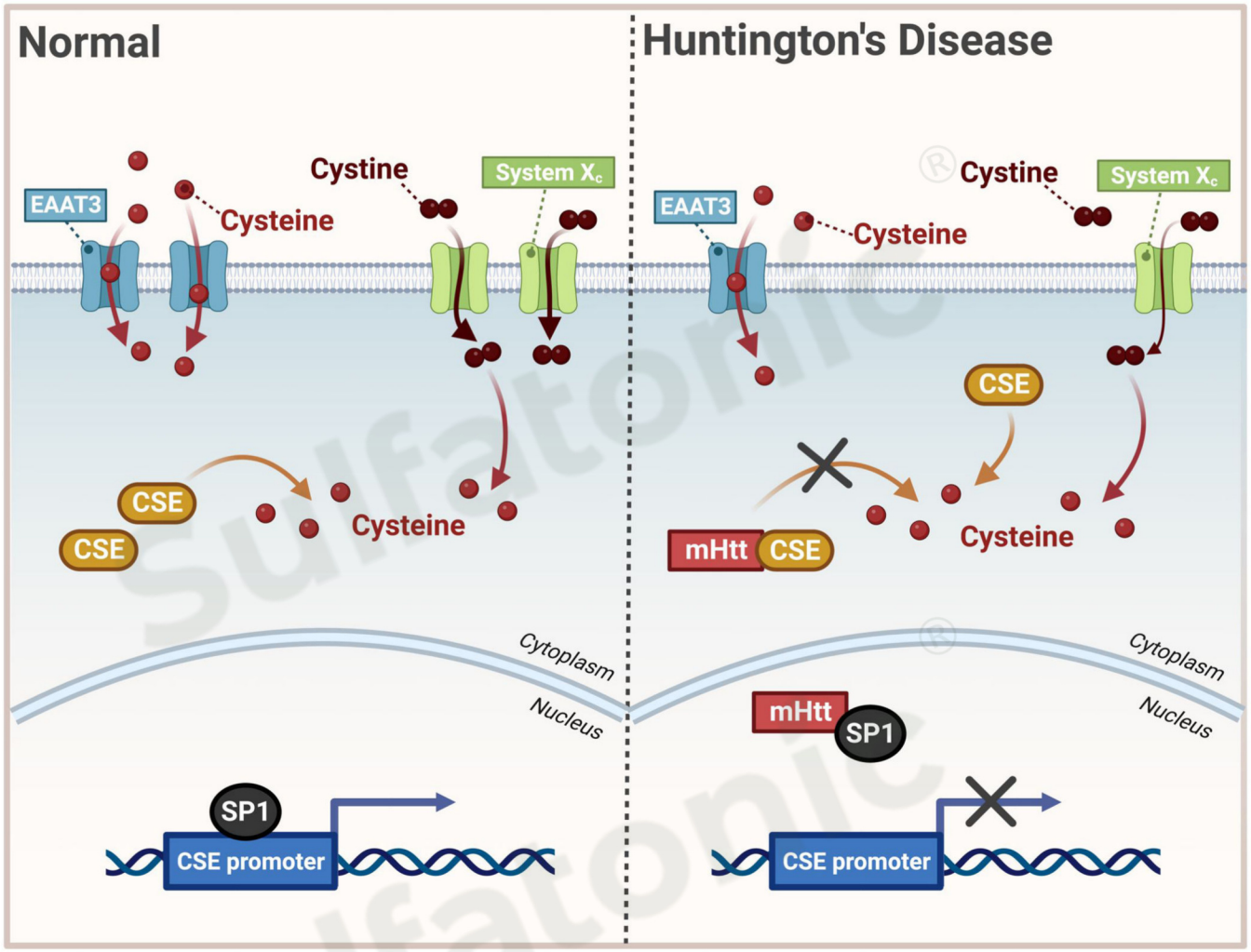


FIGURE 2.

Hydrogen sulfide (H_2S) is involved in Huntington's disease by virtue of disrupted cysteine metabolism. Cystathionine γ-lyase (CSE) basal expression is transactivated by its basal transcription factor, specificity protein 1 (SP1), which produces cysteine, a substrate for generation of H_2S and other sulfur compounds. Cysteine/cystine importation is mediated by the excitatory amino acid transporter 3 (EAAT3/EAAT1) and the system x_c^-. In HD, mutant huntingtin (mHtt) binds SP1 and inhibits its transcriptional activity, leading to decreased levels of CSE, cysteine, and H_2S. Additionally, the increased oxidative stress compromises induction of the stress-responsive transcription factor, ATF4. This prevents CSE induction, which leads to decreased uptake and biosynthesis cysteine, culminating in elevated oxidative stress and neurotoxicity.

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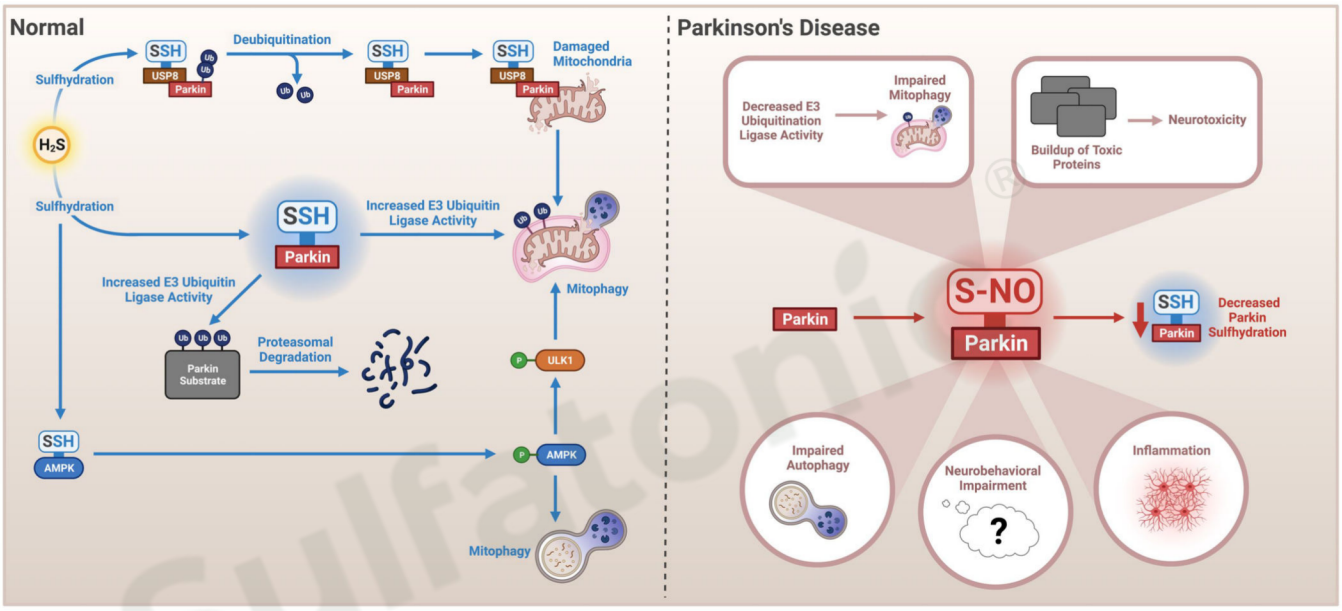


FIGURE 3.

Gasotransmitter signaling is dysregulated in Parkinson's disease (PD). In healthy states, parkin, an E3 ubiquitin ligase, ubiquitinates its substrates and targets them for proteosomal degradation. Activation of parkin is enhanced by sulfhydration. Additionally, sulfhydration of USP8 activates its deubiquitinase activity on parkin, which promotes its recruitment to damaged mitochondria to promote mitophagy. In PD, diminished sulfhydration of parkin results in its lower activity, causing accumulation of target proteins and neurotoxicity. In general, progression of PD is associated with decreased sulfhydration and increased S-nitrosylation of parkin.

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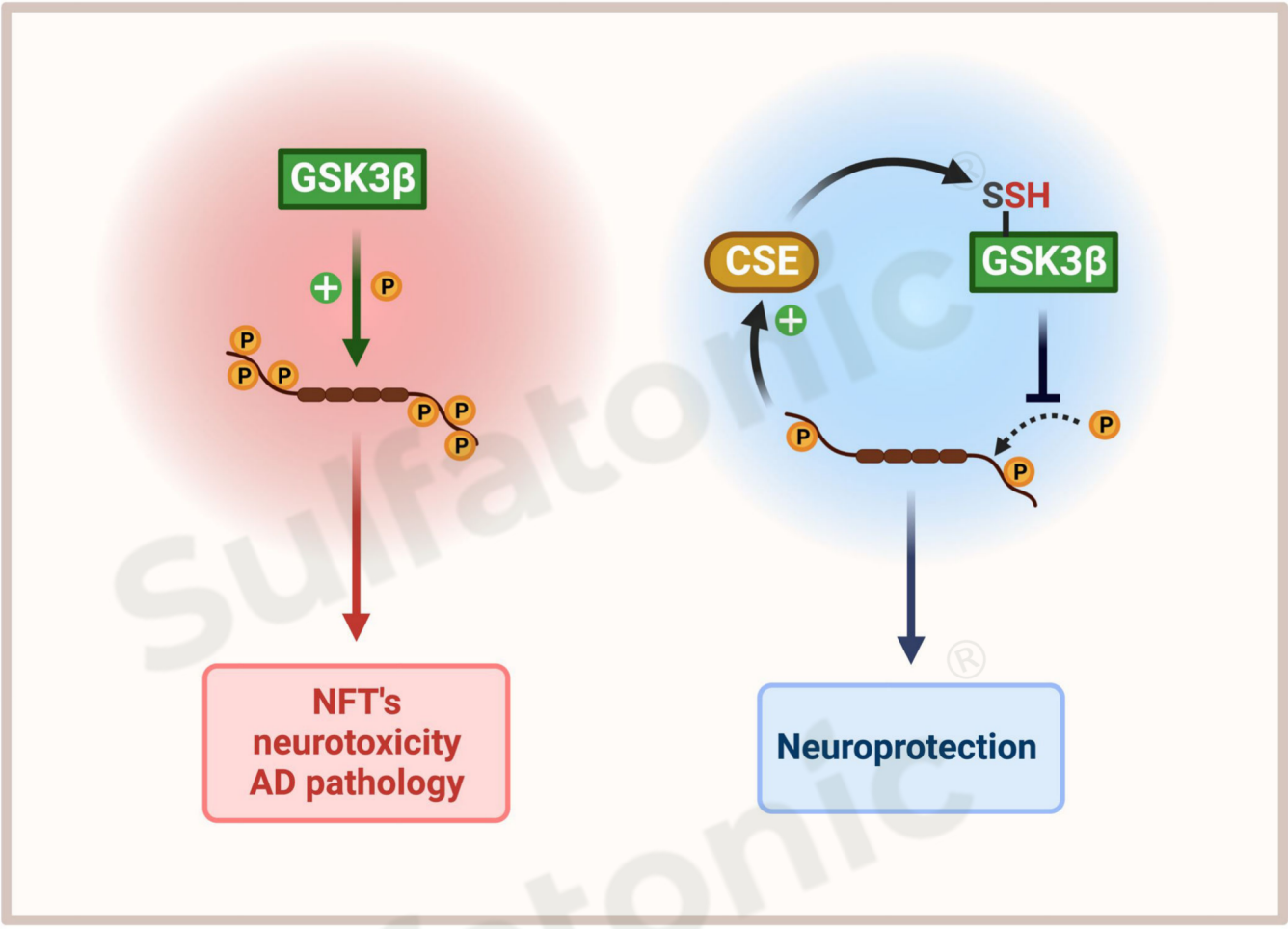


FIGURE 4.

Model depicting a mode of neuroprotection afforded by sulfhydration in Alzheimer's disease (AD). In AD, elevated glycogen synthase kinase 3β (GSK3β) activity hyperphosphorylates tau (labeled as "P"), which leads to formation of neurofibrillary tangles (NFTs) and AD pathology. Wild type tau normally binds to CSE and enhances its production of hydrogen sulfide (H_2S) (arrow with a plus sign), which sulfhydrates GSK3β ("SH" in red text) and inhibits its phosphorylation of tau.

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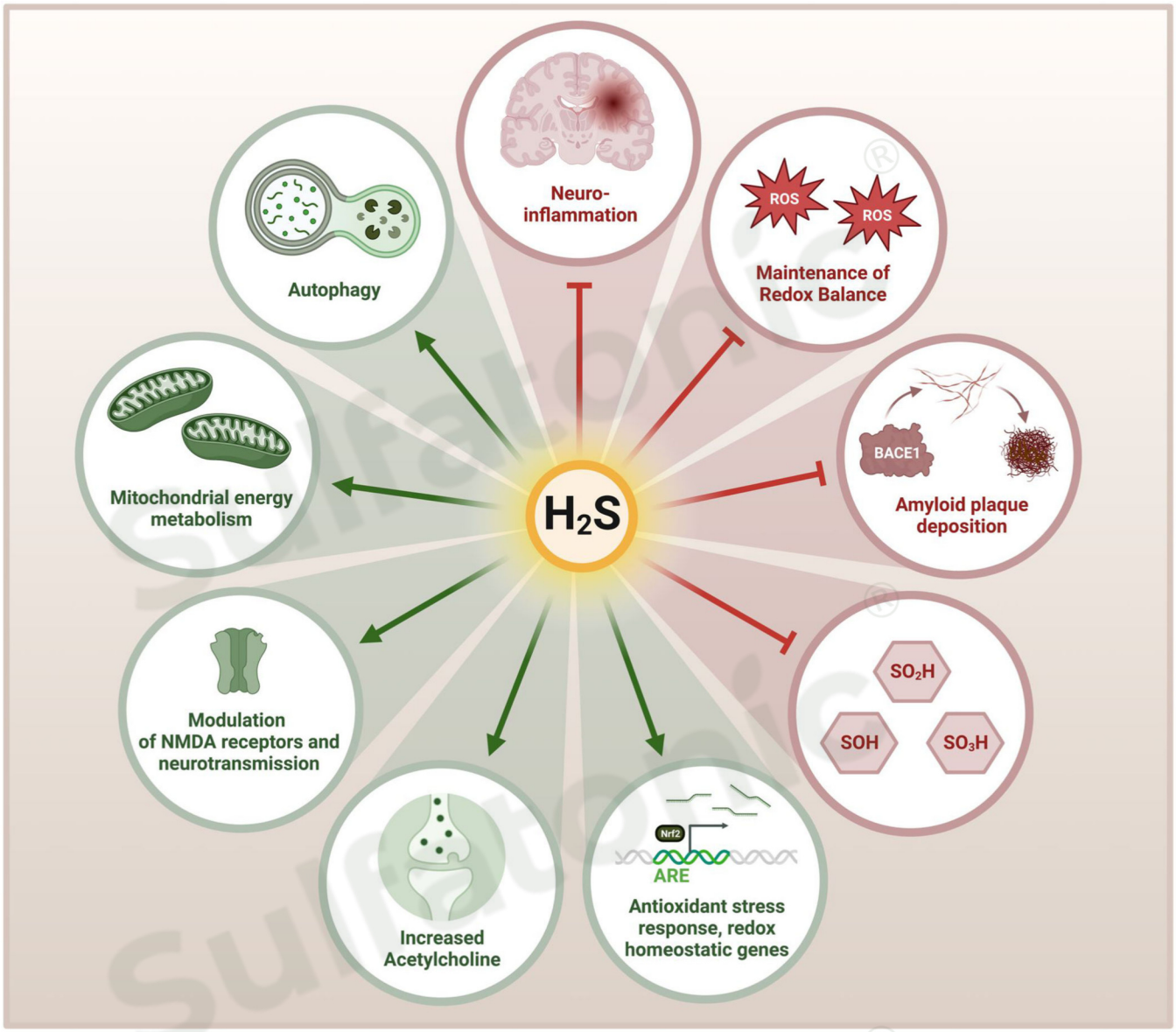


FIGURE 5.

Hydrogen sulfide (H_2S) has many neuroprotective roles in Alzheimer's disease (AD) by targeting multiple signaling pathways. These include attenuating neuroinflammation, diminishing generation of excess reactive oxygen species (ROS) and reactive nitrogen species (RNS), and activating the antioxidant stress response pathway regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) to maintain redox balance in the brain. By sulfhydrating reactive cysteine residues, H_2S prevents oxidation of cysteine sulfhydryl groups to sulfenic (-SOH), sulfinic ($-SO_2H$) and sulfonic ($-SO_2H$) groups. Additionally, H_2S inhibits the expression and activity of beta-secretase 1 (BACE1) and inhibits amyloidogenic processing of amyloid precursor protein (APP), thereby preventing accumulation of β-amyloid plaques. At physiologic concentrations, H_2S also facilitates N-methyl D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP). Other neuroprotective effects

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of H_2S in AD include maintenance of mitochondrial energy metabolism, stimulation of autophagy, and increasing catecholamine neurotransmitters such as acetylcholine.

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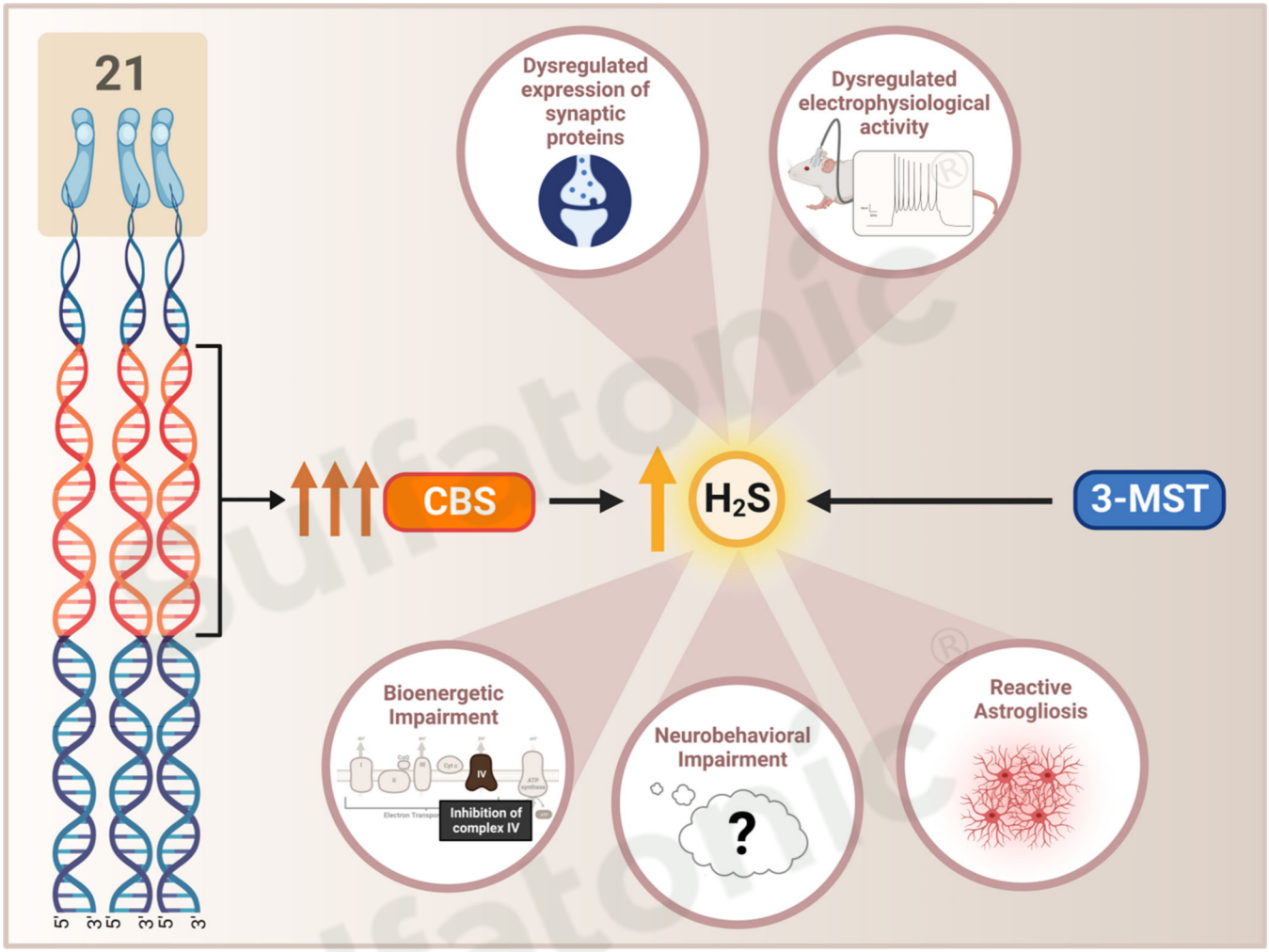


FIGURE 6.

Excess endogenous generation of hydrogen sulfide (H_2S) contributes to Down syndrome (DS). Trisomy of chromosome 21 in DS results in an extra copy of CBS, which resides on chromosome 21, leading to excess H_2S production. Elevated expression of MPST, by yet unidentified mechanisms also occurs. Elevated levels of H_2S inhibit complex IV of mitochondria, which impairs bioenergetics. Dysregulated expression of synaptic proteins, brain wave activity, reactive astrogliosis, and behavioral abnormalities also occur. Excess H_2S additionally increases formation of sulfhemoglobin, decreases oxygen (O_2)-carrying ability of red blood cells, diminishes O_2 transport to tissues, and reduces tissue metabolism.

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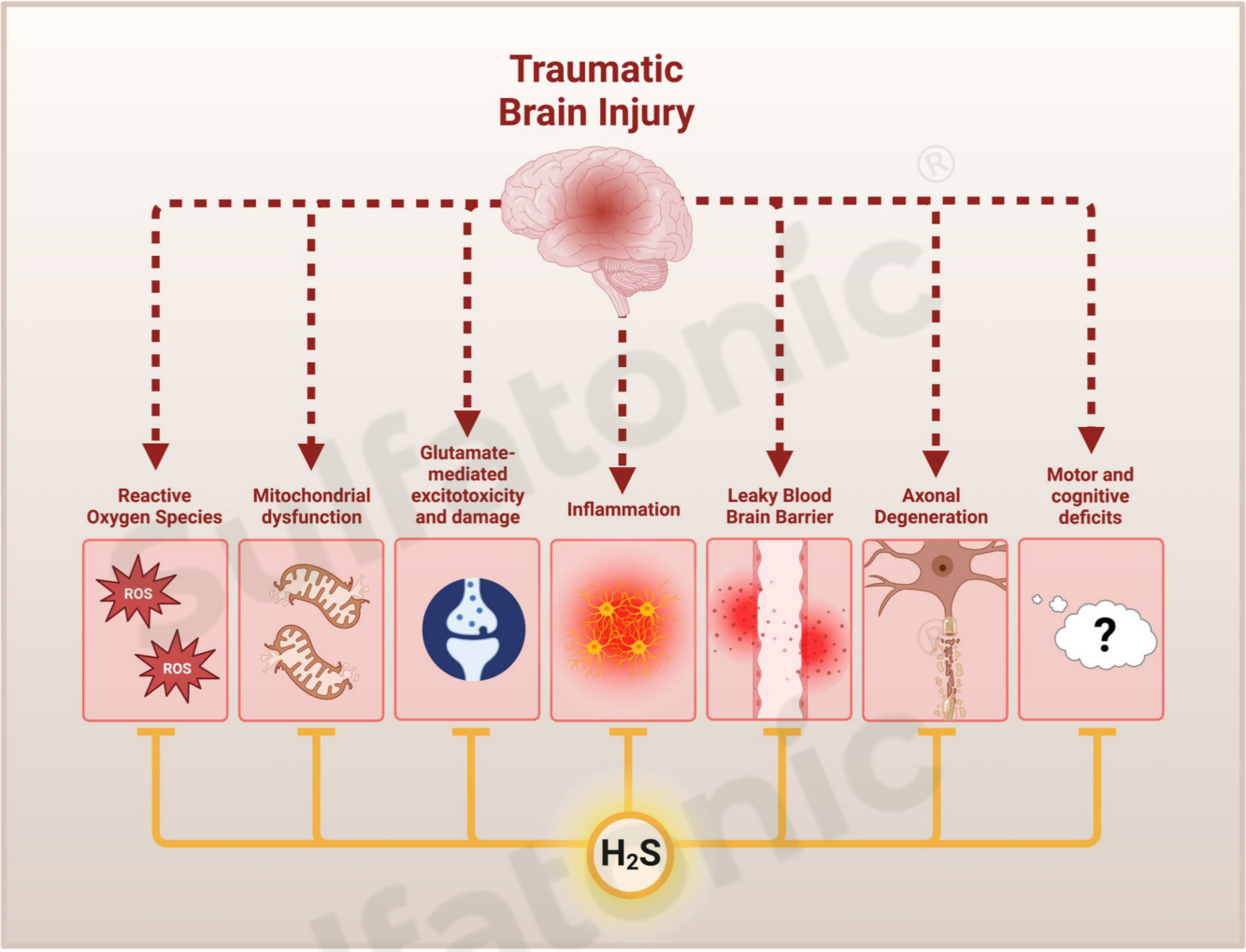


FIGURE 7.

Neuroprotection is afforded by hydrogen sulfide (H_2S) in traumatic brain injury (TBI). TBI impairs several physiological parameters that collectively impair motor and cognitive functions. TBI triggers excessive generation of reactive oxygen and nitrogen species (ROS and RNS), causing oxidative and nitrosative stress and mitochondrial dysfunction. TBI also elicits glutamate-induced neurotoxicity, axonal degeneration, and neuroinflammation, resulting in a leaky blood–brain barrier and ultimately neurodegeneration. H_2S blocks all these effects to varying degrees and may prove useful for treating patients with TBI.

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FIGURE 8.

Hydrogen sulfide (H_2S) counteracts the principal hallmarks of human aging. Accumulating evidence shows that H_2S impacts almost all hallmarks of aging, which have been updated from 9 to 12. Thus, the gaseous messenger molecule modulates the following processes: DNA instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, disabled macroautophagy, chronic inflammation, and dysbiosis (Lopez-Otin, Blasco, Partridge, Serrano & Kroemer, 2023).

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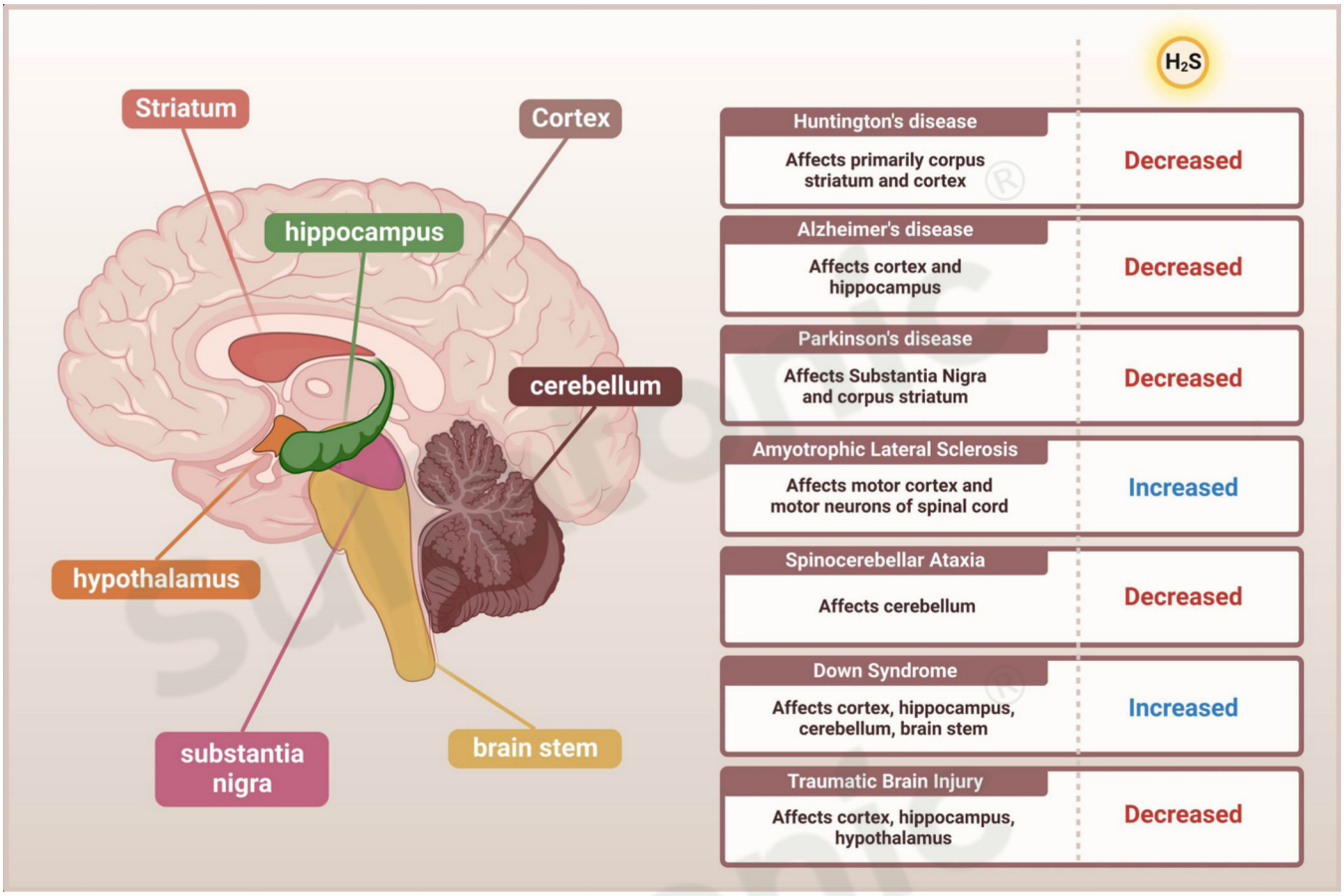


FIGURE 9.

Hydrogen sulfide (H_2S) metabolism is dysregulated across myriad neurodegenerative states with selective vulnerability of specific brain regions. Huntington's disease affects primarily the corpus striatum, followed by the cortex in advanced disease stages. In Alzheimer's disease, the cortex (starting with the entorhinal cortex) is impacted first, followed by the hippocampus, leading to cognitive decline. In Parkinson's disease, the substantia nigra and the striatum are selectively affected, causing motor dysfunction and cognitive deficits. In amyotrophic lateral sclerosis, the motor cortex of the brain and the motor neurons of the spinal cord degenerate, culminating in paralysis and death. In spinocerebellar ataxia and related ataxias, the cerebellum is damaged. In Down syndrome, the cortex, hippocampus, cerebellum and brain stem are impacted, leading to cognitive deficits. In traumatic brain injury, the cortex, hippocampus and hypothalamus are affected. In most of these diseases, H_2S levels are decreased in brain tissues. In Down syndrome and the familial form (G93A SOD1 mutation) of ALS, however, H_2S levels are increased. Thus, too much or too little H_2S is detrimental to brain health.

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