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Hydrogen Sulfide Signaling in Neurodegenerative Movement Disorders

A. A. Pieper,

Department Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Brain Health Medicines Center, Harrington Discovery Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Geriatric Psychiatry, GRECC, Louis Stokes VA Medical Center, Cleveland, USA

Institute for Transformative Molecular Medicine, School of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

B. D. Paul

Department of Physiology, Pharmacology and Therapeutics, Johns Hopkins University, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University, Baltimore, MD, USA

The Lieber Institute for Brain Development, Baltimore, MD, USA

Abstract

Hydrogen sulfide (H_2S) is a gaseous signaling molecule, also known as a gasotransmitter, present in nearly all mammalian organs. It plays crucial roles in regulating various physiological processes in both the brain and peripheral systems. The body maintains tight control over H_2S levels, as both excessive and deficient levels can disrupt normal physiological functions and lead to disease. H_2S has a significant impact on cognitive and motor functions, which are often compromised in neurodegenerative disorders. It modulates signaling and metabolism primarily by post-translationally modifying reactive cysteine residues on proteins through sulfhydration, also known as persulfidation. This chapter reviews the signaling mechanisms regulated by H_2S in neurodegenerative diseases that significantly affect motor function, specifically focusing on Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS),

bpaul8@jhmi.edu .

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spinocerebellar ataxia (SCA), and Leigh syndrome (LS), as well as other mitochondrial disorders. While PD, HD, and SCA are linked to decreased levels of H_2S, elevated levels of H_2S are associated with ALS, DS, and LS. We also explore potential therapeutic applications of modulating H_2S levels in the brain.

Keywords

Amyotrophic lateral sclerosis; Cysteine; Huntington's disease; Hydrogen sulfide; Parkinson's disease; Spinocerebellar ataxia; Sulfhydration/persulfidation

1 Introduction

Hydrogen sulfide (H_2S) is commonly recognized as a foul-smelling gas found in the environment, yet it is also produced endogenously at low levels in mammals. Here, it plays a crucial role in signaling events that regulate various physiologic processes. The earliest recorded studies of this gas, from the 1700s, focused on its environmental toxicity, as its biological significance was not known at the time.

One of the earliest contributors to H_2S research was the Italian physician Bernardino Ramazzini. In his book *De Morbis Artificum Diatriba*, he attributed eye irritation, inflammation, and bacterial infections in sewer workers to what he termed "sewer gas" (Ramazzini 1700). Ramazzini noted the gas's pungent odor from cesspits and hypothesized that it also led to the tarnishing of copper coins carried by these workers. Subsequent studies confirmed its harmful effects on the ocular system (Lambert et al. 2006). The toxicity of this "sewer gas" was further depicted by Victor Hugo in his classic novel *Les Miserables*, where he described the sewers of Paris as "the intestine of the Leviathan." In 1806, the gas in question was identified as H_2S (Dupuyturen 1806).

Before this recognition, Carl Wilhelm Scheele had synthesized H_2S in the laboratory in 1750 by demonstrating that it was released when ferrous sulfide reacted with mineral acids. This was followed by determination of its chemical composition in 1776 by the French chemist Claude Louis Berthollet, who also noted its acidic nature (Mitchell and Davenport 1924). Later research revealed that H_2S is produced by microbes and mammalian tissues, although it was initially considered merely a metabolic waste product (Rizzo 1967; Gayon 1877; Clarke 1953; Myers 1920; Shatalin et al. 2011; Mironov et al. 2017).

Much later pioneering work of Rui Wang and associates, in the early 2000s, however, suggested important roles in the vascular system (Zhao et al. 2001; Cheng et al. 2004). Specifically, H_2S was recognized as an endothelial derived relaxation factor (EDRF) with important roles in the circulatory system (Zhao et al. 2001; Yang et al. 2008). Similar to nitric oxide (NO), generation of H_2S from vascular endothelial cells was demonstrated to be triggered by muscarinic cholinergic activation, with depletion of the endothelium or depletion of CSE shown to abrogate this effect (Yang et al. 2008; Wang 2009; Tang et al. 2013; Tang et al. 2005; Mustafa et al. 2011). The endogenous production of H_2S in the brain was first observed in 1989 by Warenycia, while its function in neurotransmission was shown later by Kimura and colleagues to play a role in N-methyl D aspartate (NMDA) receptor–

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mediated long-term potentiation (LTP) in the brain (Abe and Kimura 1996; Warenycia et al. 1989).

It is now well understood that H_2S mediates its effects largely through sulfhydration or persulfidation, in which –SH groups on reactive cysteine residues of proteins are converted to persulfide (-SSH) groups (Filipovic 2015; Mustafa et al. 2009; Sen et al. 2012). Notably, altered H_2S metabolism and sulfhydration have been observed in several neurodegenerative conditions. This chapter focuses on the current understanding of H_2S signaling in neurodegenerative diseases that are highly associated with motor dysfunction: (1) Parkinson's disease (PD), (2) Huntington's disease (HD), (3) amyotrophic lateral sclerosis (ALS), (4) ataxias, and (5) Leigh syndrome (LS), as well as other mitochondrial disorders.

1.1 H_2S Biosynthesis

Due to the importance of maintaining proper homeostasis of H_2S, its production in the body is tightly regulated at multiple levels. H_2S is generated either directly or indirectly from the amino acid cysteine through the reverse trans-sulfuration pathway, with additional contributions from various non-enzymatic systems (Paul and Snyder 2012; Paul and Snyder 2015). Cysteine is a semi-essential amino acid produced within cells that can also be obtained from dietary sources via various cellular transporters (Paul et al. 2018).

The primary enzymes responsible for H_2S production in the body are cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST) (Paul and Snyder 2012; Stipanuk 2020; Stipanuk and Beck 1982; Kuo et al. 1983). CSE, also known as cystathionase and encoded by the *CTH* gene on chromosome 1, utilizes cysteine or homocysteine as substrates to generate H_2S (Paul and Snyder 2012; Filipovic et al. 2018). It is the only mammalian biosynthetic enzyme for cysteine, and its depletion can be lethal in mice fed a cysteine-deficient diet (Mani et al. 2011; Ishii et al. 2010). CBS, encoded by the *CBS* gene on human chromosome 21, catalyzes the condensation of serine and homocysteine to form cystathionine, which CSE then converts to cysteine (Paul and Snyder 2012; Paul and Snyder 2015). CBS preferentially generates H_2S through a combination of homocysteine and cysteine, or homocysteine alone (Kruger 2017; Chen et al. 2004). Notably, excessively elevated CBS levels have been linked to Down syndrome due to an additional copy of the gene (Szabo 2020; Kamoun 2001). 3-MST, also known as tRNA thiouridine modification protein, human liver rhodanese 2, and thiosulfate sulfurtransferase 2, is encoded on human chromosome 22 (Dunham et al. 1999). In the brain, 3-MST is present in both neurons and astrocytes (Ishigami et al. 2009; Shibuya et al. 2009), while CSE is predominantly localized to neurons and CBS to glial cells (Morikawa et al. 2012; Linden et al. 2008; Enokido et al. 2005). Additional sources of H_2S synthesis include the acid-labile sulfide pool, sulfane sulfur, and microbial flora, as well as non-enzymatic generation of H_2S via a reaction involving iron and vitamin B6, which also operate in the brain (Ishigami et al. 2009; Shen et al. 2012, 2013; Singh and Lin 2015; Yang et al. 2019).

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1.2 H_2S Catabolism

The pharmacological profile of H_2S follows a bell-shaped curve, with lower concentrations being protective and higher concentrations being toxic. Low levels of H_2S stimulate mitochondrial bioenergetics and protect neurons from oxidative stress, while higher concentrations of H_2S are toxic as they inhibit complex IV (cytochrome c oxidase) of the electron transport chain (Paul et al. 2021; Szabo et al. 2014; Modis et al. 2014; Modis et al. 2016; Kimura et al. 2010; Sbodio et al. 2019; Tripathi et al. 2023). To prevent toxicity, the body balances H_2S synthesis and catabolism to maintain homeostatic levels (Paul et al. 2021). The two primary pathways for H_2S degradation are methylation and oxidation, with methylation being the minor pathway (Filipovic et al. 2018).

H_2S oxidation primarily occurs through the enzyme sulfide:quinone oxidoreductase (SQOR), which is part of the sulfide oxidizing unit (SOU) in the mitochondria that also includes persulfide dioxygenase (ETHE), sulfite oxidase (SO), and thiosulfate sulfurtransferase/rhodanese (TST). This unit connects sulfide catabolism to oxidative phosphorylation (Paul et al. 2021; Hildebrandt and Grieshaber 2008). SQOR, located on the inner mitochondrial membrane, catalyzes the first step in H_2S oxidation, generating a persulfide intermediate while releasing electrons transferred to coenzyme Q (CoQ) via flavin adenine dinucleotide (FAD) (Jackson et al. 2012; Landry et al. 2021). CoQ relays these electrons to the electron transport chain, while the persulfide formed on SQOR can be transferred to acceptors like the antioxidant glutathione (GSH) to form GSSH, or sulfite (SO_3^2) to form thiosulfate ($S_2O_3^{2-}$). GSSH can be subsequently converted into GSH and sulfite by persulfide dioxygenase (ETHE)/persulfide dioxygenase (Paul et al. 2021). The resulting sulfite can be acted upon by either thiosulfate sulfurtransferase (TST) to produce $S_2O_3^{2-}$ or by sulfite oxidase (SO) to produce sulfate (SO_4^{2-}).

2 Parkinson's Disease

2.1 Background of PD

PD is the second most common neurodegenerative disorder, following Alzheimer's disease. It is characterized by classic symptoms of resting tremor, bradykinesia, rigidity, sleep disturbance, anxiety, depression, and cognitive decline (Poewe et al. 2017; Aarsland et al. 2021). While rarely occurring before the age of 50, the incidence of PD increases with age, peaking between 85 and 89 years. PD primarily affects the substantia nigra pars compacta and striatum regions of the brain, leading to the selective degeneration of dopaminergic neurons. This degeneration results in decreased dopamine levels and pathological accumulation of α-synuclein within intraneuronal inclusions, known as Lewy bodies (Bloem et al. 2021).

PD can occur both genetically and sporadically, with most cases thought to arise from a combination of genetic susceptibility and environmental factors such as exposure to pesticides, herbicides, solvents, or heavy metals (Collaborators GBDPsD 2018). Although the exact molecular mechanisms underlying PD remain unclear, several processes influenced by H_2S are implicated in disease progression. These include elevated neuroinflammation, mitochondrial dysfunction, redox imbalance, decreased sulfhydration, degeneration of

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dopaminergic neurons, deposition of α-synuclein, and impaired autophagy (Absalyamova et al. 2024; Hou et al. 2020; Liu et al. 2022) (Fig. 1). Furthermore, research has shown that cysteine-dopamine conjugates and related metabolites are elevated in the postmortem substantia nigra of PD patients, suggesting a decreased abundance of cysteine and glutathione that would be expected to contribute to oxidative damage (Spencer et al. 1998).

2.2 H_2S Signaling in PD and Therapeutic Interventions

Numerous preclinical studies using chemical and genetic PD models have demonstrated dysregulation of H_2S homeostasis. For example, reduced striatal levels of endogenous H_2S have been observed in the 6-hydroxydopamine (6-OHDA) rat model of PD (Sun et al. 2023). In this model, administration of sodium hydrosulfide (NaHS), an H_2S donor, has been shown to reduce oxidative stress and prevent motor dysfunction (Sun et al. 2023). Additionally, NaHS alleviates pathology in the rotenone model of PD, where it inhibits microglial activation and neuroinflammation in the substantia nigra that occurs in response to rotenone-mediated inhibition of mitochondrial complex I (Hu et al. 2010).

Research also indicates that overexpression of CBS using lentiviral constructs provides protection against 6-OHDA-induced PD (Yin et al. 2017). In addition, we have previously reported decreased sulfhydration in the brains of mice exposed to MPTP, as well in postmortem brain samples from PD patients, that is accompanied by excessive nitrosylation, a cysteine modification alternatively derived from NO that has detrimental effects on neuronal health (Vandiver et al. 2013). We also found decreased sulfhydration and increased nitrosylation of the E3-ubiquitin ligase parkin, a protein that clears misfolded proteins, in PD patients (Vandiver et al. 2013). Autosomal-recessive mutations in the *PARK2* gene, which encodes parkin, are the most common cause of inherited PD, while heterozygous mutations are implicated in the more prevalent sporadic form (Funayama et al. 2023; Dawson and Dawson 2010; Klein and Lohmann 2009; Sun et al. 2006).

In addition to its role in clearing damaged and misfolded protein aggregates, parkin is also essential for mitochondrial health (Clark et al. 2006). Modifications to critical cysteine residues in parkin influence its activity and, consequently, mitochondrial homeostasis. Our findings suggest that sulfhydration enhances parkin's catalytic activity, while nitrosylation reduces it, potentially contributing to the pathological accumulation of misfolded proteins in PD, including α-synuclein (Vandiver et al. 2013; Chung et al. 2004). Furthermore, sulfhydration supports protective mitophagy, a specialized form of autophagy that eliminates damaged or unnecessary mitochondria (Sun et al. 2020; Wang et al. 2008).

Inhaling H_2S has also shown neuroprotective effects in models of PD, such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. Specifically, inhaling H_2S at a concentration of 40 ppm for 8 h a day over 1 week effectively prevents MPTP-induced neurodegeneration and motor deficits (Kida et al. 2011). The neuroprotective effects of H_2S inhalation are linked to reduced neuroinflammation and increased nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated signaling in the substantia nigra and striatum (Chen et al. 2004). Interestingly, higher ambient levels of H_2S in Rotorua, New Zealand, due to its geothermal vents, correlate with faster motor response times in the finger tapping component

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of the motor function rating scale used to monitor PD progression in patients (Cakmak 2017; Reed et al. 2014). The reported neuroprotective effects to date of H_2S-mediated therapy in preclinical models of PD are summarized in Table 1, suggesting that administering H_2S or boosting its production by stimulating the trans-sulfuration pathway might be beneficial to PD patients.

3 Huntington's Disease

3.1 Background of HD

Huntington's disease (HD) is a devastating neurodegenerative condition that is inherited in an autosomal dominant manner. It primarily affects the corpus striatum of the brain and is characterized by involuntary movements (chorea), motor impairments, and a range of neuropsychiatric and cognitive impairments (Bates et al. 2015). HD is classified as a triplet repeat disorder and is caused by variable expansion of codons that encode a polyglutamine tract in the *Huntingtin (Htt)* gene (The Huntington's Disease Collaborative Research Group 1993). The length of this polyglutamine tract critically influences the age of onset and severity of HD, although other genetic modifiers also play a role (Keum et al. 2016; Andrew et al. 1993; Pengo and Squitieri 2024; Gusella et al. 2014; Genetic Modifiers of Huntington's Disease C 2015; Wright et al. 2019; Gu et al. 2022; Sawant et al. 2021). The expansion of polyglutamine repeats leads to the misfolding and aggregation of mutant Htt (mHtt) protein, resulting in neurotoxicity through various mechanisms, including dysregulation of transcription and translation, defects in nucleocytoplasmic transport, mitochondrial dysfunction, neuroinflammation, impaired stress responses, and insufficient autophagy, among other aberrations (Gu et al. 2022; Davies et al. 1997; DiFiglia et al. 1997; Ament et al. 2018; Banez-Coronel et al. 2015; Grima et al. 2017; Ament et al. 2017; Paul and Snyder 2019; Paul 2022; Sbodio et al. 2016; Oh et al. 2022; Ravikumar et al. 2002).

3.2 Disrupted Cysteine and H_2S Signaling in HD and Related Therapeutic Interventions

Research by our team and others has shown that cysteine homeostasis is disrupted in HD. This includes impaired trafficking of the neuronal cysteine transporter (excitatory amino acid transporter 3; EAAT3/EAAC1) and decreased activity of the system Xc^- transporter, which imports cystine, the oxidized form of cysteine (Paul 2022; Li et al. 2010; Frederick et al. 2014). Additionally, the CSE enzyme, responsible for producing cysteine and H_2S, is transcriptionally depleted in HD due to sequestration of specificity protein 1 (SP1) by mHtt (Paul et al. 2014; Paul and Snyder 2014). Consequently, there is an overall cysteine deficit in HD striatal cells, which rely on cysteine supplementation in culture media for survival (Paul et al. 2014). In healthy wild-type cells, expression of the *cth* gene (encoding CSE) increases during cysteine deprivation, but this does not occur in HD cells due to their inability to induce activating transcription factor 4 (ATF4), thereby further exacerbating oxidative stress (Sbodio et al. 2016). Interestingly, reduced CSE expression appears to correlate to mHtt levels (Li et al. 2016). Beyond these regulatory nodes, dysregulation of cysteine metabolism occurs post-transcriptionally in HD cells, with mHtt binding both CSE and CBS and inhibiting their catalytic activity (Paul et al. 2022). Thus, cysteine homeostasis in HD is affected at multiple levels, leading to redox imbalance (Fig. 2).

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Sulfhydration is likewise reduced in HD cells, and supplementation with cysteine or its prodrugs has been shown to enhance cell survival (Paul et al. 2014; Zivanovic et al. 2019). For example, administration of N-acetylcysteine (NAC) and cysteine prevents striatal degeneration and mitigates motor deficits and oxidative damage in the R6/2 mouse model of HD (Paul et al. 2014). Chronic administration of NAC also delays the onset and progression of motor deficits in the R6/1 mouse model of HD and unexpectedly provides an antidepressant effect in both R6/1 and wild-type mice as well (Wright et al. 2015). Notably, NAC improves the decreased mitochondrial respiratory capacity of striatal cells in R6/1 mice and reduces markers of oxidative damage in their mitochondria. Additional studies have suggested that baseline reductions in cysteine contribute to glutamatergic dysfunction and depressive-like behavior in HD, which can be alleviated with NAC treatment (Wright et al. 2016). Given that most cysteine and cystine transporters operate as antiporters for cysteine/cystine and the excitatory amino acid glutamate, it is not surprising that NAC administration can influence glutamatergic transmission. The beneficial effects of NAC on behavior have also been observed in some human cases of HD as well (Berk 2015; Berk et al. 2013). Additionally, we have shown that small molecule stimulators of the trans-sulfuration pathway in cell culture models of HD are also protective, identifying another neuroprotective strategy (Sbodio et al. 2018).

4 Amyotrophic Lateral Sclerosis

4.1 Background of ALS

ALS, commonly known as Lou Gehrig's disease, is characterized by degeneration of upper motor neurons, which connect the cortex to the brainstem and spinal cord, as well as lower motor neurons, which extend from the brainstem and spinal cord to the muscles. This leads to progressively worsening symptoms of muscle weakness, cramps, dysarthria, dysphagia, and ultimately paralysis (Hardiman et al. 2017). Approximately 50% of ALS patients also experience cognitive deficits (Phukan et al. 2012; Elamin et al. 2013).

The disease presents in two major forms: spinal-onset ALS, which typically begins with early limb weakness, and bulbar-onset ALS, which is marked by dysarthria and dysphagia. About 90% of ALS cases are sporadic, while 10% are currently understood to be inherited (Rowland and Shneider 2001). The most frequently implicated genes in familial ALS include mutations in chromosome 9 open reading frame 72 (C9orf72), Cu/Zn superoxide dismutase (SOD1), transactive response DNA binding protein 43 kDa (TDP-43), fused in sarcoma (FUS), and TANK-binding kinase 1 (TBK1) (Neumann et al. 2006; Marangi and Traynor 2015; Gurney et al. 1994; DeJesus-Hernandez et al. 2011; Brown and Al-Chalabi 2017; Rosen et al. 1993).

Multiple physiologic pathways affected by H_2S show dysfunction in ALS, and H_2S levels are most prominently elevated in patients with spinal cord onset as opposed to bulbar onset (Davoli et al. 2015). As detailed below, the role of H_2S has been most extensively characterized in models of SOD1 and C9orf72 ALS. Mutated SOD1 protein accumulates in pathological aggregates that are directly toxic to motor neurons (Gurney et al. 1994; Rosen et al. 1993), while the *C9ORF72* mutation involves expansion of the hexanucleotide repeat G4C2 and is responsible for 30–50% of familial ALS in Caucasians, termed C9-ALS

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patients (Cruts et al. 2013). In normal individuals, the wild-type *C9ORF72* gene typically contains fewer than 20–25 copies of this repeat, while in C9-ALS patients, this number can reach into the thousands (DeJesus-Hernandez et al. 2011). These repeated sequences can undergo repeat-associated non-ATG (RAN) translation, producing dipeptide repeat proteins (DPRs) such as poly Gly-Ala (GA), Gly-Pro (GP), Gly-Arg (GR), Pro-Ala (PA), and Pro-Arg (PR). Among these, poly-GA is expressed at the highest levels in the brains of C9-ALS patients and is associated with toxicity resulting from disruptions in several cellular processes, including nucleocytoplasmic transport, ER-Golgi vesicular trafficking, synaptic function, and proteostasis (Sultana et al. 2024; Jafarinia et al. 2024; Jensen et al. 2020; Beckers et al. 2021; Zhang et al. 2015).

4.2 H_2S Signaling in ALS

In contrast to the decreased H_2S observed in PD and HD, ALS is associated with elevated H_2S levels, first identified in the cerebrospinal fluid (CSF) of ALS patients and the tissues of G93A SOD1 mice (Davoli et al. 2015). The G93A SOD1 mice exhibit increased CBS levels in the mitochondria of astrocytes, as well as decreased electron transport chain complex IV activity in the brain (Davoli et al. 2015; Kirkinezos et al. 2005). This is consistent with previous research linking H_2S to the inhibition of electron transport chain complex IV. Moreover, G93A SOD1 mice showed remarkably low levels of plasma cysteine, which could indicate increased cysteine conversion to H_2S (Bame et al. 2014).

These investigators also demonstrated that motor neurons are especially susceptible to the toxic effects of H_2S (Davoli et al. 2015). A proteomic analysis of primary spinal cord cultures treated with NaHS further revealed an upregulation of oxidative stress and necroptosis pathways (Greco et al. 2018). Additionally, H_2S exposure induced morphological changes in astrocytes, decreased ATP production, reduced mitochondrial respiration rates, and caused mitochondrial depolarization (De Stefano et al. 2024). Correspondingly, when G93ASOD1 mice were treated with the CBS inhibitor amino-oxyacetic acid, H_2S levels in muscle and brain decreased, leading to improved survival in female, but not male, mice (Spalloni et al. 2019).

While H_2S levels are elevated in G93A SOD1 mice, the relationship between *C9ORF72* expansion and H_2S signaling remains less clear. Recent studies have indicated that the glycine-alanine dipeptide repeat protein (GA50), elevated in these mice, can bind SQOR, a crucial component of the sulfide oxidation pathway that detoxifies sulfide in mitochondria, which can accumulate due to H_2S production (Fu et al. 2023). The brain and spinal cord have lower levels of SQOR, which limits their ability to metabolize sulfide, making them more vulnerable to sulfide toxicity. The reaction catalyzed by SQOR is a pivotal first step in sulfide oxidation, leading to the formation of persulfide species that are further oxidized to sulfite, thiosulfate, and sulfate through subsequent enzymatic reactions involving ETHE1 or SDO, TST, and SO, as described in the section on H_2S catabolism (Paul et al. 2021).

In human microglial cells, both the expression of GA50 and the depletion of SQOR increased the accumulation of reactive oxygen species (ROS), as well as cytoplasmic escape of mitochondrial DNA that served to activate the NLRP3 inflammasome (Fig. 3). Notably, the compound irisflorentin (IFT) inhibited the interaction between GA50 and SQOR and

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reduced activation of the NLRP3 inflammasome (Fu et al. 2023). IFT, a traditional Chinese medicine that has been used for centuries, is a botanically derived compound isolated from the roots of *Belamcanda chinensis* (L.) DC that possesses anti-inflammatory and anti-tumor properties (Zhang et al. 2016).

It is anticipated that SQOR depletion may contribute to higher H_2S levels (Landry et al. 2021; Kanemaru and Ichinose 2024), which aligns with the observation of elevated H_2S in ALS patients. Thus, treatments aimed at normalizing H_2S levels may prove beneficial for managing ALS. Future research examining the sulfhydration state and the expression of the other H_2S biosynthetic enzymes (CSE and 3-MST) could provide further insights into the mechanisms involved, as well as the role of H_2S in other genetic forms of ALS.

5 Spinocerebellar Ataxia

5.1 Background of SCA

The word “ataxia’ is derived from the Greek words “a,” meaning without, and “taxis,” meaning order. Ataxia can present as a primary disorder or as a symptom of various conditions. It typically manifests through impaired coordination, balance difficulties, slurred speech, abnormally wide gait, difficulty with fine motor tasks, and slowed or involuntary eye movements, among other symptoms. The primary cause of ataxia is neurodegeneration in the cerebellum, and it can occur as either an inherited or sporadic condition (Klockgether and Paulson 2011; Ashizawa et al. 2018). Hereditary ataxias are classified as autosomal dominant, autosomal recessive, X-linked, and those involving mitochondrial inheritance (Cui et al. 2024). In this section, we discuss the role of H_2S signaling in the two forms of ataxia in which its dysregulation has been characterized: spinocerebellar ataxia 3 (SCA3) and ataxia telangiectasia, representing autosomal dominant and autosomal recessive forms of ataxia, respectively.

5.2 Spinocerebellar Ataxia 3 and H_2S Signaling

The SCAs are a group of at least 40 different conditions that are inherited in an autosomal dominant manner. These include SCAs characterized by polyglutamine (polyQ)-encoding CAG repeat expansions, as well as those caused by point mutations (Cui et al. 2024). SCA3, also known as Machado-Joseph disease, results from the expansion of a polyQ-encoding CAG repeat in exon 10 of the *ATXN3* gene (Kawaguchi et al. 1994). In normal individuals, the length of the CAG tract in ATXN3 ranges from 13 to 44 repeats, while in affected individuals, it ranges from 55 to 90 (de Mattos et al. 2019; Akcimen et al. 2020). Mutant ataxin-3 tends to aggregate, forming toxic oligomers and multimers that disrupt genetic transcription, induce oxidative stress, impair proteostasis, cause mitochondrial dysfunction, and lead to neuroinflammation (Zeng et al. 2018; Matos et al. 2019; Evert et al. 2006; Yu et al. 2009; Luo et al. 2023a; Harmuth et al. 2022; Wiatr et al. 2021; Klockgether et al. 2019; Scott et al. 2020; Quinet et al. 2024).

Notably, the trans-sulfuration pathway is disrupted in SCA3 (Fig. 4). In these patients, CSE levels and sulfhydration are reduced in the pontine tissue, an area where ataxin-3 aggregates are particularly concentrated (Snijder et al. 2016).

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Notably, overexpressing CSE restored normal sulfhydration levels, decreased oxidative stress, attenuated neuroinflammation, and provided neuroprotection in a *Drosophila* model of SCA3 (Snijder et al. 2016). Additionally, administering sodium thiosulfate (STS), an H_2S donor, also brought sulfhydration levels back to normal and protected against neurodegeneration (Snijder et al. 2016). Therefore, both genetic (increasing CSE expression) and pharmacological (administering STS) restoration of normal sulfhydration effectively prevented neurodegeneration in the SCA3 flies.

5.3 Ataxia Telangiectasia and H_2S Signaling

Ataxia telangiectasia (A-T) is an autosomal recessive disease caused by mutations in the *ATM* gene that cause cerebellar neurodegeneration. The name is derived from ataxia (unsteady gait) and dilation of blood vessels (telangiectases) that are visible in the conjunctiva of the eyes and facial skin of A-T patients (Savitsky et al. 1995). Other features of A-T include immunodeficiency, recurrent sinopulmonary infections, radiation sensitivity, premature senescence and aging, chromosomal instability, predisposition to cancer development (particularly of lymphoid origin), and immunodeficiency (Rothblum-Oviatt et al. 2016; Paull and Woolley 2024). Symptoms arise at an early age (1–4 years), and patients usually live only until early adulthood.

The *ATM* gene encodes a 350 kDa protein belonging to the phosphatidylinositol 3-kinase-related protein kinase family (PIKK) (Savitsky et al. 1995). The ATM protein is activated by oxidative stress and double-stranded DNA breaks (DSBs) and plays important roles in maintaining redox balance and DNA repair (Ditch and Paull 2012; Lee and Paull 2007; Cirotti et al. 2021). In response to DNA damage, the Mre11-Rad50-Nbs1 (MRN) complex is recruited to the site of DSBs, followed by autophosphorylation and activation of ATM, leading to conversion of inactive ATM dimers to the active monomeric forms to stimulate DNA repair (Bakkenist and Kastan 2003; Guo et al. 2010). Cells and animal models lacking ATM exhibit elevated oxidative stress, impaired antioxidant stress response, and higher accumulation of DNA damage (Guo et al. 2010; Barzilai et al. 2002; Meredith and Dodson 1987; Kamsler et al. 2001; Quick and Dugan 2001; Fang et al. 2016; McDonald et al. 2011).

Notably, aberrant H_2S signaling has been linked to this condition, as A-T patients exhibit impaired cysteine and GSH metabolism and also display lower cystine/glutamate exchanger subunit xCT, glutathione-S-transferase (GST), glutathione reductase (GR) levels, glutathione peroxidase (GPx) activity, and GSH levels in their cerebellar astrocytes (Meredith and Dodson 1987; Campbell et al. 2016). Interestingly, levels of both CSE and CBS are higher in cells lacking ATM, at both transcriptional and translational levels, and replenishing ATM suppresses the expression of both enzymes while also increasing the labile sulfide pool (Islam et al. 2022). Additionally, CSE activity has been reported to be higher in $ATM^{-/-}$ cells compared to $ATM^{+/+}$ cells, indicating that ATM is a negative regulator of CSE enzymatic activity. The effect of ATM on CSE and CBS appears to be at the post-translational level and further studies will clarify the exact relationship.

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6 Leigh Syndrome

6.1 Background of LS

LS was first described by Denis Leigh in 1951 in a 7-month-old infant and is the most commonly inherited mitochondrial disease affecting children, often leading to mortality within the early years of life (Yagensky et al. 2019; Leigh 1951). More than 75 mutations have been identified as causes of LS, predominantly affecting genes involved in mitochondrial bioenergetics (Lake et al. 2016; Chang et al. 2020). A key contributor to LS is impaired function of complex IV, a critical component of the mitochondrial electron transport chain (DiMauro et al. 1987).

Clinically, LS presents with both neurological and non-neurological symptoms, including developmental delays, epilepsy, weakness, hypotonia, feeding difficulties, and ataxia (Rahman et al. 1996). Neuropathological features of LS include focal and bilateral lesions in the brainstem, basal ganglia, cerebellum, and other regions of the brain. Pathologically, these lesions exhibit demyelination, spongiosis, gliosis, necrosis, and capillary proliferation.

6.2 H_2S Homeostasis in Leigh Syndrome

Similar to ALS, mutations in SQOR have been linked to LS, causing elevated H_2S levels and subsequent inhibition of Complex IV in the mitochondrial electron transport chain (Friederich et al. 2020). The role of H_2S in LS was confirmed in a study using a mouse LS model, which involved deficiency of mitochondrial SQOR. This model was developed by replacing the normal SQOR gene with a version lacking the sequence encoding the N-terminal mitochondrial localization sequence (SQORΔN) (Marutani et al. 2021).

By virtue of lacking mitochondrial SQOR, $SQOR^{\Delta N/\Delta N}$ mice recapitulate the clinical characteristics of LS, including progressive neurological deficits, brain lesions, and a reduced lifespan. These mice also display elevated blood lactate levels, significantly decreased complex IV activity, and increased H_2S levels in the plasma, brain, liver, and muscle (Fig. 5). Since SQOR expression is typically lower in the brain than in peripheral tissues, reduced enzyme activity in the brain can have particularly harmful effects (Linden et al. 2012).

$SQOR^{\Delta N/\Delta N}$ mice also exhibit an upregulation of the integrated stress response (ISR), evidenced by increased levels of ATF4 and DNA damage–inducible transcript 3 protein (DDIT3), both key proteins in the ISR pathway, along with elevated NADH-reductive stress. Treatment with the broad-spectrum antibiotic metronidazole reduced microbiota-produced H_2S levels, leading to increased survival of the mice. Additionally, maintaining these mice on a sulfur-restricted diet decreased systemic H_2S levels, alleviated disease symptoms, and improved lifespan (Kanemaru et al. 2024).

7 Other Mitochondrial Diseases

Mutations in any of the proteins of the sulfide oxidation unit can elevate H_2S. For instance, mutations in *ETHE1*, which encodes ETHE1, causes ethylmalonic encephalopathy (EE). EE is an infantile autosomal recessive disorder affecting the brain, gastrointestinal system,

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and blood vessels (Tiranti et al. 2004; Zafeiriou et al. 2007). In addition to increased H_2S, accumulation of lactate and ethylmalonic acid occurs as well. In a mouse model of ETHE deficiency, increase in thiosulfate levels was found, which reflects increased H_2S production (Tiranti et al. 2004). Similarly, TST depletion results in high circulating sulfide levels alongside increased gluconeogenesis, hypertriglyceridemia, and fatty liver (Carter et al. 2021). However, in TST-depleted mice, there were no changes in hepatic sulfide levels and these mice were viable, unlike the *Ethe*$^{-/-}$ mice (Morton et al. 2016). TST also generates H_2S from thiosulfate by utilizing dihydrolipoic acid (DHLA) and thus is involved in both production and detoxification of H_2S, although its role inH_2S catabolism seems to be its predominant function (Villarejo and Westley 1963; Libiad et al. 2015). The decreased persulfidation reported in these mice may stem from the elevated oxidative stress and suboptimal Nrf2 signaling that oxidizes cysteine residues irreversibly, a feature seen in Down syndrome (Luo et al. 2023b; Panagaki et al. 2024). Similarly, SO deficiency caused by pathogenic loss-of-function variants or loss of its molybdenum cofactor (Moco) is usually lethal (Schwarz 2016; Kaczmarek et al. 2022). Loss of SO will likely lead to decreased persulfidation levels and aberrant redox homeostasis.

Deficiency of CoQ, the level at which H_2S enters the mitochondrial electron transport chain, can also cause perturb sulfide catabolism (Luna-Sanchez et al. 2017; Ziosi et al. 2017), while supplementation of CoQ10 has been shown to protect against nephrotic syndrome by normalizing the sulfide oxidation pathway (Kleiner et al. 2018). Thus, the beneficial effects of CoQ10, which is commonly administered to patients with primary or secondary mitochondrial dysfunction, may stem from its role as a cofactor for sulfide:quinone oxidoreductase (SQOR) (Luna-Sanchez et al. 2017; Ziosi et al. 2017).

8 Concluding Remarks

Since the discovery and chemical synthesis of H_2S three centuries ago, research into the endogenous functions of this gasotransmitter has revealed its vital roles in both the peripheral and central nervous systems. It is now evident that H_2S is involved in nearly every biological process. However, both chronic decreases and increases in H_2S levels can be detrimental to cellular health, highlighting the importance of maintaining a balance between its biosynthesis and catabolism.

H_2S does not operate in isolation and may interact with other members of the gasotransmitter family, such as NO or other endogenous metabolites, and studying these interactions may deepen our understanding of signaling processes modulated by gasotransmitters (Coletta et al. 2012; Scrivner et al. 2021). Accordingly, an emerging focus within the field is the development of innovative therapeutics that utilize hybrid molecules (Xu et al. 2023; Dos Reis et al. 2024; Glowacka et al. 2023; Costa et al. 2020). For instance, H_2S-releasing moieties, such as 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT-OH) and allyldisulfide that are conjugated to L-DOPA methyl ester, have been shown to confer protective effects (Lee et al. 2010). These compounds released H_2S, reduced tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and nitrite from stimulated human microglia, astrocytes, THP-1 and U373 cells. Among these hybrids, ACS84 (4-(3-thioxo-3H-1,2-dithiol-4-yl)-benzoic acid) dissociated into L-DOPA and ADT-OH within

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1 h after injection into rats, with both metabolites being detected in the brain. ACS84 ameliorated motor deficits prevented neuronal loss in the substantia nigra and increased dopamine levels in the striatum in a rat model of PD (Xie et al. 2013).

Another hybrid molecule developed to counter neurodegeneration, S-memantine, is a hybrid of ADT and memantine, a clinically approved NMDA receptor antagonist used in the treatment of Alzheimer's disease (Marutani et al. 2012). Another strategy involved conjugation of memantine with isothiocyantes, which release H_2S, to generate a compound termed memit (Sestito et al. 2019; Martelli et al. 2014). Memit prevented Aβ (Abe and Kimura 1996; Chen et al. 2004; Cheng et al. 2004; Clarke 1953; Dunham et al. 1999; Dupuyturen 1806; Enokido et al. 2005; Filipovic 2015; Filipovic et al. 2018; Gayon 1877; Ishigami et al. 2009; Ishii et al. 2010; Kamoun 2001; Kruger 2017; Kuo et al. 1983; Lambert et al. 2006; Linden et al. 2008; Mani et al. 2011; Mironov et al. 2017; Mitchell and Davenport 1924; Morikawa et al. 2012; Mustafa et al. 2009, 2011; Myers 1920; Paul et al. 2018; Paul and Snyder 2012, 2015; Ramazzini 1700; Rizzo 1967; Sen et al. 2012; Shatalin et al. 2011; Shen et al. 2012; Shibuya et al. 2009; Stipanuk 2020; Stipanuk and Beck 1982; Szabo 2020; Tang et al. 2005, 2013; Wang 2009; Warenycia et al. 1989; Yang et al. 2008; Zhao et al. 2001) self-induced aggregation and Aβ oligomer-induced damage in human neurons and rat microglia cells (Sestito et al. 2019). Chimeric molecules that combine aspirin with H_2S and NO-releasing moieties have also been considered for treatment of neurodegenerative diseases (Sestito et al. 2019).

In conclusion, the pursuit of compounds or treatments that stimulate H_2S production is gaining traction. It is crucial to consider the brain penetrance of these molecules when developing drugs for neurologic diseases. Furthermore, studying H_2S homeostasis in relation to aging is of significant importance (Zivanovic et al. 2019), as aging is a substantial risk factor for several late-onset neurodegenerative diseases, including PD and HD (Hou et al. 2019). Understanding the role of H_2S in aging may pave the way for new insights and therapeutic strategies to combat these debilitating conditions.

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References

Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K et al. (2021) Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers 7(1):47 [PubMed: 34210995]

Abe K, Kimura H (1996) The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci 16(3):1066–1071 [PubMed: 8558235]

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Absalyamova M, Traktirov D, Burdinskaya V, Artemova V, Muruzheva Z, Karpenko M (2024) Molecular basis of the development of Parkinson's disease. Neuroscience 565:292–300 [PubMed: 39653246]

Akcimen F, Martins S, Liao C, Bourassa CV, Catoire H, Nicholson GA et al. (2020) Genome-wide association study identifies genetic factors that modify age at onset in Machado-Joseph disease. Aging (Albany NY) 12(6):4742–4756 [PubMed: 32205469]

Ament SA, Pearl JR, Grindeland A, St Claire J, Earls JC, Kovalenko M et al. (2017) High resolution time-course mapping of early transcriptomic, molecular and cellular phenotypes in Huntington's disease CAG knock-in mice across multiple genetic backgrounds. Hum Mol Genet 26(5): 913–922 [PubMed: 28334820]

Ament SA, Pearl JR, Cantle JP, Bragg RM, Skene PJ, Coffey SR et al. (2018) Transcriptional regulatory networks underlying gene expression changes in Huntington's disease. Mol Syst Biol 14(3):e7435 [PubMed: 29581148]

Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S et al. (1993) The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet 4(4):398–403 [PubMed: 8401589]

Ashizawa T, Oz G, Paulson HL (2018) Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol 14(10):590–605 [PubMed: 30131520]

Bakkenist CJ, Kastan MB (2003) DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 421(6922):499–506 [PubMed: 12556884]

Bame M, Grier RE, Needleman R, Brusilow WS (2014) Amino acids as biomarkers in the SOD1 (G93A) mouse model of ALS. Biochim Biophys Acta 1842(1):79–87 [PubMed: 24129262]

Banez-Coronel M, Ayhan F, Tarabochia AD, Zu T, Perez BA, Tusi SK et al. (2015) RAN translation in Huntington disease. Neuron 88(4):667–677 [PubMed: 26590344]

Barzilai A, Rotman G, Shiloh Y (2002) ATM deficiency and oxidative stress: a new dimension of defective response to DNA damage. DNA Repair (Amst) 1(1):3–25 [PubMed: 12509294]

Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR et al. (2015) Huntington disease. Nat Rev Dis Primers 1:15005 [PubMed: 27188817]

Beckers J, Tharkeshwar AK, Van Damme P (2021) C9orf72 ALS-FTD: recent evidence for dysregulation of the autophagy-lysosome pathway at multiple levels. Autophagy 17(11): 3306–3322 [PubMed: 33632058]

Berk M (2015) N-Acetylcysteine for Huntington's? Aust N Z J Psychiatry 49(11):1071–1072 [PubMed: 26377749]

Berk M, Malhi GS, Gray LJ, Dean OM (2013) The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci 34(3):167–177 [PubMed: 23369637]

Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. Lancet 397(10291):2284–2303 [PubMed: 33848468]

Brown RH, Al-Chalabi A (2017) Amyotrophic lateral sclerosis. N Engl J Med 377(2):162–172 [PubMed: 28700839]

Cakmak YO (2017) Rotorua, hydrogen sulphide and Parkinson's disease-A possible beneficial link? N Z Med J 130(1455):123–125 [PubMed: 28494485]

Campbell A, Bushman J, Munger J, Noble M, Proschel C, Mayer-Proschel M (2016) Mutation of ataxia-telangiectasia mutated is associated with dysfunctional glutathione homeostasis in cerebellar astroglia. Glia 64(2):227–239 [PubMed: 26469940]

Carter RN, Gibbins MTG, Barrios-Llerena ME, Wilkie SE, Freddolino PL, Libiad M et al. (2021) The hepatic compensatory response to elevated systemic sulfide promotes diabetes. Cell Rep 37(6):109958 [PubMed: 34758301]

Chang X, Wu Y, Zhou J, Meng H, Zhang W, Guo J (2020) A meta-analysis and systematic review of Leigh syndrome: clinical manifestations, respiratory chain enzyme complex deficiency, and gene mutations. Medicine (Baltimore) 99(5):e18634 [PubMed: 32000367]

Chen X, Jhee KH, Kruger WD (2004) Production of the neuromodulator H2S by cystathionine beta-synthase via the condensation of cysteine and homocysteine. J Biol Chem 279(50): 52082–52086 [PubMed: 15520012]

Sulfatonic®

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Cheng Y, Ndisang JF, Tang G, Cao K, Wang R (2004) Hydrogen sulfide-induced relaxation of resistance mesenteric artery beds of rats. Am J Physiol Heart Circ Physiol 287(5):H2316–H2323 [PubMed: 15191893]

Chung KK, Thomas B, Li X, Pletnikova O, Troncoso JC, Marsh L et al. (2004) S-nitrosylation of parkin regulates ubiquitination and compromises parkin's protective function. Science 304(5675):1328–1331 [PubMed: 15105460]

Cirotti C, Rizza S, Giglio P, Poerio N, Allega MF, Claps G et al. (2021) Redox activation of ATM enhances GSNOR translation to sustain mitophagy and tolerance to oxidative stress. EMBO Rep 22(1):e50500 [PubMed: 33245190]

Clark IE, Dodson MW, Jiang C, Cao JH, Huh JR, Seol JH et al. (2006) Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 441(7097):1162–1166 [PubMed: 16672981]

Clarke PH (1953) Hydrogen sulphide production by bacteria. J Gen Microbiol 8(3):397–407 [PubMed: 13061742]

Coletta C, Papapetropoulos A, Erdelyi K, Olah G, Modis K, Panopoulos P et al. (2012) Hydrogen sulfide and nitric oxide are mutually dependent in the regulation of angiogenesis and endothelium-dependent vasorelaxation. Proc Natl Acad Sci USA 109(23):9161–9166 [PubMed: 22570497]

Collaborators GBDPsD (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 17(11): 939–953 [PubMed: 30287051]

Costa S, Muscara MN, Allain T, Dallazen J, Gonzaga L, Buret AG et al. (2020) Enhanced analgesic effects and gastrointestinal safety of a novel, hydrogen sulfide-releasing anti-inflammatory drug (ATB-352): a role for endogenous cannabinoids. Antioxid Redox Signal 33(14):1003–1009 [PubMed: 32064887]

Cruts M, Gijselinck I, Van Langenhove T, van der Zee J, Van Broeckhoven C (2013) Current insights into the C9orf72 repeat expansion diseases of the FTLD/ALS spectrum. Trends Neurosci 36(8):450–459 [PubMed: 23746459]

Cui ZT, Mao ZT, Yang R, Li JJ, Jia SS, Zhao JL et al. (2024) Spinocerebellar ataxias: from pathogenesis to recent therapeutic advances. Front Neurosci 18:1422442 [PubMed: 38894941]

Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA et al. (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90(3):537–548 [PubMed: 9267033]

Davoli A, Greco V, Spalloni A, Guatteo E, Neri C, Rizzo GR et al. (2015) Evidence of hydrogen sulfide involvement in amyotrophic lateral sclerosis. Ann Neurol 77(4):697–709 [PubMed: 25627240]

Dawson TM, Dawson VL (2010) The role of parkin in familial and sporadic Parkinson's disease. Mov Disord 25(Suppl 1):S32–S39 [PubMed: 20187240]

de Mattos EP, Kolbe Musskopf M, Bielefeldt Leotti V, Saraiva-Pereira ML, Jardim LB (2019) Genetic risk factors for modulation of age at onset in Machado-Joseph disease/spinocerebellar ataxia type 3: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 90(2): 203–210 [PubMed: 30337442]

De Stefano S, Tiberi M, Salvatori I, De Bardi M, Gimenez J, Pirshayan M et al. (2024) Hydrogen sulfide modulates astrocytic toxicity in mouse spinal cord cultures: implications for amyotrophic lateral sclerosis. Antioxidants (Basel) 13(10)

DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ et al. (2011) Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72(2):245–256 [PubMed: 21944778]

DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP et al. (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 277(5334):1990–1993 [PubMed: 9302293]

DiMauro S, Servidei S, Zeviani M, DiRocco M, DeVivo DC, DiDonato S et al. (1987) Cytochrome c oxidase deficiency in Leigh syndrome. Ann Neurol 22(4):498–506 [PubMed: 2829705]

Ditch S, Paull TT (2012) The ATM protein kinase and cellular redox signaling: beyond the DNA damage response. Trends Biochem Sci 37(1):15–22 [PubMed: 22079189]

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Dos Reis RA, Sarkar I, Rodrigues MG, Matson JB, Seabra AB, Kashfi K (2024) NO- and H(2)S-releasing nanomaterials: a crosstalk signaling pathway in cancer. Nitric Oxide 151:17–30 [PubMed: 39179197]

Dunham I, Shimizu N, Roe BA, Chissoe S, Hunt AR, Collins JE et al. (1999) The DNA sequence of human chromosome 22. Nature 402(6761):489–495 [PubMed: 10591208]

Dupuyturen M (1806) Rapport sur une espéce de mephitisme des fosses d'aisance, produite par le gas azote. J Med

Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B et al. (2013) Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology 80(17): 1590–1597 [PubMed: 23553481]

Enokido Y, Suzuki E, Iwasawa K, Namekata K, Okazawa H, Kimura H (2005) Cystathionine beta-synthase, a key enzyme for homocysteine metabolism, is preferentially expressed in the radial glia/astrocyte lineage of developing mouse CNS. FASEB J 19(13):1854–1856 [PubMed: 16160063]

Evert BO, Schelhaas J, Fleischer H, de Vos RA, Brunt ER, Stenzel W et al. (2006) Neuronal intranuclear inclusions, dysregulation of cytokine expression and cell death in spinocerebellar ataxia type 3. Clin Neuropathol 25(6):272–281 [PubMed: 17140157]

Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H et al. (2016) NAD(+) replenishment improves lifespan and Healthspan in ataxia telangiectasia models via Mitophagy and DNA repair. Cell Metab 24(4):566–581 [PubMed: 27732836]

Filipovic MR (2015) Persulfidation (S-sulfhydration) and H2S. Handb Exp Pharmacol 230:29–59 [PubMed: 26162828]

Filipovic MR, Zivanovic J, Alvarez B, Banerjee R (2018) Chemical biology of H(2)S signaling through Persulfidation. Chem Rev 118(3):1253–1337 [PubMed: 29112440]

Frederick NM, Bertho J, Patel KK, Petr GT, Bakradze E, Smith SB et al. (2014) Dysregulation of system xc(−) expression induced by mutant huntingtin in a striatal neuronal cell line and in R6/2 mice. Neurochem Int 76:59–69 [PubMed: 25004085]

Friederich MW, Elias AF, Kuster A, Laugwitz L, Larson AA, Landry AP et al. (2020) Pathogenic variants in SQOR encoding sulfide:quinone oxidoreductase are a potentially treatable cause of Leigh disease. J Inherit Metab Dis 43(5):1024–1036 [PubMed: 32160317]

Fu RH, Chen HJ, Hong SY (2023) Glycine-alanine dipeptide repeat protein from C9-ALS interacts with sulfide Quinone oxidoreductase (SQOR) to induce the activity of the NLRP3 Inflammasome in HMC3 microglia: Irisflorentin Reverses This Interaction. Antioxidants (Basel) 12(10)

Funayama M, Nishioka K, Li Y, Hattori N (2023) Molecular genetics of Parkinson's disease: contributions and global trends. J Hum Genet 68(3):125–130 [PubMed: 35821405]

Gayon MU Note presentee par M. Pasteur. Sur les alterations des oeufs, a l'occasion d'une Note de MM. A. Bechamp et G. Eustache. Ann Ecole Normale Super 1877;Ser 2

Genetic Modifiers of Huntington's Disease C (2015) Identification of genetic factors that modify clinical onset of Huntington's disease. Cell 162(3):516–526 [PubMed: 26232222]

Glowacka U, Magierowski M, Sliwowski Z, Cieszkowski J, Szetela M, Wojcik-Grzybek D et al. (2023) Hydrogen sulfide-releasing indomethacin-derivative (ATB-344) prevents the development of oxidative gastric mucosal injuries. Antioxidants (Basel) 12(8):1545 [PubMed: 37627540]

Greco V, Spalloni A, Corasolla Carregari V, Pieroni L, Persichilli S, Mercuri NB et al. (2018) Proteomics and toxicity analysis of spinal-cord primary cultures upon hydrogen sulfide treatment. Antioxidants (Basel) 7(7)

Grima JC, Daigle JG, Arbez N, Cunningham KC, Zhang K, Ochaba J et al. (2017) Mutant huntingtin disrupts the nuclear pore complex. Neuron 94(1):93–107 e6 [PubMed: 28384479]

Gu X, Richman J, Langfelder P, Wang N, Zhang S, Banez-Coronel M et al. (2022) Uninterrupted CAG repeat drives striatum-selective transcriptionopathy and nuclear pathogenesis in human Huntingtin BAC mice. Neuron 110(7):1173–92 e7 [PubMed: 35114102]

Guo Z, Kozlov S, Lavin MF, Person MD, Paull TT (2010) ATM activation by oxidative stress. Science 330(6003):517–521 [PubMed: 20966255]

Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD et al. (1994) Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science 264(5166):1772–1775 [PubMed: 8209258]

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Gusella JF, MacDonald ME, Lee JM (2014) Genetic modifiers of Huntington's disease. Mov Disord 29(11):1359–1365 [PubMed: 25154728]

Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W et al. (2017) Amyotrophic lateral sclerosis. Nat Rev Dis Primers 3:17071 [PubMed: 28980624]

Harmuth T, Weber JJ, Zimmer AJ, Sowa AS, Schmidt J, Fitzgerald JC et al. (2022) Mitochondrial dysfunction in spinocerebellar ataxia type 3 is linked to VDAC1 Deubiquitination. Int J Mol Sci 23(11)

Hildebrandt TM, Grieshaber MK (2008) Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. FEBS J 275(13):3352–3361 [PubMed: 18494801]

Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL et al. (2019) Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol 15(10):565–581 [PubMed: 31501588]

Hou X, Watzlawik JO, Fiesel FC, Springer W (2020) Autophagy in Parkinson's disease. J Mol Biol 432(8):2651–2672 [PubMed: 32061929]

Hu LF, Lu M, Tiong CX, Dawe GS, Hu G, Bian JS (2010) Neuroprotective effects of hydrogen sulfide on Parkinson's disease rat models. Aging Cell 9(2):135–146 [PubMed: 20041858]

Ishigami M, Hiraki K, Umemura K, Ogasawara Y, Ishii K, Kimura H (2009) A source of hydrogen sulfide and a mechanism of its release in the brain. Antioxid Redox Signal 11(2):205–214 [PubMed: 18754702]

Ishii I, Akahoshi N, Yamada H, Nakano S, Izumi T, Suematsu M (2010) Cystathionine gamma-Lyase-deficient mice require dietary cysteine to protect against acute lethal myopathy and oxidative injury. J Biol Chem 285(34):26358–26368 [PubMed: 20566639]

Islam MZ, Shen X, Pardue S, Kevil CG, Shackelford RE (2022) The ataxia-telangiectasia mutated gene product regulates the cellular acid-labile sulfide fraction. DNA Repair (Amst) 116:103344 [PubMed: 35696854]

Jackson MR, Melideo SL, Jorns MS (2012) Human sulfide:quinone oxidoreductase catalyzes the first step in hydrogen sulfide metabolism and produces a sulfane sulfur metabolite. Biochemistry 51(34):6804–6815 [PubMed: 22852582]

Jafarinia H, van der Giessen E, Onck PR (2024) C9orf72 polyPR directly binds to various nuclear transport components. elife 12:12

Jensen BK, Schuldi MH, McAvoy K, Russell KA, Boehringer A, Curran BM et al. (2020) Synaptic dysfunction induced by glycine-alanine dipeptides in C9orf72-ALS/FTD is rescued by SV2 replenishment. EMBO Mol Med 12(5):e10722 [PubMed: 32347002]

Jiang W, Zou W, Hu M, Tian Q, Xiao F, Li M et al. (2022) Hydrogen sulphide attenuates neuronal apoptosis of substantia nigra by re-establishing autophagic flux via promoting leptin signalling in a 6-hydroxydopamine rat model of Parkinson's disease. Clin Exp Pharmacol Physiol 49(1): 122–133 [PubMed: 34494284]

Kaczmarek AT, Bender D, Gehling T, Kohl JB, Daimaguler HS, Santamaria-Araujo JA et al. (2022) A defect in molybdenum cofactor binding causes an attenuated form of sulfite oxidase deficiency. J Inherit Metab Dis 45(2):169–182 [PubMed: 34741542]

Kamoun P (2001) Mental retardation in down syndrome: a hydrogen sulfide hpothesis. Med Hypotheses 57(3):389–392 [PubMed: 11516234]

Kamsler A, Daily D, Hochman A, Stern N, Shiloh Y, Rotman G et al. (2001) Increased oxidative stress in ataxia telangiectasia evidenced by alterations in redox state of brains from Atm-deficient mice. Cancer Res 61(5):1849–1854 [PubMed: 11280737]

Kanemaru E, Ichinose F (2024) Essential role of sulfide oxidation in brain health and neurological disorders. Pharmacol Ther 266:108787 [PubMed: 39719173]

Kanemaru E, Shimoda K, Marutani E, Morita M, Miranda M, Miyazaki Y et al. (2024) Exclusion of sulfide:quinone oxidoreductase from mitochondria causes Leigh-like disease in mice by impairing sulfide metabolism. J Clin Invest 134(15)

Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S et al. (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8(3):221–228 [PubMed: 7874163]

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Keum JW, Shin A, Gillis T, Mysore JS, Abu Elneel K, Lucente D et al. (2016) The HTT CAG-expansion mutation determines age at death but not disease duration in Huntington disease. Am J Hum Genet 98(2):287–298 [PubMed: 26849111]

Kida K, Yamada M, Tokuda K, Marutani E, Kakinohana M, Kaneki M et al. (2011) Inhaled hydrogen sulfide prevents neurodegeneration and movement disorder in a mouse model of Parkinson's disease. Antioxid Redox Signal 15(2):343–352 [PubMed: 21050138]

Kimura Y, Goto Y, Kimura H (2010) Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. Antioxid Redox Signal 12(1):1–13 [PubMed: 19852698]

Kirkinezos IG, Bacman SR, Hernandez D, Oca-Cossio J, Arias LJ, Perez-Pinzon MA et al. (2005) Cytochrome c association with the inner mitochondrial membrane is impaired in the CNS of G93A-SOD1 mice. J Neurosci 25(1):164–172 [PubMed: 15634778]

Klein C, Lohmann K (2009) Parkinson disease(s): is "Parkin disease" a distinct clinical entity? Neurology 72(2):106–107 [PubMed: 18987349]

Kleiner G, Barca E, Ziosi M, Emmanuele V, Xu Y, Hidalgo-Gutierrez A et al. (2018) CoQ (10) supplementation rescues nephrotic syndrome through normalization of H(2)S oxidation pathway. Biochim Biophys Acta Mol basis Dis 1864(11):3708–3722 [PubMed: 30251690]

Klockgether T, Paulson H (2011) Milestones in ataxia. Mov Disord 26(6):1134–1141 [PubMed: 21626557]

Klockgether T, Mariotti C, Paulson HL (2019) Spinocerebellar ataxia. Nat Rev Dis Primers 5(1):24 [PubMed: 30975995]

Kruger WD (2017) Cystathionine beta-synthase deficiency: of mice and men. Mol Genet Metab 121(3):199–205 [PubMed: 28583326]

Kuo SM, Lea TC, Stipanuk MH (1983) Developmental pattern, tissue distribution, and subcellular distribution of cysteine: alpha-ketoglutarate aminotransferase and 3-mercaptopyruvate sulfurtransferase activities in the rat. Biol Neonate 43(1–2):23–32 [PubMed: 6573924]

Lake NJ, Compton AG, Rahman S, Thorburn DR (2016) Leigh syndrome: one disorder, more than 75 monogenic causes. Ann Neurol 79(2):190–203 [PubMed: 26506407]

Lambert TW, Goodwin VM, Stefani D, Strosher L (2006) Hydrogen sulfide (H2S) and sour gas effects on the eye. A historical perspective. Sci Total Environ 367(1):1–22 [PubMed: 16650463]

Landry AP, Ballou DP, Banerjee R (2021) Hydrogen sulfide oxidation by sulfide Quinone oxidoreductase. Chembiochem 22(6):949–960 [PubMed: 33080111]

Lee JH, Paull TT (2007) Activation and regulation of ATM kinase activity in response to DNA double-strand breaks. Oncogene 26(56):7741–7748 [PubMed: 18066086]

Lee M, Tazzari V, Giustarini D, Rossi R, Sparatore A, Del Soldato P et al. (2010) Effects of hydrogen sulfide-releasing L-DOPA derivatives on glial activation: potential for treating Parkinson disease. J Biol Chem 285(23):17318–17328 [PubMed: 20368333]

Leigh D (1951) Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry 14(3):216–221 [PubMed: 14874135]

Li X, Valencia A, Sapp E, Masso N, Alexander J, Reeves P et al. (2010) Aberrant Rab11-dependent trafficking of the neuronal glutamate transporter EAAC1 causes oxidative stress and cell death in Huntington's disease. J Neurosci 30(13):4552–4561 [PubMed: 20357106]

Li L, Liu H, Dong P, Li D, Legant WR, Grimm JB et al. (2016) Real-time imaging of Huntingtin aggregates diverting target search and gene transcription. elife:5

Li H, Shi G, Zha H, Zheng L, Luo Z, Wang Y (2024) Inhibition of histone deacetylase promotes a neuroprotective mechanism in an experimental model of Parkinson's disease. Arch Med Sci 20(2):664–674 [PubMed: 38757033]

Libiad M, Sriraman A, Banerjee R (2015) Polymorphic variants of human Rhodanese exhibit differences in thermal stability and sulfur transfer kinetics. J Biol Chem 290(39):23579–23588 [PubMed: 26269602]

Linden DR, Sha L, Mazzone A, Stoltz GJ, Bernard CE, Furne JK et al. (2008) Production of the gaseous signal molecule hydrogen sulfide in mouse tissues. J Neurochem 106(4):1577–1585 [PubMed: 18513201]

Sulfatonic®

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Linden DR, Furne J, Stoltz GJ, Abdel-Rehim MS, Levitt MD, Szurszewski JH (2012) Sulphide quinone reductase contributes to hydrogen sulphide metabolism in murine peripheral tissues but not in the CNS. Br J Pharmacol 165(7):2178–2190 [PubMed: 21950400]

Liu TW, Chen CM, Chang KH (2022) Biomarker of Neuroinflammation in Parkinson's disease. Int J Mol Sci 23(8)

Liu F, Tian Q, Tang HL, Cheng X, Zou W, Zhang P (2024) Hydrogen sulfide attenuates depression-like behaviours in Parkinson's disease model rats by improving synaptic plasticity in a hippocampal Warburg effect-dependent manner. Pharmacol Biochem Behav 234:173677 [PubMed: 37967673]

Luna-Sanchez M, Hidalgo-Gutierrez A, Hildebrandt TM, Chaves-Serrano J, Barriocanal-Casado E, Santos-Fandila A et al. (2017) CoQ deficiency causes disruption of mitochondrial sulfide oxidation, a new pathomechanism associated with this syndrome. EMBO Mol Med 9(1):78–95 [PubMed: 27856619]

Luo H, Todi SV, Paulson HL, Costa MDC (2023a) Regional and age-dependent changes in ubiquitination in cellular and mouse models of spinocerebellar ataxia type 3. Front Mol Neurosci 16:1154203 [PubMed: 37122622]

Luo Y, Chatre L, Melhem S, Al-Dahmani ZM, Homer NZM, Miedema A et al. (2023b) Thiosulfate sulfurtransferase deficiency promotes oxidative distress and aberrant NRF2 function in the brain. Redox Biol 68:102965 [PubMed: 38000344]

Mani S, Yang G, Wang R (2011) A critical life-supporting role for cystathionine gamma-lyase in the absence of dietary cysteine supply. Free Radic Biol Med 50(10):1280–1287 [PubMed: 21310231]

Marangi G, Traynor BJ (2015) Genetic causes of amyotrophic lateral sclerosis: new genetic analysis methodologies entailing new opportunities and challenges. Brain Res 1607:75–93 [PubMed: 25316630]

Martelli A, Testai L, Citi V, Marino A, Bellagambi FG, Ghimenti S et al. (2014) Pharmacological characterization of the vascular effects of aryl isothiocyanates: is hydrogen sulfide the real player? Vasc Pharmacol 60(1):32–41

Marutani E, Kosugi S, Tokuda K, Khatri A, Nguyen R, Atochin DN et al. (2012) A novel hydrogen sulfide-releasing N-methyl-D-aspartate receptor antagonist prevents ischemic neuronal death. J Biol Chem 287(38):32124–32135 [PubMed: 22815476]

Marutani E, Morita M, Hirai S, Kai S, Grange RMH, Miyazaki Y et al. (2021) Sulfide catabolism ameliorates hypoxic brain injury. Nat Commun 12(1):3108 [PubMed: 34035265]

Matos CA, de Almeida LP, Nobrega C (2019) Machado-Joseph disease/spinocerebellar ataxia type 3: lessons from disease pathogenesis and clues into therapy. J Neurochem 148(1):8–28 [PubMed: 29959858]

McDonald CJ, Ostini L, Wallace DF, John AN, Watters DJ, Subramaniam VN (2011) Iron loading and oxidative stress in the Atm−/− mouse liver. Am J Physiol Gastrointest Liver Physiol 300(4): G554–G560 [PubMed: 21292994]

Meredith MJ, Dodson ML (1987) Imparied glutathione biosynthesis in cultured human ataxia-telangiectasia cells. Cancer Res 47(17):4576–4581 [PubMed: 3621155]

Mironov A, Seregina T, Nagornykh M, Luhachack LG, Korolkova N, Lopes LE et al. (2017) Mechanism of H(2)S-mediated protection against oxidative stress in Escherichia coli. Proc Natl Acad Sci USA 114(23):6022–6027 [PubMed: 28533366]

Mitchell CW, Davenport SJ (1924) Hydrogen sulphide literature. Public Health Rep 39:1–13 [PubMed: 19314911]

Modis K, Bos EM, Calzia E, van Goor H, Coletta C, Papapetropoulos A et al. (2014) Regulation of mitochondrial bioenergetic function by hydrogen sulfide. Part II. Pathophysiological and therapeutic aspects. Br J Pharmacol 171(8):2123–2146 [PubMed: 23991749]

Modis K, Ju Y, Ahmad A, Untereiner AA, Altaany Z, Wu L et al. (2016) S-Sulfhydration of ATP synthase by hydrogen sulfide stimulates mitochondrial bioenergetics. Pharmacol Res 113 (Pt A):116–124 [PubMed: 27553984]

Morikawa T, Kajimura M, Nakamura T, Hishiki T, Nakanishi T, Yukutake Y et al. (2012) Hypoxic regulation of the cerebral microcirculation is mediated by a carbon monoxide-sensitive hydrogen sulfide pathway. Proc Natl Acad Sci USA 109(4):1293–1298 [PubMed: 22232681]

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Morton NM, Beltram J, Carter RN, Michailidou Z, Gorjanc G, McFadden C et al. (2016) Genetic identification of thiosulfate sulfurtransferase as an adipocyte-expressed antidiabetic target in mice selected for leanness. Nat Med 22(7):771–779 [PubMed: 27270587]

Mustafa AK, Gadalla MM, Sen N, Kim S, Mu W, Gazi SK et al. (2009) H2S signals through protein S-sulfhydration. Sci Signal 2(96):ra72 [PubMed: 19903941]

Mustafa AK, Sikka G, Gazi SK, Steppan J, Jung SM, Bhunia AK et al. (2011) Hydrogen sulfide as endothelium-derived hyperpolarizing factor sulfhydrates potassium channels. Circ Res 109(11): 1259–1268 [PubMed: 21980127]

Myers JT (1920) The production of hydrogen Sulphide by bacteria. J Bacteriol 5(3):231–252 [PubMed: 16558873]

Nagashima F, Miyazaki Y, Kanemaru E, Ezaka M, Hara H, Sugiura K et al. (2023) Sulfide:quinone oxidoreductase ameliorates neurodegeneration in a murine model of Parkinson's disease. Redox Biol 59:102562 [PubMed: 36470130]

Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT et al. (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314(5796):130–133 [PubMed: 17023659]

Oh YM, Lee SW, Kim WK, Chen S, Church VA, Cates K et al. (2022) Age-related Huntington's disease progression modeled in directly reprogrammed patient-derived striatal neurons highlights impaired autophagy. Nat Neurosci 25(11):1420–1433 [PubMed: 36303071]

Panagaki T, Janickova L, Petrovic D, Zuhra K, Ditroi T, Juranyi EP et al. (2024) Neurobehavioral dysfunction in a mouse model of Down syndrome: upregulation of cystathionine beta-synthase, H(2)S overproduction, altered protein persulfidation, synaptic dysfunction, endoplasmic reticulum stress, and autophagy. Geroscience 46(5):4275–4314 [PubMed: 38558215]

Paul BD (2022) Cysteine metabolism and hydrogen sulfide signaling in Huntington's disease. Free Radic Biol Med 186:93–98 [PubMed: 35550919]

Paul BD, Snyder SH (2012) H(2)S signalling through protein sulfhydration and beyond. Nat Rev Mol Cell Biol 13(8):499–507 [PubMed: 22781905]

Paul BD, Snyder SH (2014) Neurodegeneration in Huntington's disease involves loss of cystathionine gamma-lyase. Cell Cycle 13(16):2491–2493 [PubMed: 25486189]

Paul BD, Snyder SH (2015) H2S: a novel Gasotransmitter that signals by Sulfhydration. Trends Biochem Sci 40(11):687–700 [PubMed: 26439534]

Paul BD, Snyder SH (2019) Impaired redox signaling in Huntington's disease: therapeutic implications. Front Mol Neurosci 12:68 [PubMed: 30941013]

Paul BD, Sbodio JI, Xu R, Vandiver MS, Cha JY, Snowman AM et al. (2014) Cystathionine gamma-lyase deficiency mediates neurodegeneration in Huntington's disease. Nature 509(7498):96–100 [PubMed: 24670645]

Paul BD, Sbodio JI, Snyder SH (2018) Cysteine metabolism in neuronal redox homeostasis. Trends Pharmacol Sci 39(5):513–524 [PubMed: 29530337]

Paul BD, Snyder SH, Kashfi K (2021) Effects of hydrogen sulfide on mitochondrial function and cellular bioenergetics. Redox Biol 38:101772 [PubMed: 33137711]

Paul BD, Sbodio JI, Snyder SH (2022) Mutant huntingtin derails cysteine metabolism in Huntington's disease at both transcriptional and post-translational levels. Antioxidants (Basel) 11(8)

Paull TT, Woolley PR (2024) A-T neurodegeneration and DNA damage-induced transcriptional stress. DNA Repair (Amst) 135:103647 [PubMed: 38377644]

Pengo M, Squitieri F (2024) Beyond CAG repeats: the multifaceted role of genetics in Huntington disease. Genes (Basel) 15(6)

Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S et al. (2012) The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 83(1):102–108 [PubMed: 21836033]

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J et al. (2017) Parkinson disease. Nat Rev Dis Primers 3:17013 [PubMed: 28332488]

Quick KL, Dugan LL (2001) Superoxide stress identifies neurons at risk in a model of ataxia-telangiectasia. Ann Neurol 49(5):627–635 [PubMed: 11357953]

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Quinet G, Paz-Cabrera MC, Freire R (2024) Biochemical analysis to study wild-type and polyglutamine-expanded ATXN3 species. PLoS One 19(12):e0315868 [PubMed: 39715253]

Rahman S, Blok RB, Dahl HH, Danks DM, Kirby DM, Chow CW et al. (1996) Leigh syndrome: clinical features and biochemical and DNA abnormalities. Ann Neurol 39(3):343–351 [PubMed: 8602753]

Ramazzini B (1700) De Morbis Artificum Diatriba. Antonii Capponi, Mutinae (Modena)

Ravikumar B, Duden R, Rubinsztein DC (2002) Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. Hum Mol Genet 11(9):1107–1117 [PubMed: 11978769]

Reed BR, Crane J, Garrett N, Woods DL, Bates MN (2014) Chronic ambient hydrogen sulfide exposure and cognitive function. Neurotoxicol Teratol 42:68–76 [PubMed: 24548790]

Rizzo AA (1967) The possible role of hydrogen sulfide in human periodontal disease. I. Hydrogen sulfide production in periodontal pockets. Periodontics 5(5):233–236 [PubMed: 4861566]

Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A et al. (1993) Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362(6415):59–62 [PubMed: 8446170]

Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM (2016) Ataxia telangiectasia: a review. Orphanet J Rare Dis 11(1):159 [PubMed: 27884168]

Rowland LP, Shneider NA (2001) Amyotrophic lateral sclerosis. N Engl J Med 344(22):1688–1700 [PubMed: 11386269]

Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L et al. (1995) A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 268(5218):1749–1753 [PubMed: 7792600]

Sawant N, Morton H, Kshirsagar S, Reddy AP, Reddy PH (2021) Mitochondrial abnormalities and synaptic damage in Huntington's disease: a focus on defective Mitophagy and mitochondria-targeted therapeutics. Mol Neurobiol 58(12):6350–6377 [PubMed: 34519969]

Sbodio JI, Snyder SH, Paul BD (2016) Transcriptional control of amino acid homeostasis is disrupted in Huntington's disease. Proc Natl Acad Sci USA 113(31):8843–8848 [PubMed: 27436896]

Sbodio JI, Snyder SH, Paul BD (2018) Golgi stress response reprograms cysteine metabolism to confer cytoprotection in Huntington's disease. Proc Natl Acad Sci USA 115(4):780–785 [PubMed: 29317536]

Sbodio JI, Snyder SH, Paul BD (2019) Redox mechanisms in neurodegeneration: from disease outcomes to therapeutic opportunities. Antioxid Redox Signal 30(11):1450–1499 [PubMed: 29634350]

Schwarz G (2016) Molybdenum cofactor and human disease. Curr Opin Chem Biol 31:179–187 [PubMed: 27055119]

Scott SSO, Pedroso JL, Barsottini OGP, Franca-Junior MC, Braga-Neto P (2020) Natural history and epidemiology of the spinocerebellar ataxias: insights from the first description to nowadays. J Neurol Sci 417:117082 [PubMed: 32791425]

Scrivner O, Kumar MR, Sorokolet K, Wong A, Kebaara B, Farmer PJ (2021) Characterization of endogenous and extruded H(2)S and small oxoacids of sulfur (SOS) in cell cultures. ACS Chem Biol 16(8):1413–1424 [PubMed: 34374506]

Sen N, Paul BD, Gadalla MM, Mustafa AK, Sen T, Xu R et al. (2012) Hydrogen sulfide-linked sulfhydration of NF-kappaB mediates its antiapoptotic actions. Mol Cell 45(1):13–24 [PubMed: 22244329]

Sestito S, Daniele S, Pietrobono D, Citi V, Bellusci L, Chiellini G et al. (2019) Memantine prodrug as a new agent for Alzheimer's disease. Sci Rep 9(1):4612 [PubMed: 30874573]

Shatalin K, Shatalina E, Mironov A, Nudler E (2011) H2S: a universal defense against antibiotics in bacteria. Science 334(6058):986–990 [PubMed: 22096201]

Shen X, Peter EA, Bir S, Wang R, Kevil CG (2012) Analytical measurement of discrete hydrogen sulfide pools in biological specimens. Free Radic Biol Med 52(11–12):2276–2283 [PubMed: 22561703]

Sulfatonic®

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Shen X, Carlstrom M, Borniquel S, Jadert C, Kevil CG, Lundberg JO (2013) Microbial regulation of host hydrogen sulfide bioavailability and metabolism. Free Radic Biol Med 60:195–200 [PubMed: 23466556]

Shibuya N, Tanaka M, Yoshida M, Ogasawara Y, Togawa T, Ishii K et al. (2009) 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. Antioxid Redox Signal 11(4):703–714 [PubMed: 18855522]

Singh SB, Lin HC (2015) Hydrogen sulfide in physiology and diseases of the digestive tract. Microorganisms 3(4):866–889 [PubMed: 27682122]

Snijder PM, Baratashvili M, Grzeschik NA, Leuvenink HGD, Kuijpers L, Huitema S et al. (2016) Overexpression of cystathionine gamma-Lyase suppresses detrimental effects of spinocerebellar ataxia type 3. Mol Med 21(1):758–768 [PubMed: 26467707]

Spalloni A, Greco V, Ciriminna G, Corasolla Carregari V, Marini F, Pieroni L et al. (2019) Impact of pharmacological inhibition of hydrogen Sulphide production in the SOD1G93A-ALS mouse model. Int J Mol Sci 20(10)

Spencer JP, Jenner P, Daniel SE, Lees AJ, Marsden DC, Halliwell B (1998) Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. J Neurochem 71(5):2112–2122 [PubMed: 9798937]

Stipanuk MH (2020) Metabolism of sulfur-containing amino acids: how the body copes with excess methionine, cysteine, and sulfide. J Nutr 150(Suppl 1):2494S–2505S [PubMed: 33000151]

Stipanuk MH, Beck PW (1982) Characterization of the enzymic capacity for cysteine desulphhydration in liver and kidney of the rat. Biochem J 206(2):267–277 [PubMed: 7150244]

Sultana J, Ragagnin AMG, Parakh S, Saravanabavan S, Soo KY, Vidal M et al. (2024) C9orf72-associated dipeptide repeat expansions perturb ER-Golgi vesicular trafficking, inducing Golgi fragmentation and ER stress, in ALS/FTD. Mol Neurobiol 61(12):10318–10338 [PubMed: 38722513]

Sun M, Latourelle JC, Wooten GF, Lew MF, Klein C, Shill HA et al. (2006) Influence of heterozygosity for parkin mutation on onset age in familial Parkinson disease: the GenePD study. Arch Neurol 63(6):826–832 [PubMed: 16769863]

Sun Y, Lu F, Yu X, Wang B, Chen J, Lu F et al. (2020) Exogenous H(2)S promoted USP8 Sulfhydration to regulate Mitophagy in the hearts of db/db mice. Aging Dis 11(2):269–285 [PubMed: 32257541]

Sun Y, Li D, Su Y, Zhao H, Pang W, Zhao W et al. (2023) Protective effect of hydrogen sulfide is mediated by negative regulation of epigenetic histone acetylation in Parkinson's disease. Arch Med Sci 19(4):1124–1135 [PubMed: 37560727]

Szabo C (2020) The re-emerging pathophysiological role of the cystathionine-beta-synthase – hydrogen sulfide system in Down syndrome. FEBS J 287(15):3150–3160 [PubMed: 31955501]

Szabo C, Ransy C, Modis K, Andriamihaja M, Murghes B, Coletta C et al. (2014) Regulation of mitochondrial bioenergetic function by hydrogen sulfide. Part I. Biochemical and physiological mechanisms. Br J Pharmacol 171(8):2099–2122 [PubMed: 23991830]

Tang G, Wu L, Liang W, Wang R (2005) Direct stimulation of K(ATP) channels by exogenous and endogenous hydrogen sulfide in vascular smooth muscle cells. Mol Pharmacol 68(6): 1757–1764 [PubMed: 16150926]

Tang G, Yang G, Jiang B, Ju Y, Wu L, Wang R (2013) H(2)S is an endothelium-derived hyperpolarizing factor. Antioxid Redox Signal 19(14):1634–1646 [PubMed: 23418650]

The Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72(6):971–983 [PubMed: 8458085]

Tiranti V, D'Adamo P, Briem E, Ferrari G, Mineri R, Lamantea E et al. (2004) Ethylmalonic encephalopathy is caused by mutations in ETHE1, a gene encoding a mitochondrial matrix protein. Am J Hum Genet 74(2):239–252 [PubMed: 14732903]

Tripathi SJ, Chakraborty S, Miller E, Pieper AA, Paul BD (2023) Hydrogen sulfide signalling in neurodegenerative diseases. Br J Pharmacol. 10.1111/bph.16170

Vandiver MS, Paul BD, Xu R, Karuppagounder S, Rao F, Snowman AM et al. (2013) Sulfhydration mediates neuroprotective actions of parkin. Nat Commun 4:1626 [PubMed: 23535647]

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Villarejo M, Westley J (1963) Rhodanese-catalyzed reduction of thiosulfate by reduced lipoic acid. J Biol Chem 238:1185–1186 [PubMed: 13997286]

Wang R (2009) Hydrogen sulfide: a new EDRF. Kidney Int 76(7):700–704 [PubMed: 19536086]

Wang Y, Clark LN, Louis ED, Mejia-Santana H, Harris J, Cote LJ et al. (2008) Risk of Parkinson disease in carriers of parkin mutations: estimation using the kin-cohort method. Arch Neurol 65(4):467–474 [PubMed: 18413468]

Warenycia MW, Goodwin LR, Benishin CG, Reiffenstein RJ, Francom DM, Taylor JD et al. (1989) Acute hydrogen sulfide poisoning. Demonstration of selective uptake of sulfide by the brainstem by measurement of brain sulfide levels. Biochem Pharmacol 38(6):973–981 [PubMed: 2930598]

Wiatr K, Marczak L, Perot JB, Brouillet E, Flament J, Figiel M (2021) Broad influence of mutant Ataxin-3 on the proteome of the adult brain, young neurons, and axons reveals central molecular processes and biomarkers in SCA3/MJD using Knock-in mouse model. Front Mol Neurosci 14: 658339 [PubMed: 34220448]

Wright DJ, Renoir T, Smith ZM, Frazier AE, Francis PS, Thorburn DR et al. (2015) N-Acetylcysteine improves mitochondrial function and ameliorates behavioral deficits in the R6/1 mouse model of Huntington's disease. Transl Psychiatry 5:e492 [PubMed: 25562842]

Wright DJ, Gray LJ, Finkelstein DI, Crouch PJ, Pow D, Pang TY et al. (2016) N-acetylcysteine modulates glutamatergic dysfunction and depressive behavior in Huntington's disease. Hum Mol Genet 25(14):2923–2933 [PubMed: 27179791]

Wright GEB, Collins JA, Kay C, McDonald C, Dolzhenko E, Xia Q et al. (2019) Length of uninterrupted CAG, independent of Polyglutamine size, results in increased somatic instability, hastening onset of Huntington disease. Am J Hum Genet 104(6):1116–1126 [PubMed: 31104771]

Xie L, Hu LF, Teo XQ, Tiong CX, Tazzari V, Sparatore A et al. (2013) Therapeutic effect of hydrogen sulfide-releasing L-Dopa derivative ACS84 on 6-OHDA-induced Parkinson's disease rat model. PLoS One 8(4):e60200 [PubMed: 23573240]

Xu S, Shieh M, Paul BD, Xian M (2023) Hydrogen sulfide: recent development of its dual donors and hybrid drugs. Br J Pharmacol. 10.1111/bph.16211

Yagensky O, Kohansal-Nodehi M, Gunaseelan S, Rabe T, Zafar S, Zerr I et al. (2019) Increased expression of heme-binding protein 1 early in Alzheimer's disease is linked to neurotoxicity. elife 8:8

Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K et al. (2008) H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science 322(5901):587–590 [PubMed: 18948540]

Yang J, Minkler P, Grove D, Wang R, Willard B, Dweik R et al. (2019) Non-enzymatic hydrogen sulfide production from cysteine in blood is catalyzed by iron and vitamin B(6). Commun Biol 2:194 [PubMed: 31123718]

Yin WL, Yin WG, Huang BS, Wu LX (2017) Neuroprotective effects of lentivirus-mediated cystathionine-beta-synthase overexpression against 6-OHDA-induced parkinson's disease rats. Neurosci Lett 657:45–52 [PubMed: 28764908]

Yu YC, Kuo CL, Cheng WL, Liu CS, Hsieh M (2009) Decreased antioxidant enzyme activity and increased mitochondrial DNA damage in cellular models of Machado-Joseph disease. J Neurosci Res 87(8):1884–1891 [PubMed: 19185026]

Zafeiriou DI, Augoustides-Savvopoulou P, Haas D, Smet J, Triantafyllou P, Vargiami E et al. (2007) Ethylmalonic encephalopathy: clinical and biochemical observations. Neuropediatrics 38(2): 78–82 [PubMed: 17712735]

Zeng L, Zhang D, McLoughlin HS, Zalon AJ, Aravind L, Paulson HL (2018) Loss of the spinocerebellar ataxia type 3 disease protein ATXN3 alters transcription of multiple signal transduction pathways. PLoS One 13(9):e0204438 [PubMed: 30231063]

Zhang K, Donnelly CJ, Haeusler AR, Grima JC, Machamer JB, Steinwald P et al. (2015) The C9orf72 repeat expansion disrupts nucleocytoplasmic transport. Nature 525(7567):56–61 [PubMed: 26308891]

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Zhang L, Wei K, Xu J, Yang D, Zhang C, Wang Z et al. (2016) Belamcanda chinensis (L.) DC-An ethnopharmacological, phytochemical and pharmacological review. J Ethnopharmacol 186:1–13 [PubMed: 27032710]

Zhao W, Zhang J, Lu Y, Wang R (2001) The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. EMBO J 20(21):6008–6016 [PubMed: 11689441]

Ziosi M, Di Meo I, Kleiner G, Gao XH, Barca E, Sanchez-Quintero MJ et al. (2017) Coenzyme Q deficiency causes impairment of the sulfide oxidation pathway. EMBO Mol Med 9(1):96–111 [PubMed: 27856618]

Zivanovic J, Kouroussis E, Kohl JB, Adhikari B, Bursac B, Schott-Roux S et al. (2019) Selective Persulfide detection reveals evolutionarily conserved antiaging effects of S-Sulfhydration. Cell Metab 30(6):1152–70 e13 [PubMed: 31735592]

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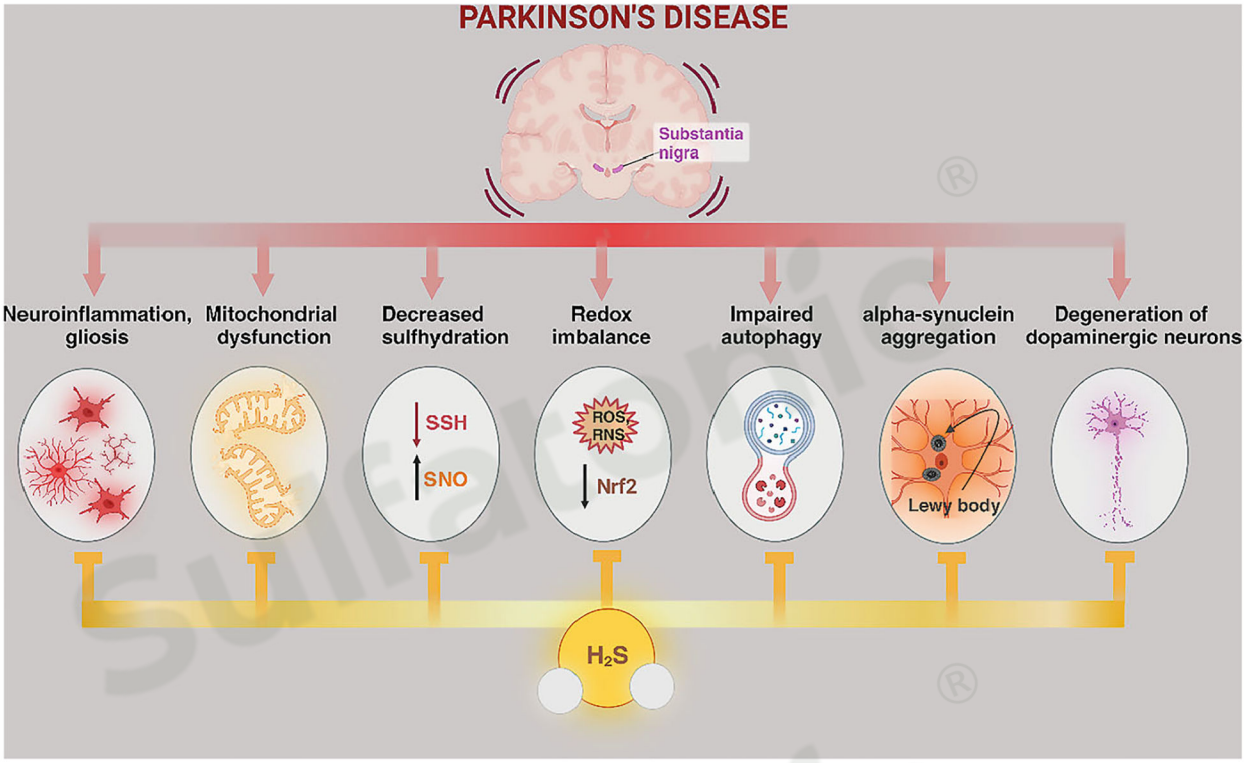


Fig. 1.

Neuroprotective effects of H_2S homeostasis in Parkins on's disease. Parkinson's disease profoundly affects the substantia nigra of the brain and is disrupts several brain functions. The brains of PD patients exhibit heightened neuroinflammation, mitochondrial dysfunction, redox imbalance with impaired antioxidant stress responses involving the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling cascade, leading to elevated reactive oxygen species (ROS) and reactive nitrogen species (RNS) accumulation. Abnormal gasotransmitter signaling involving H_2S and nitric oxide (NO) is also observed accompanied by reduced sulfhydration and increased nitrosylation of cysteine residues. Degeneration of dopaminergic neurons follows leading to abnormal dopaminergic neurotransmission. All these abnormalities are prevented by administration of H 2S donors

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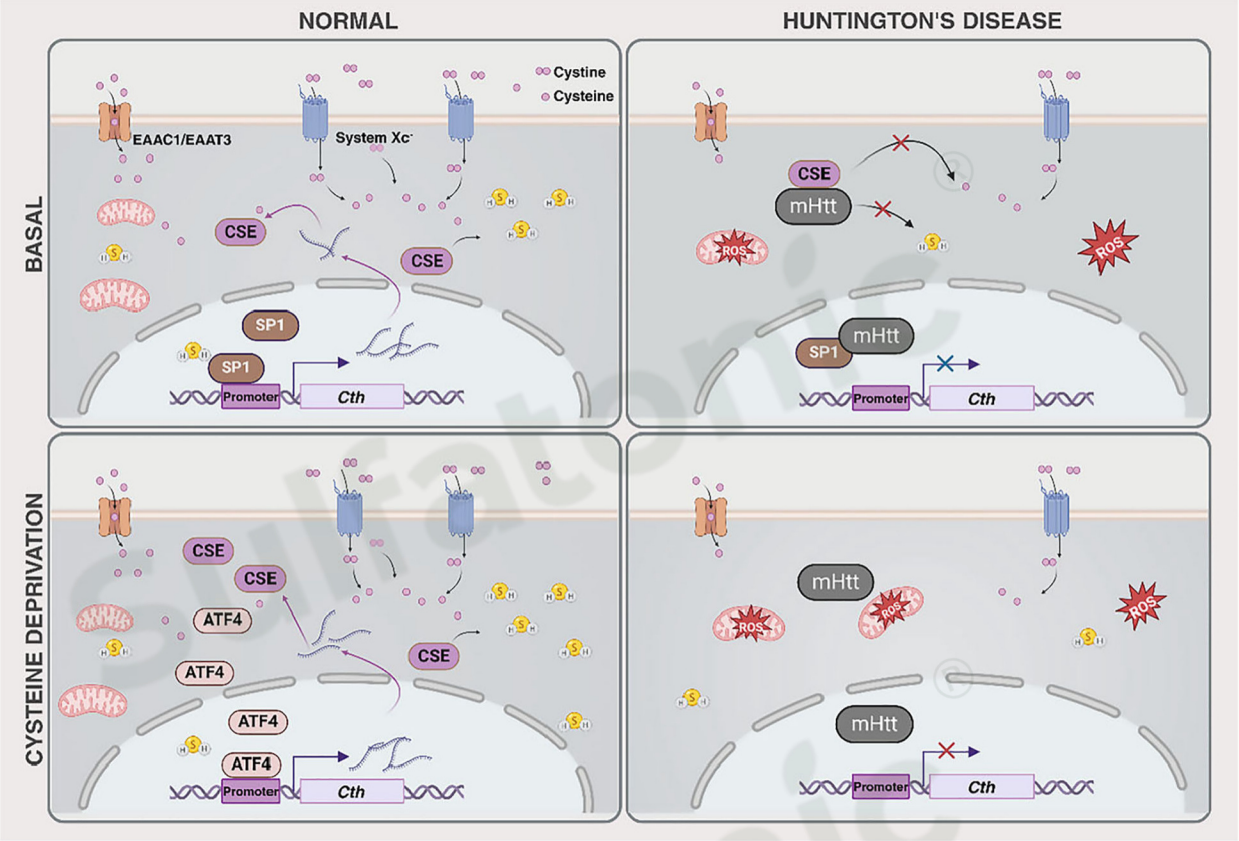


Fig. 2.

Disrupted cysteine and H_2S homeostasis in Huntington's disease. In normal cells under basal conditions, transcription of CSE is regulated by specificity protein 1 (SP1). CSE produces both cysteine and hydrogen sulfide (H_2S) which modulate redox balance and multiple signaling pathways. Cysteine is also imported through the excitatory amino acid transporter 3 (EAAT3/EAAC1). The oxidized form of cysteine, cystine, is taken up by the system Xc^- transporter. The cystine imported is reduced to cysteine in the reducing atmosphere of the cell. In HD cells, SP1 is sequestered by mutant huntingtin (mHtt), which prevents transcription and expression of CSE. The activities of the EAAC1 and system Xc^- transporters are also decreased in HD, leading to reduced uptake of this amino acid. Furthermore, mHtt binds to CSE and inhibits its catalytic activity, leading to an overall cysteine deficit and attendant oxidative stress though increased accumulation of reactive oxygen species (ROS) in the mitochondria and cytosol. During conditions of cysteine scarcity, in normal cells, activating transcription factor 4 (ATF4) is induced, which regulates expression of CSE to augment cysteine and H_2S production. These processes are compromised in HD, further elevating oxidative stress

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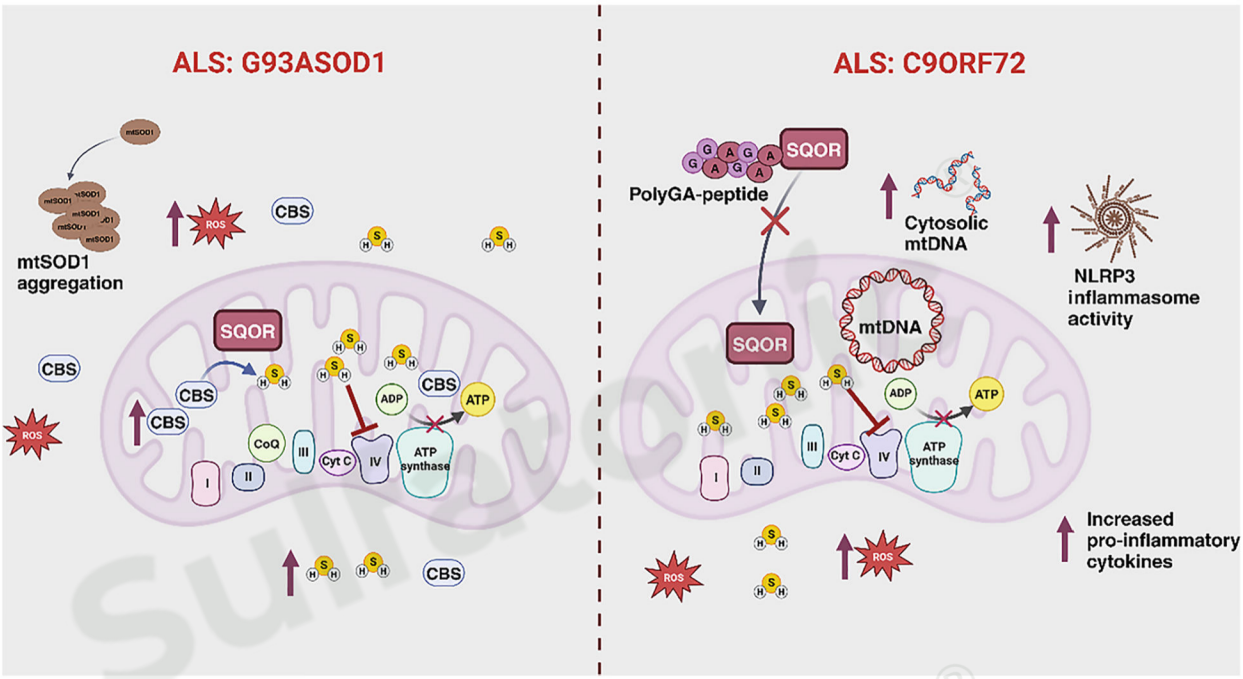


Fig. 3.

H_2S homeostasis in amyotrophic lateral sclerosis. In ALS caused by the G93ASOD1 mutation, mtSOD1 aggregates and causes elevated oxidative stress due to increased CBS activity that elevates H_2S, in turn dangerously inhibiting complex IV of the mitochondrial electron transport chain. In ALS caused by an expansion of hexanucleotide repeats in the *C9ORF72* locus, production of dipeptide repeats such as polyGA peptide increases levels of reactive oxygen species (ROS), activates the NLRP3 inflammasome, and increases levels of proinflammatory cytokines. Additionally, the polyGA aggregates also bind sulfide-quinone oxidoreductase (SQOR) and inhibit its activity, leading to further increase in H_2S levels

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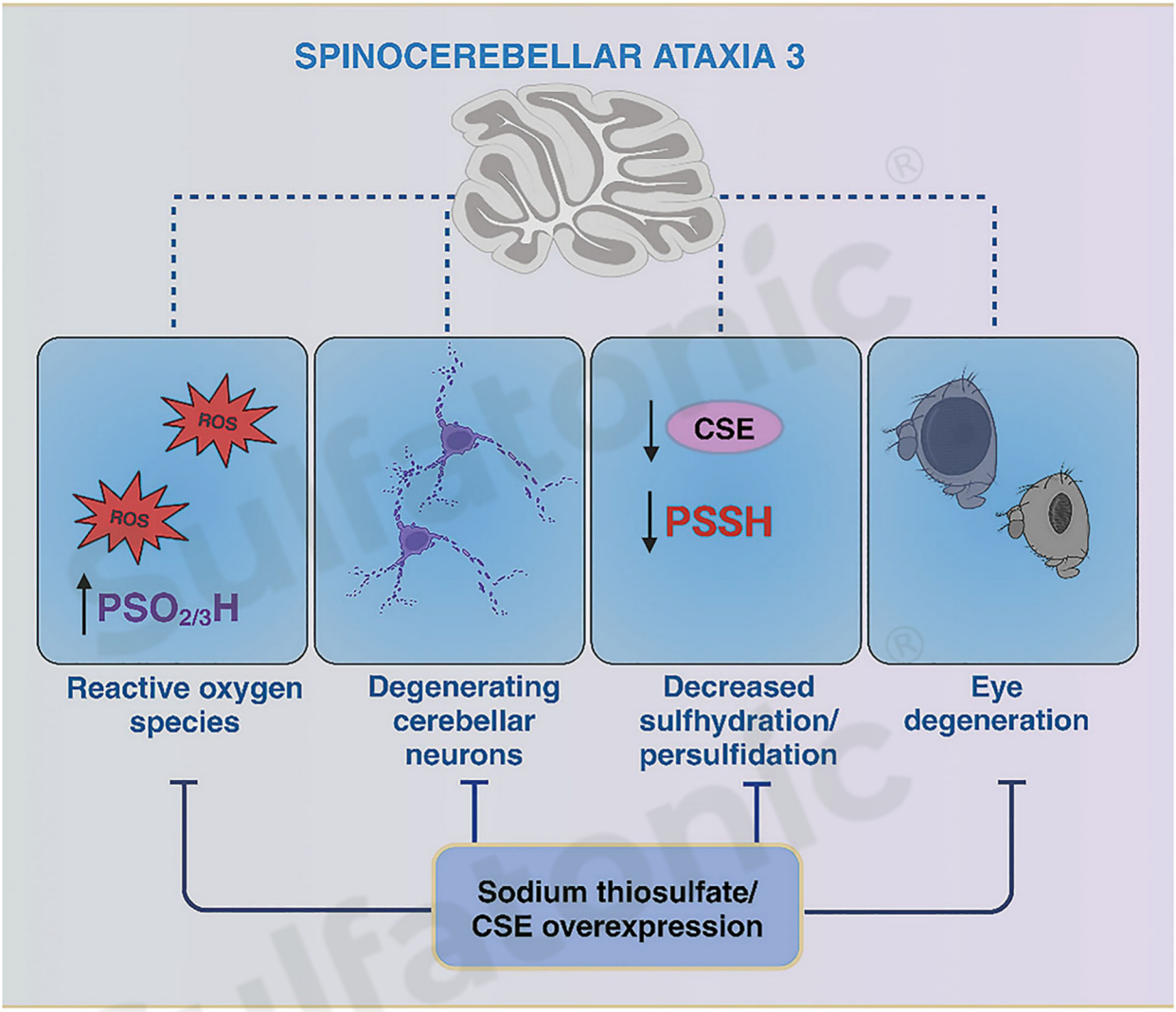


Fig. 4.

Dysregulated H_2S signaling in spinocerebellar ataxia 3. Depletion of CSE was observed in both human SCA3 and a *Drosophila* model expressing mutant ataxin 3, leading to elevated ROS levels and protein oxidation accompanied by decreased sulfhydration and degeneration of cerebellar neurons. In *Drosophila*, degeneration of the eye was observed. All these abnormalities were ameliorated either by overexpression of CSE or by administering the slow release H_2S donor, sodium thiosulfate (STS)

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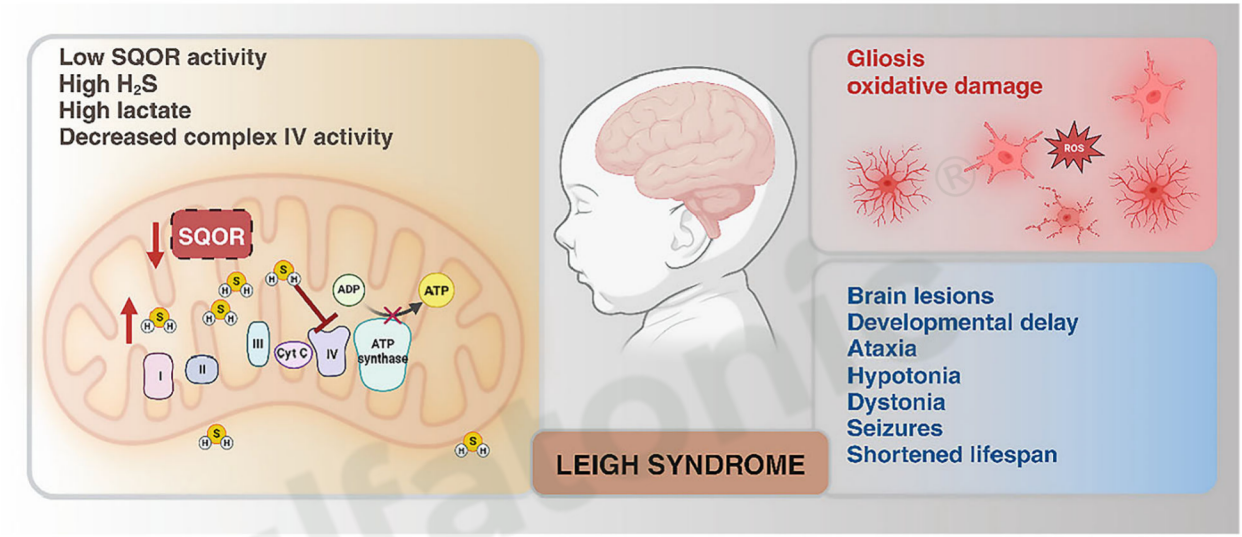


Fig. 5.

Elevated H_2S production in Leigh syndrome. Leigh's disease is an infantile mitochondrial disease caused by mutations in genes involved in mitochondrial function. The disease is characterized by brain lesions, developmental delay, ataxia, hypotonia, dystonia, seizures, and shortened lifespan. Gliosis, oxidative damage, lactate accumulation, and neuroinflammation are pathological hallmarks. Cases with loss-of-function mutations in sulfide quinone oxidoreductase (SQOR) are associated with the complications of decreased catabolism, accumulation of H_2S, decreased complex IV activity, and reduced ATP production

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Table 1

Therapeutic effects of H_2S donors on Parkinson's disease

PD model	Intervention	Physiological efficacy	References
6-Hydroxydopamine (6-OHDA), rats	NaHS in conjunction with the HDAC inhibitor TSA	NaHS decreased neuronal cell death, increased dopamine (DA), tyrosine hydroxylase (TH), and DOPAC levels, decreased glial fibrillary acidic protein (GFAP), neuroinflammatory cytokines, and HDAC activity	Sun et al. (2023)
6-OHDA, rats	NaHS (30 or 100 μmol/kg/d, i.p).	Decreased activity of caspase-3 and expression of Bax, prevented the decrease of Bcl-2 in substantia nigra, promoted autophagy, and prevented the downregulation of leptin	Jiang et al. (2022)
6-OHDA, rats	NaHS (1.68 or 5.6 mg kg^{-1}) for 3 weeks	Prevented dopaminergic neuronal loss in the substantia nigra and striatum, decreased malondialdehyde (MDA) and NADPH oxidase levels and ATP depletion in striatum.	Hu et al. (2010)
6-OHDA, rats	Overexpression of CBS	Increased H_2S production in the substantia nigra, decreased loss of the nigral DA neurons, inhibited 6-OHDA-induced oxidative stress injury, and downregulated the expression of α-synuclein	Yin et al. (2017)
Rotenone, rats	Entinostat (20 mg/kg), i.p.	Administration of entinostat (20 mg/kg) intraperitoneally restored H_2S levels, DA, DOPAC, and TH levels	Li et al. (2024)
Rotenone, rats	NaHS (1.68 mg kg^{-1}) for 3 day before and 4 weeks after rotenone	Ameliorated motor deficits, prevented microglial activation in the SN, and accumulation of pro-inflammatory factors (TNF-α and nitric oxide) in the striatum via NF-κB pathway	Hu et al. (2010)
Rotenone, rats	NaHS (30–100 μmol/kg/day for 7d pre- and post-rotenone injection)	Ameliorated depression, enhanced expression of synaptic plasticity proteins in the hippocampus, and preserved the ultrastructure of synapses	Liu et al. (2024)
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Inhalation of H_2S at 40 ppm for 8 h/day for a week	Inhibition of MPTP-induced loss of dopaminergic neurons, neuroinflammation in substantia nigra and striatum, and upregulation of Nrf2 signaling	Kida et al. (2011)
MPTP, mice	Air mixed with 80 ppm H_2S for 4 h/day for 5 day	Prevented motor deficits, anxiety, and degeneration of TH neurons in the nigrostriatal region	Nagashima et al. (2023)

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