REVIEW

Therapeutic importance of hydrogen sulfide in age-associated neurodegenerative diseases

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Abstract
Hydrogen sulfide (H_2S) is a gasotransmitter that acts as an antioxidant and exhibits a wide variety of cytoprotective and physiological functions in age-associated diseases. One of the major causes of age-related diseases is oxidative stress. In recent years, the importance of H_2S has become clear, although its antioxidant function has not yet been fully explored. The enzymes cystathionine β-synthase, cystathionine γ-lya-se, and 3-mercaptopyruvate sulfurtransferase are involved in the enzymatic production of H_2S. Previously, H_2S was considered a neuromodulator, given its role in long-term hippocampal potentiation, but it is now also recognized as an antioxidant in age-related neurodegeneration. Due to aerobic metabolism, the central nervous system is vulnerable to oxidative stress in brain aging, resulting in age-associated degenerative diseases. H_2S exerts its antioxidant effect by limiting free radical reactions through the activation of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, which protect against the effects of aging by regulating apoptosis-related genes, including p53, Bax, and Bcl-2. This review explores the implications and mechanisms of H_2S as an antioxidant in age-associated neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Down syndrome.

Key Words: *3-mercaptopyruvate sulfurtransferase; aging; antioxidant; cystathionine β-synthase; cystathionine γ-lyase; glutathione; hydrogen sulfide; neurodegenerative disease; oxidative stress; reactive oxygen species*

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Introduction
Hydrogen sulfide (H_2S) has organic outcomes in living organisms, especially with respect to cell signaling and post-transcriptional modifications. H_2S is the third gasotransmitter identified in mammalian cells (Gemici et al., 2015). H_2S has been recently shown to be produced by a number of tissues where it exerts biochemical and physiological effects (Rose et al., 2017). As an endogenous signaling molecule, H_2S has significant effects on the nervous system. Substantial evidence also exists that H_2S inhibits free radical reactions in aging and age-associated neurodegenerative diseases.

Cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate (3MST) are important for H_2S production (Xie et al., 2016). The expression of H_2S is catalyzed by these enzymes. Parkinson's disease (PD) is expressed in the murine brain and kidney, CSE in the liver and peripheral tissue, and 3MST in the brain, liver, kidney, and aorta (Kabil and Banerjee, 2014). The proper contribution of 3MST compared with CBS and CSE in the production of endogenous H_2S is currently under investigation (Singh and Banerjee, 2011). H_2S also acts as a modulator in age-associated neurodegenerative diseases of the CNS, including Alzheimer's disease (AD), PD, Huntington disease (HD), and Down's syndrome (DS). The thiol containing the toxic molecule homocysteine enhances the vulnerability of neural cells through excitotoxicity and an elevated level of plasma homocysteine (Cai et al., 2016). H_2S reduces the neurotoxicity of homocysteine by acting as a synaptic modulator (Seshadri et al., 2002). H_2S exerts its antioxidant function through superoxide super oxide dismutase (SOD), glutathione peroxidase (Gpx), and catalase (CAT) which combat free radicals (Dorrell et al., 2009). As H_2S is an antioxidant signaling molecule that interacts with other gasotransmitters, including nitric oxide (NO) and carbon monoxide, which increase or decrease the action of H_2S. In this review, we describe the potential causes of oxidative stress and the antioxidant function of H_2S in age-associated neurodegenerative diseases.

Database Search Strategy
We searched NCBI, Google scholar, and Medline for literatures regarding oxidative stress, H_2S, aging, reactive oxygen species, antioxidant and therapeutic importance of H_2S in neurodegenerative diseases published from inception to March 1, 2019 (**Additional Table 1**).

Oxidative Stress and Aging
Aging is the common result of oxidative stress. Reactive oxygen species (ROS) accumulation by mitochondria is mostly found in aged tissue (Viña et al., 2013). High levels of 8-Oxo-2′-deoxyguanosine, which result in oxidative harm, are commonly found in mtDNA (Hipkiss, 2006). According to the free radical theory of aging, discovered by Harman

in 1954, aggregation of protein, lipid, and DNA molecules in mitochondria are responsible for cellular senescence (Miquel et al., 1980). Protein oxidation due to excessive oxidative stress is triggered by several signaling pathways, including transforming growth factor-β signaling, the DNA damage response, and mitogen activated protein kinase 2K3 (MAPK2K3) signaling, which is responsible for increased regulation of the cell cycle inhibitor, p53 (Muñoz-Espín and Serrano, 2014).

On the other hand, ongoing research has demonstrated that thiol and thiol-related enzymes, including Gpx, are linked with the progression of aging (Muñoz-Espín and Serrano, 2014). Gpx deficiency leads to increased levels of oxidative stress. Although the balance of ROS plays a vital role in enhancing or suppressing cellular fates such as proliferation and differentiation, the increased level of oxidative stress is considered a major mediator of aging (Ben-Porath and Weinberg, 2005). Moreover, protein aggregation has also been linked with aging. In particular, the aggregated protein, lipofuscin, is a hallmark of aging. Transitional metals bind lipofuscin to produce more ROS through the Fenton reaction (Ben-Porath and Weinberg, 2005). Under pathophysiological conditions, the aggregation of oxidized protein is irreversible. Proteins may appear as inclusion bodies, lysosomes, aggresomes, or plaques, and may affect normal cellular metabolism (Chin et al., 2008).

Taken together, these data suggest that oxidative stress is the root cause of aging that increases with age-related diseases. The contribution of ROS in protein oxidation is still unclear and will require further investigation.

Oxidative Stress and Mitochondrial Dysfunction in Neurodegeneration

Neurodegeneration is very common in elderly people. Oxidative stress is one of the major causes of these neurodegenerative diseases in aging (Ganguly et al., 2017). The molecular link between oxidative stress and neurodegeneration can vary disease to disease like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), and Down's syndrome (DS). For example, ROS-rseponsive transcription factors can alter the expression of genes encoding such toxic proteins or the enzymes involved in the synthesis, processing, and degradation of such proteins which causes mitochondrial dysfunctions (Ganguly et al., 2017). In some conditions, the mutant gene produces an abnormal product that is not readily cleared by the protein degradation machinery, leading to its accumulation, and a similar thing can happen if the protein is posttranscriptionally modified because of redox status and the activity of kinases (Ciechanover and Kwon, 2015). In AD pathology, oxidative damage results in deposition of Aβ protein which triggers the neurodegeneration process (Dinda et al., 2019). In addition to this, oxidative damage causes decreased synthesis of adenosine tri phosphate (ATP), leading to mitochondrial membrane depolarization. In particular, extensive studies have been conducted using transgenic AD models, postmortem AD brain, cultured cells and isolated mitochondria through multiple mechanisms (Onyango et al., 2016). In transgenic AD mice and postmortem AD brain, progressive deposition of Aβ occurs in brain mitochondria (Onyango et al., 2016). Moreover, human induced pluripotent stem cell (hiPSC) models of AD have been generated from patients with amyloid precursor proteins (APP) mutations, including an E693 deletion which showed oxidative stress (Ross and Akimov, 2014). Oxidative stress is also responsible for accumulation of phosphorylated tau proteins within the neurons which might result in translation of a specific mRNA (Oliver and Reddy, 2019). In AD, increased phosphorylation of tau protein is the result of increased activities of glycogen synthase kinase 3 beta (GSK3β) and cluster of differentiation (CDK5) (Mondragón-Rodríguez et al., 2013). Moreover, significant accumulation of transitional metals such as Fe, Cu, and Zn causes impaired antioxidant defense (Butterfield et al., 2013).

Oxidative stresses also have their detrimental effects on PD and HD. The most common mitochondrial proteins PINK1 and PARK2 show dysfunctional properties (Rocha et al., 2018). PINK1 is normally on the inner mitochondrial membrane, but it migrates to the outer membrane to phosphorylate proteins due to oxidative stress when there is a reduction in mitochondrial membrane (Bose and Beal, 2019). Parkin protein is involved in mitochondrial homeostasis and the loss of parkin protein causes the loss of quality control of mitochondria and degeneration of dopaminergic neurons in mid brain (Cartelli et al., 2018). Neurons derived from a hiPSC of patients who harbor the α-synuclein mutation show increased sensitivity to environmental toxins such as rotenone, paraquat which leads to the inhibition of the myocyte enhancer factor 2C-peroxisome proliferator activated receptor-γ coactivator-α (MEF2C-PGC1α), which in turn contributes to mitochondrial dysfunctions (Bose and Beal, 2019). HD is the autosomal-dominant neurodegenerative disorder that is caused by abnormal expansion of polyglutamine (CAG) repeats in the huntingtin (HTT) (An et al., 2012). HD is considered as an ideal disorder model for exploring the effectiveness of iPSCs, because it is induced by a single gene, and there is a strong correlation between the length of the CAG repeat expansion and the onset of age disease (Cao et al., 2015). Cao et al. (2015) reported on the successful correction of the CAG repeat-expanded HTT allele in HD patient iPSCs. When evaluated with a series of experiments, HD consortium revealed that cells carrying the longer repeats were more vulnerable to cellular stresses and brain-derived neurotrophic factor deprivation, demonstrating the correlation of CAG repeat lengths with disease onset.

DS represents one of the best documented cases of a human disorder related to the redox imbalance that has been attributed by Cu, Zn-SOD1 and encoded by trisomic chromosome 21 (Rodríguez-Sureda et al., 2015). As an essential link to oxidative stress, mitochondrial dysfunctions are observed whenever redox imbalances occur. Bambrick and Fiskum (2008) reported a defective repair of oxidative damage to mitochondrial DNA (mtDNA) in fibroblasts from DS patients, while Schuchmann and Heinemann found

mitochondria-associated anomalies in neurons from Ts16 mice. Superoxide formation was significantly increased in Ts16 neurons compared with control neurons (Schuchmann and Heinemann, 2000). A selective decrease in respiration was detected with the Complex I substrates malate and glutamate but not with the Complex II substrate succinate in isolated cortex mitochondria from Ts16 mice (Bambrick and Fiskum, 2008). Under oxidative stress condition, some markers like AGEs, dityrosine, and H_2S are found at increased levels in DS patients which are responsible for aging and neurodegeneration (Perluigi and Butterfield, 2012).

In a nutshell, oxidative stress has a progressive role in age-associated neurodegenerative diseases. H_2S might act as a therapeutic target for these neurodegenerative diseases from different perspectives.

Role of H_2S in the Regulation of Aging

H_2S plays various physiological roles in the human body by preventing oxidative damage or deterioration. Most age-associated diseases are a result of oxidative stress, whereas antioxidants increase longevity. Oxidative stress derivatives appear as ROS and RNS, such as super oxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and NO (Zhu et al., 2007; Tyagi et al., 2009). H_2S has been shown to exhibit protective effects on mouse endothelial cells (bEnd3) against methionine-induced oxidative stress. According to the free radical theory, SOD converts $O_2^{\bullet-}$ to H_2O_2, which is then converted into H_2O and O_2 by CAT (Kimura et al., 2010). In the presence of reduced GSH, low concentration of H_2S broadly inhibits cellular damage by the reactive nitrogen species (RNS) derivative $ONOO^-$ (Viña et al., 2013). H_2S also inhibits toxicity in human neuroblastoma SH-SY5Y cells through inhibition of $ONOO^-$ (Viña et al., 2013).

The interrelationship between H_2S and aging is based on several factors, including genomic instability (Attene-Ramos et al., 2006). Genomic integrity and stability is affected by exogenous and endogenous treats where most damage occurs in the nuclear genome (López-Otín et al., 2013). Nuclear DNA damage are one of the causes of neurodegeneration, whereas H_2S attenuates DNA damage (López-Otín et al., 2013). In contrast to the nuclear genome, protection of mitochondrial DNA is not efficient and is heavily dependent on the machinery of nuclear DNA repair (Perridon et al., 2016). Mitochondrial DNA is more vulnerable to mutations due to the oxidative stress and the lack of protective histones on mitochondrial DNA (Perridon et al., 2016). Therefore, aging-associated mutations and deletions in the mitochondrial genome may also contribute to the aging process (Perridon et al., 2016). For instance, DNA is damaged by the treatment of fibroblasts with the H_2S donor, NaHS, resulting in apoptotic cell death in a Bax and cytochrome C-dependent manner (Kimura et al., 2010). Telomerase, a specialized DNA polymerase, is required to elongate telomers as the replicative DNA polymerase lacks his capacity (Hewitt et al., 2012). Dysfunctional telomeres are highly efficient in inducing apoptosis during aging (Hewitt et al., 2012). In addition to this, epigenetic alterations such as posttranslation of histones, alterations in DNA methylation pattern and chromatin remodeling, can regulate the accessibility of DNA and underlie the differential gene transcription observed between cell types during aging (López-Otín et al., 2013). S-sulfhydration, as well as extracellular regulated kinase (ERK1/2), prevents DNA damage. H_2S can activate poly ADP-ribose polymerase (PARP-1) and inhibit DNA damage in endothelial cells. PARP activation is mediated by the MEK/ERK pathway (Hancock and Whiteman, 2014). S-sulfhydrated MEK1 at cys341 induces ERK1/2 phosphorylation in the nucleus, which activates PARP-1 (Hancock and Whiteman, 2014). On the other hand, mutation of cys341 prevents the activation of PARP-1 (Zhao et al., 2014).

Experimental studies have reported that H_2S provides protection when chronic restraint stress-exposed rats are treated with NaHS. In particular, H_2S increased SOD activity and the level of GSH at an NaHS concentration of 30 or 100 μmol/kg, indicating the role of H_2S in oxidative stress (Li et al., 2017). Kimura (2014) also reported that the concentration of intracellular cysteine in the presence of H_2S exhibits an anti-aging function by inhibiting SIRT1, whereas SIRT1 has been identified in yeast as an NAD^+-dependent histone deacetylase, which increases DNA stability. SIRT1 deficiency has been shown to hamper cognitive abilities and the anti-aging role of SIRT1 is associated with the drug resveratrol (**Figure 1B**; Li et al., 2017).

Enzymatic Contribution to the Biosynthesis of H_2S

The biosynthesis of H_2S is mediated by three enzymes: CSE, CBS, and 3MST. Cystathionine is the metabolite formed by CBS via the condensation of homocysteine (Kimura, 2015), while CSE converts L-cysteine and α-ketoglutarate (α-KG). H_2S is produced by the generation of pyruvate, ammonia, and L-cysteine. 3MST generates H_2S through the formation of pyruvate from 3-mercaptopyruvate (3MP), which undergoes cysteine and α-KG metabolism associated with cysteine amino transferase (**Figure 1A**).

Contribution of CBS

CBS has traditionally been introduced as the initial enzyme in the transsulfuration pathway (Régnier et al., 2012). As the physiological function of CBS is to eliminate homocysteine, CBS deficiency results in homocystinuria, which is characteristic of many metabolic diseases (Yamanishi et al., 2006). The catalytic function of CBS is mediated by 63-kDa subunits, which bind to the co-factor, heme, and pyridoxal 5′ phosphate (PLP). CBS individually binds to two substrates (homocysteine and serine) whose activity is mediated by S-adenosyl-L-methionine (SAM) (Mikami et al., 2013). Moreover, CBS can produce H_2S by three distinct pathways: (1) Converting cysteine and H_2O to form serine and H_2S; (2) condensation of cysteine and homocysteine to generate cystathionine and H_2S; and (3) condensation of two cysteine molecules to form lanthionine and H_2S (Singh and Banerjee, 2011). Under physiological conditions, CBS is cytosolic and

H_2S acts as a neurotransmitter under high expression of CBS (Kabil et al., 2014b). CBS has also been shown to translocate to the nucleus and mitochondria (Teng et al., 2013).

Contribution of CSE

CSE mediates H_2S synthesis in smooth muscle cells through a PLP-dependent α, β-elimination reaction combined with cysteine. A high level of potentiation is observed during H_2S synthesis by CSE, particularly in the presence of PLP, while suppression is observed at 300 nM Ca^{2+}. This indicates that when H_2S is generated by CSE in cells, the Ca^{2+} concentration is increased (Mikami et al., 2013). The binding site of CSE indicates the expression of CSE and explains the antiapoptotic function of H_2S (Sen et al., 2012) produced by CSE, which makes an addition to the cysteine residues of nuclear factor kappa-B (NF-κB), activating antiapoptotic genes (Sen et al., 2012). Moreover, in western blot analysis, CSE has been detected as an H_2S generator in the brain. Additionally, in a mouse model of HD, the level of CSE expression is low.

Contribution of 3MST and CAT

3MST and CAT also take part in H_2S synthesis in brain tissue (Gadalla and Snyder, 2010), which is recognized as the third source of H_2S production. 3MST also acts as alternative source to CBS for the synthesis of H_2S (Shibuya et al., 2009). 3MP is a substrate of 3MST and is produced through cysteine metabolism and α-KG by CAT. 3MST and CAT localize to the mitochondria and synaptosomes, where the molecular weight of α-KG is 3 kDa (Shibuya et al., 2009). 3MST is found in cerebral Purkinje cells, mitral cells, hippocampal pyramidal neurons, and astrocytes (Shibuya et al., 2009). For H_2S synthesis through the 3MST/CAT pathway, the mitochondrial cysteine concentration should be approximately 1 mM.

Under physiological conditions, CBS, CSE, and 3MST all play a vital role in H_2S synthesis and facilitate the protective function of H_2S in the CNS during aging and disease conditions.

Therapeutic Target and Cell Signaling of H_2S

In several cell types, including human inducible pluripotent stem cell (hiPSC)-derived neurons, sulfide molecule inhibits mitochondrial complex IV and induces apoptosis (Jiang et al., 2016). At 3–30 fold higher concentrations, sulfide becomes toxic by binding to and inhibiting cytochrome C oxidase in complex IV of the electron transport chain (Jiang et al., 2016). On the other hand, sulfide at low concentrations (0.01 to 1 μM) donates electrons to complex II of the mitochondrial electron transport chain which stimulates ATP production (Kabil et al., 2014a). In addition to this, the electrophysiological characteristics of H9 embryonic stem cells (hESCs) are affected by H_2S. At different concentrations, NaHS shows consistently altered hyper polarization (Wei et al., 2012). H_2S might be a therapeutic target for neurodegenerative diseases in hiPSC-derived cortical neurons.

S-sulfhydration is a common process of cellular proteins initiated by H_2S. With this process, H_2S maintains the altered regulation of cellular proteins and enzymes (Gadalla and Snyder, 2010). During S-sulfhydration, the –SSH group is synthesized by the association of thiol groups, where –SSH shows enhanced chemical reactivity (Li et al., 2011). Most importantly, S-sulfhydration of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) can determine cytokine-induced memory impairment in the brain under physiological conditions (Mir et al., 2014). A cysteine must be oxidized prior to modification with H_2S, as H_2S cannot directly react with reduced thiols (Paul and Snyder, 2015). Although the cytosol is a predominantly reducing environment, S-sulfhydration can occur under certain conditions when the generation of ROS occurs in response to physiological stimuli (Paul and Snyder, 2015). Du et al. (2014) observed that macrophage inflammation by oxidized lipoproteins via the sulfhydration of NF-κB p65 at cys38 controlled the phosphorylation of NF-κB p65 (Gade et al., 2013). Exogenous H_2S in microglial cells helps to increase Ca^{2+} influx through the plasma membrane (Abdulle et al., 2018). Elevated levels of Ca^{2+} are also necessary to activate microglial cells following lipopolysaccharide (LPS) challenge (Hoffmann et al., 2003), in which H_2S plays an active role. To increase GSH synthesis, H_2S also activates Cl- channels through K-ATP channels (Kabil et al., 2014a).

Antoxidative Regulatory Role of H_2S

H_2S exerts its antioxidant activity through the metabolism of GSH. Hamar et al. (2012) demonstrated that H_2S is a poor antioxidant compared with other antioxidative agents (Jain et al., 2014). H_2S increases the activity of cysteine and cysteine transporters to enhance the production of GSH. Additionally, oxidative stress is suppressed by H_2S when 3MST is combined with CAT (Kolluru et al., 2013). Cellular damage occurs in newborn rats as a result of GSH deficiency. In the absence of mitochondrial CAT, mitochondria depend on GSH for the removal of H_2O_2 (**Figure 2**; Meister, 1992). Moreover, in astrocytes, H_2S exerts its antioxidative effects against H_2O_2 by altering glutamate uptake. Several lines of evidence have shown that H_2S enhances the GSH biosynthetic enzyme, γ-glutamyl cysteine sulfurtransferase (Searcy et al., 1995). H_2S increases intracellular reduced glutathione (GSSH), where GSH is an important antioxidant and consists of glutamate, glycine, and cysteine. Among oxidized and reduced forms of cysteine, the reduced state is most prominent for GSH generation (Majid et al., 2013). When the ratio of GSH/GSSG decreases (**Figure 2**), oxidative stress increases and extracellular cysteine is reduced to produce GSH through the cysteine/glutamate antiport system (Kimura et al., 2010).

ROS are responsible for alterations of cellular diversity. SOD maintains various aspects of normal physiology by reducing oxidative stress. The initial function of SOD is to reduce $O_2^{\bullet-}$, although another oxidative agent, H_2O_2, is generated in the process. In particular, SOD does not interfere with the generation of H_2O_2; rather, it retards the adjustment of ROS. For instance, SOD connects with Rac1, which regulates an isoform of nitric oxide synthase (NOX) (Harraz et al., 2008). Following this, NOX produces $O_2^{\bullet-}$, indicating the position of SOD1 (**Figure 3**) (Nunomura et al., 2006).

By contrast, the antioxidant function of SOD2 facilitates the function of proteases and DNA repair enzymes (Nunomura et al., 2006).

Cellular components are damaged by oxidative enzymes ROS or RNS. When free radicals like H_2O_2, $O_2^{\bullet-}$ are produced by cellular metabolic activities and environmental factors, Gpx provides antioxidant function against oxidative stress. Gpx is an intracellular enzyme of mitochondria and cytosol. The reducing equivalents produced by GSH help Gpx reduce high levels of H_2O_2 (**Figure 3**). Moreover, the reducing capacity of Gpx is mediated by GR, which catalyzes the reaction to form GSSH. The production of H_2O_2 causes microglial GSSH to increase by 30% (Navarro-Yepes et al., 2014). Gpx also neutralizes lipid peroxides from lipid alcohol. GSSH can induce the formation of disulfide bonds during oxidative stress. During the catalytic reaction, GSH is recycled (Dringen et al., 2000). The level of GSH in neurons, which is measured using a cysteine precursor, is low compared with that in astroglial cells (Navarro-Yepes et al., 2014).

CAT is a tetrameric enzyme found in numerous tissues that converts H_2O_2 to water molecules. According to Michaelis-Menten steady-state kinetics, CAT has a rate of 50 U/mL, where 1 U oxidizes 1 μmol of H_2O_2 (Scaglione et al., 2016). Additionally, due to oxidative stress, reduced levels of Aβ have been shown in hAPP mice that overexpress mitochondrial CAT. Catalase decreases 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced ROS aggregation (Perier et al., 2010). CAT activity has been shown to increase with age as CAT inhibits the aggregation of 8-OHdG during aging (Perier et al., 2010). It triggers activation of glutathione S-transferases, which detoxifies endogenous electrophiles by binding GSH sites. To increase the catalytic function of above antioxidants, it will be necessary to increase binding site affinity, which would include the use of thiol substrates.

Contribution of H_2S in Neurodegenerative Diseases

As an endogenous gasotransmitter, H_2S is thought to play an important role in the CNS. The interrelationships between the cellular antioxidant function of H_2S and age-associated diseases are discussed below (**Figure 4**).

H_2S and AD

AD is an age-associated neurodegenerative disease characterized by senile plaques containing Aβ peptide. H_2S provides protection against oxidative stress by enhancing cell growth and storing mitochondrial function in a p38 and c-jun-N-terminal (JNK)-MAPK-dependent manner (Butterfield and Sultana, 2007). H_2S also provides antioxidant function by enhancing the activity of γ-glutamyl cysteine sulfur transferase and cysteine transport, altering the levels of GSH in glutamate-mediated oxidative stress (Kimura and Kimura, 2004). Moreover, H_2S inhibits the formation of Hcy-induced oxidative stress because the auto-oxidation of Hcy leads to $O_2^{\bullet-}$ and H_2O_2 formation (Wei et al., 2014). Therefore, Hcy is regarded as a novel therapeutic target for AD where H_2S releases sildenafil to prevent against Hcy-induced oxidative stress and neurotxicity (Wei et al., 2014). S-propargyl-cyysteine, an S-allyl cysteine, might inhibit $A\beta_{25-35}$-induced cognitive dysfunction in rats (Tan et al., 2010). Both S-allyl cysteine and S-propargyl-cyysteine are H_2S-modulating agents (Tan et al., 2010). Additionally, H_2S ameliorates oxidative stress-induced compounds, lipid oxidative products, and 4-HNE, to exert its antioxidant function (Mitani et al., 2002). H_2S donor, NaHS, provides neural protection and significantly increases SOD activity in brain tissue to exert its antioxidant function. NaHS significantly inhibits hypochlorous acid-induced cytotoxicity, intracellular ROS, protein oxidation, and lipid peroxidation (Praschberger et al., 2013). Hypochlorous acid is an oxidative stress factor that is found at an elevated level in temporal and frontal cortex of the AD brains (Wei et al., 2014).

Although the effects of H_2S have been elucidated using drug treatment, H_2S donors via ROS signaling, and the formation of different oxidative stress-induced molecules, it will also be important to determine the abnormal characteristics of CBS during H_2S release in AD.

H_2S and PD

The mitochondrial complex I inhibitor, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, has been observed as MPP^+ in PD. Oxidative damage in PD has also been demonstrated by mutations in mtDNA. In the familial forms of PD, PINK1 and DJ-1, and their roles in reducing levels of oxidative ROS have been linked to the familial forms of PD. The DJ-1 protein was detected as an oxidatively-damaged molecule in the brains of PD (Lu et al., 2012), and diminished function of PINK1 has been shown to result in decreased mitochondrial complex 1, which results in increased SOD activity and damage to proteins, lipids, and DNA. On the other hand, antioxidant activity of GSH has been demonstrated in the SN of PD patients at a reduced level that is capable of reducing oxidative damage. GSH either inhibits monoamine oxidase to mediate neuroprotection or increases the function of the electron transport system. Coenzyme Q10, such as selenium, is one example of a compound that can slow the generation of free radicals. Following administration of L-3,4-dihydroxyphenylalanine (L-DOPA), glycine/cysteine molecules are reduced in the presence of oxidative stress with the deposition of GSH, where GSH is oxidized to form GSSH, as previously described by Muller and Muhlack (2007).

On the other hand, many studies have addressed that generating hiPSC-derived neurons from patients with defined genetic mutations associated with PD (Ohnuki et al., 2009; Li et al., 2018). α-Syn, encoded by the substantia compacta nigra, is a pathological hallmark of PD (LaMarca et al., 2018). Cortical neurons generated from hiPSC lines of patients with α-Syn mutations exhibited nitrosative and endoplasmic reticulum stress and accumulation, leading to increased expression of α-Syn (Dettmer et al., 2015). L-DOPA is also used to treat PD patients, although it cannot retard the progression of PD and dyskinesia is a common side effect (Zhang et al., 2017). Moreover, plasma levels of homocysteine in

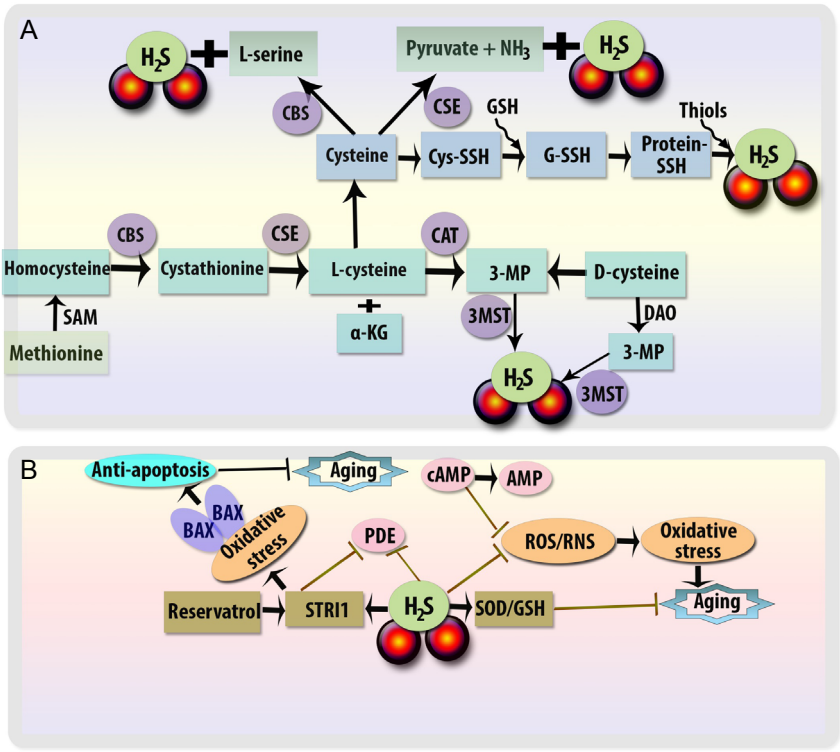

Figure 1 Biosynthesis of H_2S from enzymatic source and anti-aging function of H_2S.
(A) The synthetic procedure of H_2S. (B) Anti-aging effect of H_2S. This diagrammatic illustration reveals H_2S formation in mitochondria. Most prominently, three enzymes, cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3MST) are the main precursors for H_2S formation, where cytosol contains CBS and CSE and mitochondria contains 3MST. The origins of cytosolic H_2S formation are homocysteine, cysteine, and L-cysteine which are derived from proteins and cysteine. In mitochondria, H_2S is produced from 3 mercaptopyruvate (3-MP) and L-cysteine. H_2S exerts metabolic function through upregulation of silent information regulator 1 (SIRT1) and inhibiting free radical-induced oxidative stress. H_2S also inhibits cell aging through mediating super oxide dismutase/glutathione (SOD/GSH). Resveratrol, an anti-aging drug, initiates age-associated metabolic phenotypes by the inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE). H_2S enhances SIRT1 and inhibits PDE activity to provide anti-aging function. CAT: Cysteine acetyl transferase; DAO: diamine oxidase; H_2S: hydrogen sulfide; RNS: reactive nitrogen species; ROS: reactive oxygen species.

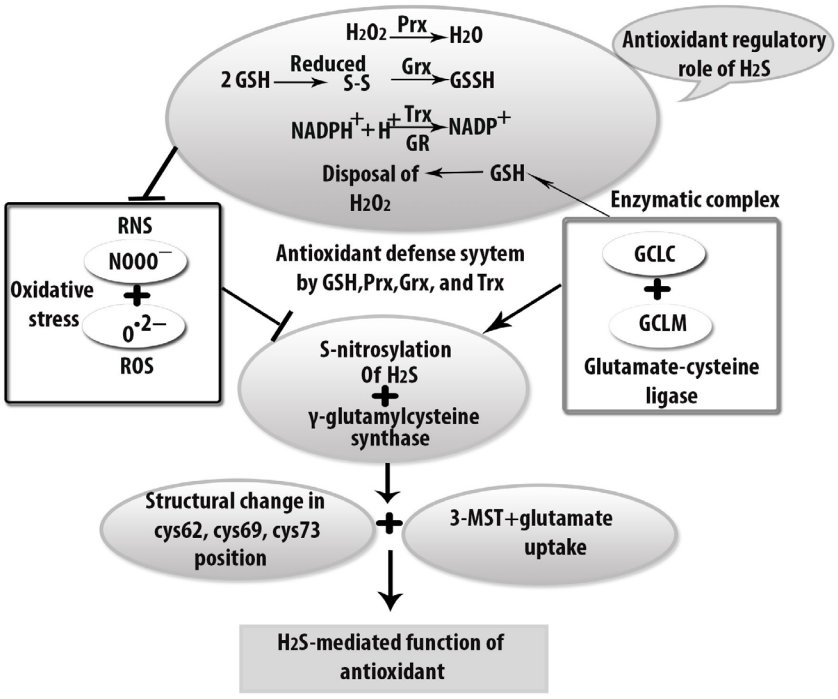

Figure 2 Schematic representation of antioxidant regulatory role of H_2S.
Under oxidative stress, the source of ROS increases hydrogen peroxide (H_2O_2) and super oxide ($O•_2^-$). RNS increases peroxynitrite ($NOOO^-$). Simultaneously, glutathione (GSH) creates a redox cycle using nicotinamide adenine dinucleotide phosphate (NADPH) reducing agent associated with the enzyme, glutathione reductase (GR). On the other hand, peroxiredoxin (Prx) is a thiol based antioxidant, reacts with H_2O_2 at a very high rate to neutralize ROS from cell. Prx1, Prx2, and Prx4 are mostly found in nuclei rather than in cytoplasm. Oxidized thioredoxin (Trx) can be reversibly reduced by thioredoxin reductase (TrxR) enzyme in an NADPH-dependent manner, where Trx1 and Trx2 are localized in mitochondria. The combined action of glutamate-cysteine ligase catalytic subunit (GCLC) and glutamate-cysteine ligase modifier subunit (GCLM) helps GSH in the disposal of H_2O_2 in mitochondria as well as GSH reduced to GSSH in the presence of glutaredoxin (Grx). However, during S-nitrosylation of H_2S, cysteine protein structure is being changed and increases the glutamate uptake which mediates H_2S-induced antioxidative function. Overall, GSH, Trx, Prx, and Grx appear to have a protective action against oxidative stress. 3MST: 3-Mercaptopyruvate sulfurtransferase; H_2S: hydrogen sulfide.

cells become elevated in PD when L-DOPA is administered (Zhang et al., 2017). H_2S release of the L-DOPA derivative ACS84 in a 6-OHDA-induced PD model demonstrated therapeutic action, particularly in SH-SY5Y neuroblastoma cells against 6-OHDA-induced oxidative stress, identifying MDA and decreased levels of GSH (Predmore et al., 2012). In addition, H_2S induces nucleus translocation of Nrf2 by s-sulfhydrating cysteine-151 of keap1 and thereby enhances the anti-oxidative capacity of mammalian cells (Hu et al., 2010). H_2S also inhibits the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase possibly through its suppressive effect on ERK phosphorylation (Cao et al., 2018).

Thus, the H_2S-releasing L-DOPA derivative ACS84 reduces

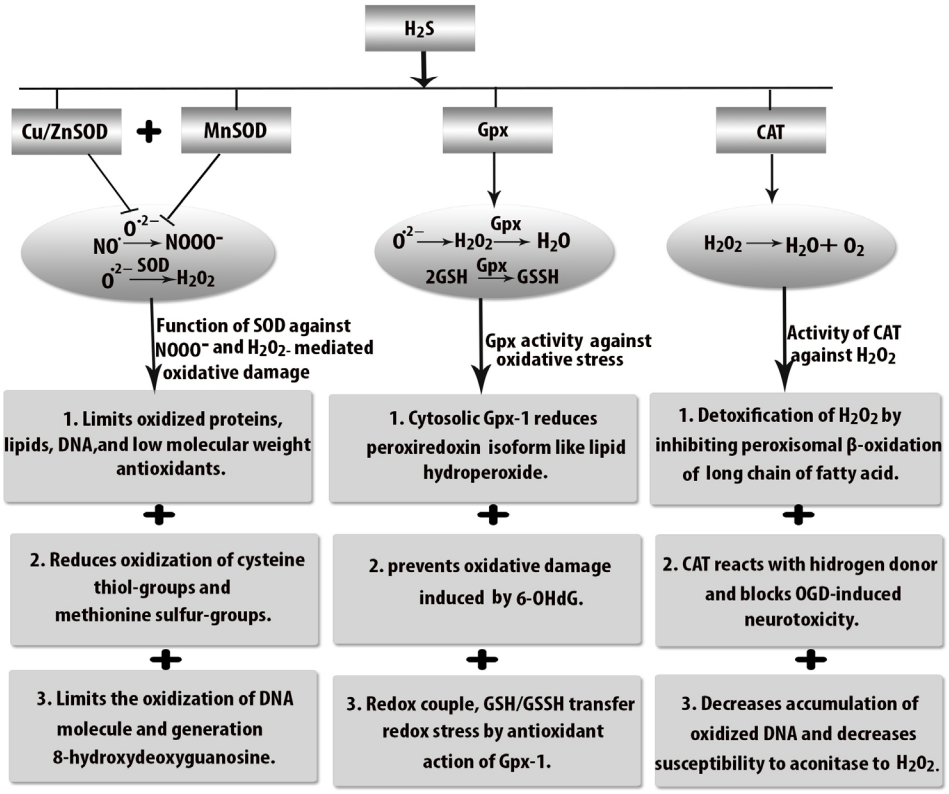

Figure 3 Enzymatic antioxidant function of H_2S against oxidative stress.
This schematic diagram explains various enzymatic antioxidant functions of H_2S against oxidative stress. Among the antioxidants, the enzymatic antioxidants mostly take part in retard oxidative stress. Super oxide dismutase (SOD) is one of them and both cytosolic, Cu/Zn, SOD (SOD1), and mitochondrial MnSOD (SOD2) inhibit superoxide ($O_2^{\bullet-}$) to form peroxynitrite ($NOOO^-$). The presence of $NOOO^-$ causes tyrosine nitration, whereas tyrosine is an oxidative marker of oxidative stress. Moreover, SOD interferes with H_2O_2 formation from $O_2^{\bullet-}$ which forms 8-hydrodeoxyguanosine (8-OHdG), an oxidative damage of DNA. Exposure to excessive H_2O_2, oxidative degradation of cysteine to pyruvate and sulfate are prohibited by SOD and catalase (CAT). At the same time, glutathione peroxidase (Gpx) exhibits antioxidant function examined knockout mice that show specifically 21.8% at the age of 7 weeks against 8-OHdG-induced degradation. GSH: glutathione; GSSH: oxidized glutathione; H_2S: hydrogen sulfide; OGD: oxygen glucose deprivation.

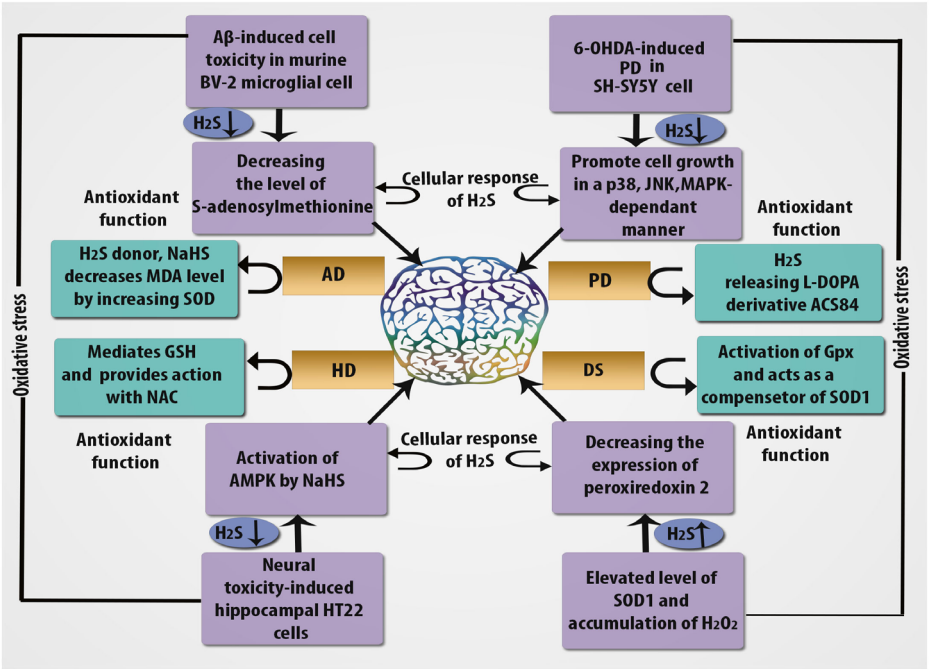

Figure 4 The interrelationship between antioxidant effects of H_2S and oxidative stress-induced factors in age-related neurodegeneration.
This figure explains the cellular response of H_2S against Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Down's syndrome (DS). The increased and decreased levels of H_2S in cells play different roles in each neurodegenerative disease. H_2S retards oxidative derivatives malonaldehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) in AD. In PD, cellular growth is regulated through protein kinases C (PKC), c-Jun NH2-terminal enzyme (JNK), and p38 mitogen activated protein kinase (p38 MAPK). These protein kinases decrease oxidative stress and facilitate antiapoptotic function. H_2S also inhibits MDA in HD cells and facilitates N-acetylcysteine (NAC) function with GSH. In the case of DS, GSH retards overexpression of SOD1 and increased level of GSH inhibits oxidative deterioration. H_2S: Hydrogen sulfide; SOD1: Cu/ZnSOD.

cellular damage by reducing oxidative stress in PD. H_2S-mediated sulfhydration is an important mechanism for the attenuation of ROS generation, especially with respect to ACS84, and thus ACS84 may be useful in the treatment of PD.

H_2S and HD

HD is a prototypical age-associated disease caused by CAG trinucleotide repeats in the HTT protein, for which neural dysfunction and death occur due to excitotoxicity, oxidative damage, and apoptosis. Ca^{2+} signaling in the mitochondria implies mitochondrial dysfunction. H_2S exerts antioxidant function in HD patients through enzymatic antioxidants, including SOD, CAT, and Gpx. The GSH precursor N-acetyl transferase (NAC) provides protection against oxidative damage in HD (Schumann and Subramani, 2008). Moreover, administration of 3-nitropropainic acid before application of

NAC reduces lesions in HD (Kimura and Kimura, 2004).

The level of CSE in HTT repeating cells (111 repeats) has been shown to be reduced by more than 90%. Similarly, the Q_{175} and R6/2 mouse models also exhibit reduced levels of CSE (Ali et al., 2007). In HD patients, CSE provides cytoprotection, which originates from cysteine proteins, and CSE depletion suggests cysteine loss (Truong et al., 2006). On the other hand, cystamine, the decarboxylated form of cysteine, provides neuroprotection in HD (Zhai et al., 2005). In response to enzymatic dysfunction in HD, Gpx provides broad-spectrum antioxidant function (Fraunberger et al., 2016). In the clinical study of patients affected by HD, it has been observed that cysteamine treated HD patients showed intolerance and cysteamine treatment showed adverse effects such as nausea and weight loss (Dubinsky and Gray, 2006). Moreover, motor subscales of the unified HD rating scale showed motoric impairment after 2 weeks (Dubinsky and Gray, 2006).

In summary, the combined action of GSH and NAC suggest new therapeutic possibilities for HD patients, although further studies will be necessary to understand the antioxidant mechanism induced by GSH and NAC in HD.

H_2S and DS

The neuropathology of DS associated with dementia is related to age. The free radical metabolism of DS, which contributes to neuronal degradation, is also related to age. The mental retardation of DS occurs as a result of trisomy 21 (Das and Reeves, 2011). The overexpression of SOD1 gene as a response to the oxidative stress is observed in DS patients by the trisomic state, where SOD1 gene is located in chromosome 21. Apart from this, the main cause of DS is the elevated level of CBS enzyme. According to the study of Pogribna et al. (2001), DS patients with an increased level of CBS show decreased plasma levels of cystathionine, homocysteine, and SAM. Decreased homocysteine might play a role in the cognitive disability of DS. To maintain homocysteine levels, CBS catalyzes the folate and methionine cycle. CBS protein levels and enzymatic activity are increased in DS, and in particular, elevated CBS activity can lower the level of homocysteine (Hensley et al., 2010). As a consequence, carboxy transulfuration (1C-Ts) metabolism becomes imbalanced and H_2S reaches toxic levels. Metabolism of the 1C-Ts complex, which includes the enzyme CBS (Hensley et al., 2010), has been linked with DS (Hensley et al., 2010). This metabolic alteration associated with CBS causes cognitive disability in DS (Kamoun, 2001). Accumulation of 8-OHdG is an oxidative hallmark found in the cytoplasm of cells in DS patients (Nunomura et al., 2000). SOD1 mediates antioxidant defense by catalyzing the dismutation of $O_2^{\bullet-}$ to molecular O_2 and H_2O_2, which can be converted to water by CAT and Gpx (Perluigi and Butterfield, 2012).

In summary, DS is a result of the accumulation of H_2S in the brain, particularly the increase in CBS. In general, Gpx activity in DS is not broad. For a better understanding of the antioxidant function of H_2S as a gasotransmitter, clinical investigation will be necessary.

Interrelationship between H_2S and Other Gasotransmitters

In spite of the several biological functions of H_2S as a gasotransmitter, a recent study demonstrated an interaction between H_2S and NO, which exhibited combined kinetics (Wu et al., 2018). According to reaction basis analysis, the reaction of H_2S or –SH with disulfide represents a pathway of potential importance in the detection of H_2S. To form S-nitrosothiols, nitroxyl, and nucleophiles, as well as reducing agents, H_2S provides complementary action (Bruce King, 2013). The combined action of H_2S and NO exhibits positive inotropic effects during inflammation (Kolluru et al., 2013). $NOOO^-$ rapidly interacts with H_2S, which produces sulfinyl nitrite and reduces oxidative molecules (Kolluru et al., 2013). Additionally, to observe H_2S bioavailability in cells, endothelial cells treated with NO donors exhibited increased cysteine uptake in a dose-dependent manner (Kolluru et al., 2013).

Complementary action of CO and H_2S has also been observed. To exert a physiological effect, CO and H_2S act as a signaling molecule, depending on the cellular state. Generally, while hypoxia inhibits HO-1, more H_2S is produced in the brain and CBS is considered a sensor for CO (Farrugia and Szurszewski, 2014). In the presence of HO-2 in neurons, CO inhibits the potential activity of CBS of astrocytes. In astrocytes, as well as other cell types, CO-mediated inhibition of CBS inhibits H_2S release during vasodilation. In the presence of hypoxia, CO also inhibits CSE and, as a consequence, Ca^{2+}-dependent K^+ channels are closed in neurons (Olson, 2013). The enzymatic activity of CBS is changed when CO binds to the heme moiety of CBS.

In summary, the interactions between H_2S, NO, and CO induce potential reactions capable of generating other biologically active species. Thus, further studies will be necessary to determine the complementary action of H_2S, NO, and CO.

Future Perspectives and Concluding Remarks

Based on previous investigations, lower levels of H_2S in the body are the root cause of age-associated diseases that hamper antioxidant function through cell signaling pathways in AD, PD, HD, and DS. Proper levels of H_2S in the body have been shown to be necessary for GSH generation as well as to provide protection against oxidative damage.

As the antioxidant function of H_2S involves GSH, the mechanisms underlying transsulfuration signaling and sulfur-containing molecules that include cysteine molecules may be helpful to clarify the antioxidant function. To address and understand further the biological as well as the clinical potential of H_2S, suitable selection of H_2S donors will also be crucial for the proper release of H_2S *in vitro* and *in vivo*. Properly maintained enzymatic pathways are important for H_2S release as well as its ability to induce the antioxidant functions of SOD, Gpx, and CAT. The role of H_2S is likely to be cell-specific under different pathological conditions wherein H_2S can provide proper neuromodulation against oxidative stress. Additional experimental and clinical studies

will be necessary to understand further the pathophysiological pathways underlying aging to determine the possible therapeutic use of H_2S-mediated antioxidant function.

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Additional Table 1: *Database search strategy.*
Additional file 1: *Open peer review reports 1 and 2.*

References

Abdulle A, van Goor H, Mulder D (2018) Hydrogen sulfide: a therapeutic option in systemic sclerosis. Int J Mol Sci 19:4121.
Ali MY, Whiteman M, Low CM, Moore PK (2007) Hydrogen sulphide reduces insulin secretion from HIT-T15 cells by a KATP channel-dependent pathway. J Endocrinol 195:105-112.
An MC, Zhang N, Scott G, Montoro D, Wittkop T, Mooney S, Melov S, Ellerby LM (2012) Genetic correction of Huntington's disease phenotypes in induced pluripotent stem cells. Cell Stem Cell 11:253-263.
Attene-Ramos MS, Wagner ED, Plewa MJ, Gaskins HR (2006) Evidence that hydrogen sulfide is a genotoxic agent. Mol Cancer Res 4:9-14.
Bambrick LL, Fiskum G (2008) Mitochondrial dysfunction in mouse trisomy 16 brain. Brain Res 1188:9-16.
Ben-Porath I, Weinberg RA (2005) The signals and pathways activating cellular senescence. Int J Biochem Cell Biol 37:961-976.
Bose A, Beal MF (2019) Mitochondrial dysfunction and oxidative stress in induced pluripotent stem cell models of Parkinson's disease. Eur J Neurosci 49:525-532.
Bruce King S (2013) Potential biological chemistry of hydrogen sulfide (H_2S) with the nitrogen oxides. Free Radic Biol Med 55:1-7.
Butterfield DA, Sultana R (2007) Redox proteomics identification of oxidatively modified brain proteins in Alzheimer's disease and mild cognitive impairment: insights into the progression of this dementing disorder. J Alzheimers Dis 12:61-72.
Butterfield DA, Swomley AM, Sultana R (2013) Amyloid β-peptide (1–42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression. Antioxid Redox Signal 19:823-835.
Cai J, Shi X, Wang H, Fan J, Feng Y, Lin X, Yang J, Cui Q, Tang C, Xu G, Geng B (2016) Cystathionine γ lyase–hydrogen sulfide increases peroxisome proliferator-activated receptor γ activity by sulfhydration at C139 site thereby promoting glucose uptake and lipid storage in adipocytes. Biochim Biophys Acta 1861:419-429.
Cao L, Tan L, Jiang T, Zhu XC, Yu JT (2015) Induced pluripotent stem cells for disease modeling and drug discovery in neurodegenerative diseases. Mol Neurobiol 52:244-255.
Cao X, Cao L, Ding L, Bian JS (2018) A new hope for a devastating disease: hydrogen sulfide in Parkinson's disease. Mol Neurobiol 55:3789-3799.
Cartelli D, Amadeo A, Calogero AM, Casagrande FVM, De Gregorio C, Gioria M, Kuzumaki N, Costa I, Sassone J, Ciammola A (2018) Parkin absence accelerates microtubule aging in dopaminergic neurons. Neurobiol Aging 61:66-74.
Chin LS, Olzmann JA, Li L (2008) Aggresome formation and neurodegenerative diseases: therapeutic implications. Curr Med Chem 15:47-60.
Ciechanover A, Kwon YT (2015) Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. Exp Mol Med 47:e147.
Das I, Reeves RH (2011) The use of mouse models to understand and improve cognitive deficits in Down syndrome. Dis Model Mech 4:596-606.
Dettmer U, Newman AJ, Soldner F, Luth ES, Kim NC, Von Saucken VE, Sanderson JB, Jaenisch R, Bartels T, Selkoe D (2015) Parkinson-causing α-synuclein missense mutations shift native tetramers to monomers as a mechanism for disease initiation. Nat Commun 6:7314.
Dinda B, Dinda M, Kulsi G, Chakraborty A, Dinda S (2019) Therapeutic potentials of plant iridoids in Alzheimer's and Parkinson's diseases: A review. Eur J Med Chem 169:185-199.
Dorrell MI, Aguilar E, Jacobson R, Yanes O, Gariano R, Heckenlively J, Banin E, Ramirez GA, Gasmi M, Bird A, Siuzdak G, Friedlander M (2009) Antioxidant or neurotrophic factor treatment preserves function in a mouse model of neovascularization-associated oxidative stress. J Clin Invest 119:611-623.
Dringen R, Gutterer JM, Hirrlinger J (2000) Glutathione metabolism in brain: Metabolic interaction between astrocytes and neurons in the defense against reactive oxygen species. Eur J Biochem 267:4912-4916.
Du J, Huang Y, Yan H, Zhang Q, Zhao M, Zhu M, Liu J, Chen SX, Bu D, Tang C (2014) Hydrogen sulfide suppresses oxidized low-density lipoprotein (ox-LDL)-stimulated monocyte chemoattractant protein 1 generation from macrophages via the nuclear factor κB (NF-κB) pathway. J Biol Chem 289:9741-9753.
Dubinsky R, Gray C (2006) CYTE-I-HD: Phase I dose finding and tolerability study of cysteamine (Cystagon) in Huntington's disease. Mov Disord Off J Mov Disord Soc 21:530-533.
Farrugia G, Szurszewski JH (2014) Carbon monoxide, hydrogen sulfide, and nitric oxide as signaling molecules in the gastrointestinal tract. Gastroenterology 147:303-313.
Fraunberger EA, Scola G, Laliberté VLM, Duong A, Andreazza AC (2016) Redox modulations, antioxidants, and neuropsychiatric disorders. Oxid Med Cell Longev 2016:4729192.
Gadalla MM, Snyder SH (2010) Hydrogen sulfide as a gasotransmitter. J Neurochem 113:14-26.
Gade AR, Kang M, Akbarali HI (2013) Hydrogen sulfide as an allosteric modulator of ATP-sensitive potassium channels in colonic inflammation. Mol Pharmacol 83:294-306.
Ganguly G, Chakrabarti S, Chatterjee U, Saso L (2017) Proteinopathy, oxidative stress and mitochondrial dysfunction: Cross talk in alzheimer's disease and parkinson's disease. Drug Des Devel Ther 11:797-810.
Gemici B, Elsheikh W, Feitosa KB, Costa SKP, Muscara MN, Wallace JL (2015) H_2S-releasing drugs: anti-inflammatory, cytoprotective and chemopreventative potential. Nitric Oxide 46:25-31.
Hamar J, Solymar M, Tanai E, Cseplo P, Springo Z, Berta G, Debreceni B, Koller A (2012) Bioassay-comparison of the antioxidant efficacy of hydrogen sulfide and superoxide dismutase in isolated arteries and veins. Acta Physiol Hung 99:411-419.
Hancock JT, Whiteman M (2014) Hydrogen sulfide and cell signaling: team player or referee? Plant Physiol Biochem 78:37-42.
Harraz MM, Marden JJ, Zhou W, Zhang Y, Williams A, Sharov VS, Nelson K, Luo M, Paulson H, Schöneich C (2008) SOD1 mutations disrupt redox-sensitive Rac regulation of NADPH oxidase in a familial ALS model. J Clin Invest 118:659.
Hensley K, Venkova K, Christov A (2010) Emerging biological importance of central nervous system lanthionines. Molecules 15:5581-5594.
Hewitt G, Jurk D, Marques FDM, Correia-Melo C, Hardy T, Gackowska A, Anderson R, Taschuk M, Mann J, Passos JF (2012) Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nat Commun 3:708.
Hipkiss AR (2006) Accumulation of altered proteins and ageing: causes and effects. Exp Gerontol 41:464-473.
Hoffmann A, Kann O, Ohlemeyer C, Hanisch UK, Kettenmann H (2003) Elevation of basal intracellular calcium as a central element in the activation of brain macrophages (microglia): suppression of receptor-evoked calcium signaling and control of release function. J Neurosci 23:4410-4419.
Hu L, Lu M, Tiong CX, Dawe GS, Hu G, Bian J (2010) Neuroprotective effects of hydrogen sulfide on Parkinson's disease rat models. Aging Cell 9:135-146.
Jain SK, Huning L, Micinski D (2014) Hydrogen sulfide upregulates glutamate–cysteine ligase catalytic subunit, glutamate–cysteine ligase modifier subunit, and glutathione and inhibits interleukin-1β secretion in monocytes exposed to high glucose levels. Metab Syndr Relat Disord 12:299-302.
Jiang J, Chan A, Ali S, Saha A, Haushalter KJ, Lam WL, Glasheen M, Parker J, Brenner M, Mahon SB, Patel HH, Ambasudhan R, Lipton SA, Pilz RB, Boss GR (2016) Hydrogen sulfide--mechanisms of toxicity and development of an antidote. Sci Rep 6:20831.
Kabil O, Banerjee R (2014) Enzymology of H_2S biogenesis, decay and signaling. Antioxid Redox Signal 20:770-782.
Kabil O, Motl N, Banerjee R (2014a) H_2S and its role in redox signaling. Biochim Biophys Acta 1844:1355-1366.
Kabil O, Vitvitsky V, Banerjee R (2014b) Sulfur as a signaling nutrient through hydrogen sulfide. Annu Rev Nutr 34:171-205.
Kamoun P (2001) Mental retardation in Down syndrome: a hydrogen sulfide hpothesis. Med Hypotheses 57:389-392.
Kimura H (2014) Hydrogen sulfide and polysulfides as biological mediators. Molecules 19:16146-16157.

Kimura H (2015) Hydrogen sulfide and polysulfides as signaling molecules. Proc Japan Acad Ser B 91:131-159.
Kimura Y, Goto YI, Kimura H (2010) Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. Antioxid Redox Signal 12:1-13.
Kimura Y, Kimura H (2004) Hydrogen sulfide protects neurons from oxidative stress. FASEB J 18:1165-1167.
Kolluru GK, Shen X, Bir SC, Kevil CG (2013) Hydrogen sulfide chemical biology: pathophysiological roles and detection. Nitric oxide 35:5-20.
LaMarca EA, Powell SK, Akbarian S, Brennand KJ (2018) Modeling neuropsychiatric and neurodegenerative diseases with induced pluripotent stem cells. Front Pediatr 6:82.
Li H, Jiang H, Zhang B, Feng J (2018) Modeling Parkinson's disease using patient-specific induced pluripotent stem cells. J Parkinsons Dis 8:479-493.
Li L, Rose P, Moore PK (2011) Hydrogen sulfide and cell signaling. Annu Rev Pharmacol Toxicol 51:169-187.
Li XN, Chen L, Luo B, Li X, Wang CY, Zou W, Zhang P, You Y, Tang XQ (2017) Hydrogen sulfide attenuates chronic restrain stress-induced cognitive impairment by upreglulation of Sirt1 in hippocampus. Oncotarget 8:100396.
López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194-1217.
Lu M, Zhao FF, Tang JJ, Su CJ, Fan Y, Ding JH, Bian JS, Hu G (2012) The neuroprotection of hydrogen sulfide against MPTP-induced dopaminergic neuron degeneration involves uncoupling protein 2 rather than ATP-sensitive potassium channels. Antioxid Redox Signal 17:849-859.
Majid AS, Majid AM, Yin ZQ, Ji D (2013) Slow regulated release of H_2S inhibits oxidative stress induced cell death by influencing certain key signaling molecules. Neurochem Res 38:1375-1393.
Meister A (1992) Biosynthesis and functions of glutathione, an essential biofactor. J Nutr Sci Vitaminol (Tokyo) Spec No:1-6.
Mikami Y, Shibuya N, Ogasawara Y, Kimura H (2013) Hydrogen sulfide is produced by cystathionine γ-lyase at the steady-state low intracellular Ca2+ concentrations. Biochem Biophys Res Commun 431:131-135.
Miquel J, Economos AC, Fleming J, Johnson Jr JE (1980) Mitochondrial role in cell aging. Exp Gerontol 15:575-591.
Mir S, Sen T, Sen N (2014) Cytokine-induced GAPDH sulfhydration affects PSD95 degradation and memory. Mol Cell 56:786-795.
Mitani H, Ishizaka N, Aizawa T, Ohno M, Usui S, Suzuki T, Amaki T, Mori I, Nakamura Y, Sato M (2002) In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. Hypertension 39:838-843.
Mondragón-Rodríguez S, Perry G, Zhu X, Moreira PI, Acevedo-Aquino MC, Williams S (2013) Phosphorylation of tau protein as the link between oxidative stress, mitochondrial dysfunction, and connectivity failure: implications for Alzheimer's disease. Oxid Med Cell Longev 2013:940603.
Muhlack S, Welnic J, Woitalla D, Müller T (2007) Exercise improves efficacy of levodopa in patients with Parkinson's disease. Mov Disord 22:427-430.
Muñoz-Espín D, Serrano M (2014) Cellular senescence: from physiology to pathology. Nat Rev Mol cell Biol 15:482.
Navarro-Yepes J, Zavala-Flores L, Anandhan A, Wang F, Skotak M, Chandra N, Li M, Pappa A, Martinez-Fong D, Del Razo LM (2014) Antioxidant gene therapy against neuronal cell death. Pharmacol Ther 142:206-230.
Nunomura A, Castellani RJ, Zhu X, Moreira PI, Perry G, Smith MA (2006) Involvement of oxidative stress in Alzheimer disease. J Neuropathol Exp Neurol 65:631-641.
Nunomura A, Perry G, Pappolla MA, Friedland RP, Hirai K, Chiba S, Smith MA (2000) Neuronal oxidative stress precedes amyloid-β deposition in Down syndrome. J Neuropathol Exp Neurol 59:1011-1017.
Ohnuki M, Takahashi K, Yamanaka S (2009) Generation and characterization of human induced pluripotent stem cells. Curr Protoc Stem Cell Biol Chapter 4:Unit 4A.2.
Oliver DMA, Reddy PH (2019) Small molecules as therapeutic drugs for Alzheimer's disease. Mol Cell Neurosci 96:47-62.
Olson KR (2013) Hydrogen sulfide as an oxygen sensor. Clin Chem Lab Med 51:623-632.
Onyango IG, Dennis J, Khan SM (2016) Mitochondrial dysfunction in Alzheimer's disease and the rationale for bioenergetics based therapies. Aging Dis 7:201.
Paul BD, Snyder SH (2015) H_2S: a novel gasotransmitter that signals by sulfhydration. Trends Biochem Sci 40:687-700.
Perier C, Bove J, Dehay B, Jackson-Lewis V, Rabinovitch PS, Przedborski S, Vila M (2010) Apoptosis-inducing factor deficiency sensitizes dopaminergic neurons to parkinsonian neurotoxins. Ann Neurol 68:184-192.
Perluigi M, Butterfield DA (2012) Oxidative stress and down syndrome: A route toward Alzheimer-like dementia. Curr Gerontol Geriatr Res 2012:724904.
Perridon BW, Leuvenink HG, Hillebrands JL, van Goor H, Bos EM (2016) The role of hydrogen sulfide in aging and age-related pathologies. Aging (Albany NY) 8:2264-2289.
Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ (2001) Homocysteine metabolism in children with Down syndrome: in vitro modulation. Am J Hum Genet 69:88-95.
Praschberger M, Hermann M, Laggner C, Jirovetz L, Exner M, Kapiotis S, Gmeiner BMK, Laggner H (2013) Carbamoylation abrogates the antioxidant potential of hydrogen sulfide. Biochimie 95:2069-2075.
Predmore BL, Lefer DJ, Gojon G (2012) Hydrogen sulfide in biochemistry and medicine. Antioxid Redox Signal 17:119-140.
Régnier V, Billard JM, Gupta S, Potier B, Woerner S, Paly E, Ledru A, David S, Luilier S, Bizot JC (2012) Brain phenotype of transgenic mice overexpressing cystathionine β-synthase. PLoS One 7:e29056.
Rocha EM, De Miranda B, Sanders LH (2018) Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiol Dis 109:249-257.
Rodríguez-Sureda V, Vilches Á, Sánchez O, Audí L, Domínguez C (2015) Intracellular oxidant activity, antioxidant enzyme defense system, and cell senescence in fibroblasts with trisomy 21. Oxid Med Cell Longev 2015:509241.
Rose P, Moore PK, Zhu YZ (2017) H_2S biosynthesis and catabolism: new insights from molecular studies. Cell Mol Life Sci 74:1391-1412.
Ross CA, Akimov SS (2014) Human-induced pluripotent stem cells: potential for neurodegenerative diseases. Hum Mol Genet 23:R17-26.
Scaglione CN, Xu Q, Ramanujan VK (2016) Direct measurement of catalase activity in living cells and tissue biopsies. Biochem Biophys Res Commun 470:192-196.
Schuchmann S, Heinemann U (2000) Increased mitochondrial superoxide generation in neurons from trisomy 16 mice: a model of Down's syndrome. Free Radic Biol Med 28:235-250.
Schumann U, Subramani S (2008) Special delivery from mitochondria to peroxisomes. Trends Cell Biol 18:253-256.
Searcy DG, Whitehead JP, Maroney MJ (1995) Interaction of Cu, Zn superoxide dismutase with hydrogen sulfide. Arch Biochem Biophys 318:251-263.
Sen N, Paul BD, Gadalla MM, Mustafa AK, Sen T, Xu R, Kim S, Snyder SH (2012) Hydrogen sulfide-linked sulfhydration of NF-κB mediates its antiapoptotic actions. Mol Cell 45:13-24.
Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'agostino RB, Wilson PWF, Wolf PA (2002) Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 346:476-483.
Shibuya N, Tanaka M, Yoshida M, Ogasawara Y, Togawa T, Ishii K, Kimura H (2009) 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. Antioxid Redox Signal 11:703-714.
Singh S, Banerjee R (2011) PLP-dependent H_2S biogenesis. Biochim Biophys Acta (BBA)-Proteins Proteomics 1814:1518-1527.
Tan BH, Wong PT-H, Bian J-S (2010) Hydrogen sulfide: a novel signaling molecule in the central nervous system. Neurochem Int 56:3-10.
Teng H, Wu B, Zhao K, Yang G, Wu L, Wang R (2013) Oxygen-sensitive mitochondrial accumulation of cystathionine β-synthase mediated by Lon protease. Proc Natl Acad Sci U S A 110:12679-12684.
Truong DH, Eghbal MA, Hindmarsh W, Roth SH, O'brien PJ (2006) Molecular mechanisms of hydrogen sulfide toxicity. Drug Metab Rev 38:733-744.
Tyagi N, Moshal KS, Sen U, Vacek TP, Kumar M, Hughes Jr WM, Kundu S, Tyagi SC (2009) H_2S protects against methionine-induced oxidative stress in brain endothelial cells. Antioxid Redox Signal 11:25-33.
Viña J, Borras C, Abdelaziz KM, Garcia-Valles R, Gomez-Cabrera MC (2013) The free radical theory of aging revisited: the cell signaling disruption theory of aging. Antioxid Redox Signal 19:779-787.
Wei H, Zhang G, Qiu S, Lu J, Sheng J, Tan G, Wong P, Gan SU, Shim W (2012) Hydrogen sulfide suppresses outward rectifier potassium currents in human pluripotent stem cell-derived cardiomyocytes. PLoS One 7:e50641.
Wei HJ, Li X, Tang XQ (2014) Therapeutic benefits of H_2S in Alzheimer's disease. J Clin Neurosci 21:1665-1669.
Wu D, Hu Q, Zhu D (2018) An update on hydrogen sulfide and nitric oxide interactions in the cardiovascular system. Oxid Med Cell Longev 2018:4579140.
Xie ZZ, Liu Y, Bian JS (2016) Hydrogen sulfide and cellular redox homeostasis. Oxid Med Cell Longev 2016:1-12.
Yamanishi M, Kabil O, Sen S, Banerjee R (2006) Structural insights into pathogenic mutations in heme-dependent cystathionine-β-synthase. J Inorg Biochem 100:1988-1995.
Zhai W, Jeong H, Cui L, Krainc D, Tjian R (2005) In vitro analysis of huntingtin-mediated transcriptional repression reveals multiple transcription factor targets. Cell 123:1241-1253.
Zhang J, Ding Y, Wang Z, Kong Y, Gao R, Chen G (2017) Hydrogen sulfide therapy in brain diseases: from bench to bedside. Med Gas Res 7:113.
Zhao K, Ju Y, Li S, Altaany Z, Wang R, Yang G (2014) S-sulfhydration of MEK1 leads to PARP-1 activation and DNA damage repair. EMBO Rep 15:792-800.
Zhu YZ, Wang ZJ, Ho P, Loke YY, Zhu YC, Huang SH, Tan CS, Whiteman M, Lu J, Moore PK (2007) Hydrogen sulfide and its possible roles in myocardial ischemia in experimental rats. J Appl Physiol 102:261-268.

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