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REVIEW ARTICLE

Role of Hydrogen Sulfide and Polysulfides in Neurological Diseases: Focus on Protein S-Persulfidation

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Abstract: Hydrogen sulfide (H_2S) and hydrogen polysulfides are recognized as important signaling molecules that are generated physiologically in the body, including the central nervous system (CNS). Studies have shown that these two molecules are involved in cytoprotection against oxidative stress and inflammatory response. In the brain system, H_2S and polysulfides exert multiple functions in both health and diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), memory decline, and glioma. Mechanistically, S-Persulfidation (also known as S-sulfuration or S-sulfhydration) of target proteins is believed to be a fundamental mechanism that underlies H_2S-regulated signaling pathways. Cysteine S-Persulfidation is an important paradigm of post translational protein modification in the process of H_2S signaling. This model is established as a critical redox mechanism to regulate numerous biological functions, especially in H_2S-mediated neuroprotection and neurogenesis. Although the current research of S-Persulfidation is still in its infancy, accumulative evidence suggests that protein S-Persulfidation may share similar characteristics with protein S-nitrosylation. In this review, we will provide a comprehensive insight into the S-Persulfidation biology of H_2S and polysulfides in neurological ailments and presume potential avenues for therapeutic development in these disorders based on S-Persulfidation of target proteins.

Keywords: Hydrogen sulfide, polysulfides, cysteine, S-Persulfidation, neurodegeneration, central nervous system.

1. INTRODUCTION

Hydrogen sulfide (H_2S) is previously known as an environmental hazard with a rotten egg smell [1]. However, mounting evidence suggests that H_2S, independently of any transporters, confers a diversity of physiological actions on various systems [2-7], including the central nervous system (CNS) [8-11]. H_2S is distinctly expressed in mammalian tissues where it could freely cross through the cell membranes [12]. It has now been well accepted that H_2S acts as the third gaseous signal molecule in conjunction with nitric oxide (NO) and carbon monoxide (CO) [13]. As a gasotransmitter, H_2S is taken as a key regulator in a wide spectrum of physiological and pathological processes in the brain tissues [10]. Studies of H_2S in the CNS were initiated by the discovery of sulfides in the brain [14]. In this study, the authors demonstrated that inhalation of H_2S led to increased brain sulfide deposition; this may be associated with the mortality in rats [14]. After that, H_2S biosynthesis is detected in the brain, and H_2S is found to facilitate long-term hippocampal potentiation (LTP) by raising N-methyl-D-aspartic acid receptors (NMDARs)-induced responses [15]. Besides, it has been unveiled that H_2S could directly modulate pH homeostasis and intracellular Ca^{2+} release in microglial cells, neurons, and astrocytes [16-20]. Most importantly, impaired H_2S synthesis participates in the development of various neurological diseases, such as ischemic stroke, Alzheimer's disease (AD), and Parkinson's disease (PD) [9].

Polysulfides are H_2S-derived endogenous molecules with a distinct number of inner sulfur atoms [21]. In brief, H_2S is sequentially oxidized to polysulfides until the number of sulfur atoms reaches eight, and the sulfur molecules cyclize and separate from polysulfides [22-24]. In comparison with H_2S, polysulfides grant a greater potency toward ion channels, transcription factors, or tumor suppressors [1]. Similar to the effects of H_2S, recent studies have demonstrated that polysulfides also exhibit neuroprotective effects by sulfurating the target proteins, such as Kelch-like ECH-associating protein 1 (Keap1), transient receptor potential cation channel subfamily A member 1 (TRPA1) channels, and phosphatase and tensin homolog (PTEN), much more potently than H_2S [18, 25]. The significance of polysulfides in the regulation of neurobiology has been gradually recognized, especially their roles in S-Persulfidation of target protein cysteine sites [26, 27]. The additional sulfur of polysulfides

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could be incorporated into the cysteine residues, termed as S-Persulfidation, an important post-translational modification [25, 28]. For example, polysulfides-induced S-Persulfidation of parkin, a neuroprotective ubiquitin E3 ligase, is remarkably depleted in the brain tissues of subjects suffering from with PD, hinting that this collapse might play a critical role in the pathophysiology of PD [29].

S-Persulfidation, a chemical modification, is characterized by adding sulfur atoms to specific cysteine residues of target proteins, thus generating persulfide adducts on both small molecules and proteins [30, 31]. This process is considered to be a critical step for the biological functions of reactive sulfur species, including H_2S and polysulfides [32]. Similar to S-nitrosation, S-Persulfidation of target proteins could be reversed by the thioredoxin system [26, 32], which is closely linked to various neurological diseases [32, 33]. In this regard, we will summarize the current studies of protein S-Persulfidation induced by H_2S and polysulfides in the CNS, and discuss the advanced mechanistic concepts that underpin the signaling events of protein S-Persulfidation in neurodegenerative disorders.

2. PRODUCTION OF H_2S AND POLYSULFIDES IN THE CNS

H_2S, a weak acid, is slightly dissolved in water and easily dissociated into H^+, HS^-, and S^{2-} [15]. It is estimated that less than 20% of H_2S exists as H_2S and the remaining 80% as HS^- and S^{2-} under physiological conditions [11]. The expression of H_2S in mammalian brain tissues was first detected in 1989 [14, 34, 35]. Compelling evidence has demonstrated that H_2S biosynthesis is mainly regulated by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) or 3-mercaptopyruvate sulfurtransferase (3-MST) together with cysteine aminotransferase (CAT) [3, 21, 36-40]. Excepting the classic H_2S-generating pathway, D-cysteine can be metabolized by D-amino acid oxidase (DAO) to 3-mercaptopyruvate (3-MP), which is decomposed to H_2S by 3-MST [41]. The fourth pathway is predominantly observed in the kidney and cerebellum, where D-cysteine-derived H_2S protects the kidney tissues from the ischemia-reperfusion injury and cerebellar neurons from oxidative stress [42-45]. In the embryonic brain, the expression of CBS is low, and it will increase significantly from the prenatal period to the early postpartum period, and then reduces in the adult brain tissues [46]. The expressions of CBS are ubiquitously localized to the radial glia/astrocyte lineage, and CBS is indispensable for the differentiation of glial cells and astrocytes during brain development [46]. In the presence of various insults, such as ischemia-reperfusion injury or oxidative stress, the elevated CBS and H_2S in astrocytes may contribute to the recovery of injured neurons [46-49]. It is likely that the levels of CSE in the brain are very low; thus its contribution to neuronal H_2S production might be extremely minimal [50]. As CSE is not observed in the brain tissues, CBS seems to be the H_2S-generating enzyme in the brain tissues. Nevertheless, the production of H_2S is still detectable in the brain tissues from mice with a deficiency of CBS [51, 52]. This leads to a third pathway that the brain H_2S production can be regulated by 3-MST along with CAT [53, 54]. 3-MST is found to be expressed in pyramidal neurons in the cerebral cortex, Purkinje cells in the cerebellum, mitral cells in the olfactory bulb, and also in the hippocampus and retinal neurons [55, 56]. Although 3-MST is localized in both mitochondria and cytosol, the 3-MST/CAT pathway might mainly give rise to H_2S in the mitochondria [57, 58]. Interestingly, overexpression of 3-MST along with CAT may noticeably yield more bound sulfane sulfur, a cellular storage form of H_2S, but not increased in neuron cells expressing functionally defective mutant enzymes [55]. In addition, CBS overexpression only slightly raises the content of bound sulfane sulfur [55, 59]. These findings suggest that the 3-MST/CAT pathway rather than CBS may be a major resource for H_2S production in the brain. These published papers provide a novel perspective on the modulation of brain H_2S generation.

As to the metabolic ways of H_2S, it has been recommended that the fate of H_2S's catabolism may comprise several pathways, including methylation to methanethiol and dimethyl sulfide, reactions with metalloor cysteine-containing proteins in cells [60], and oxidation to sulfate (Fig. **1**) [11, 61]. As aforementioned, H_2S could also be stored as bound sulfane sulfur in cells, such as polysulfides and persulfides [18, 59]. However, this may be taken as an internal storage of H_2S rather than its metabolic catabolism. Compared with the biosynthesis of H_2S, the metabolic approaches of this gaseous mediator are not fully understood yet. Therefore, further validation is required to examine the exact metabolic turnover of H_2S in experimental settings of physiological and pathophysiological conditions.

Polysulfides, novel H_2S-derived molecules, are generated in mammal cells *via*either enzymatic or non-enzymatic pathways [21]. Besides, polysulfides could also be formed by the chemical interactions between H_2S and NO [62-64]. However, this crosstalk between H_2S and NO might be responsible for the production of polysulfides in mammalian tissues as such a reaction could occur under physiological conditions [63]. In the brain, oxidation of H_2S-derived polysulfides is revealed to activate the TRPA1 channels approximately 300 times more potent than H_2S in astrocytes [18]. Intriguingly, the same group also demonstrates that interactions of H_2S with NO generate polysulfides to activate the TRPA1 channels [65]. This study offers a novel insight into the potential mechanisms for polysulfides production upon an interaction between H_2S and NO. It is noted that the proportion of polysulfides produced by these pathways remains undefined, and the regulatory mechanism of polysulfides formation have yet to be fully elucidated. Therefore, a better understanding of polysulfide production and functions will certainly facilitate the therapeutic potential of H_2S-related compounds in neurological diseases.

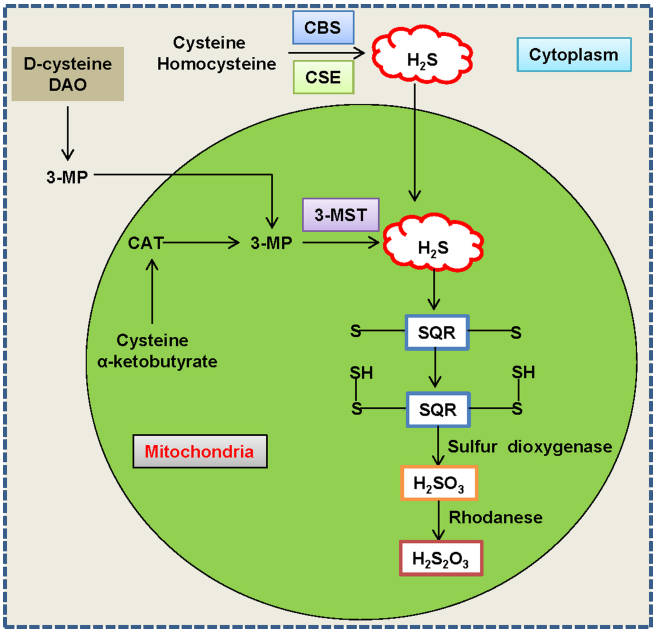

Fig. (1). The metabolic turnover of H_2S. The endogenous synthesis of H_2S is synthesized by CBS, CSE, 3-MST, D-cysteine with DAO. In the mitochondria, H_2S could be oxidized to persulfides by sulfide quinone oxidoreductase (SQR). The persulfides is then oxidized to sulfite (H_2SO_3) using sulfur dioxygenase, and H_2SO_3 is then metabolized to $H_2S_2O_3$ with the aid of rhodanese. The appropriate production and clearance of H_2S is essential for normal cellular functions. CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; 3-MST, 3-mercaptopyruvatesulfurtransferase; CAT, cysteine aminotransferase; DAO, D-amino acidoxidase; 3-mercapto pyruvate, 3-MP; SQR, sulfide quinone oxidoreductase. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. A BRIEF OVERVIEW OF PROTEIN S-PERSULFIDATION

S-Persulfidation (also termed as S-perthiolation or S--sulfhydration) is a modification of specific cysteine residues of target proteins by H_2S or polysulfides [24]. In the process of S-Persulfidation, the thiols could be transformed to persulfides, whereby R may be small molecules or proteins [31]. More studies have revealed that S-Persulfidation is a crucial post-translational modification that contributes to H_2S-mediated signal transduction in mammalian systems [44, 49]. In view of its chemistry characteristics, H_2S is directly unable to react with protein cysteine residues to give rise to persulfides. However, persulfides could be generated by the interactions of H_2S with oxidative cysteine residues, including disulfides, sulfenic acid, and nitrosothiol. Notably, the reactions of H_2S occur majorly through its anion (HS^-), the main form of H_2S in aqueous solutions. The reactions between H_2S and low molecular weight disulfides (including cysteine and glutathione disulfide) may produce mixture products in a slow and reversible manner [66]. It should be emphasized that the concentrations of protein disulfides and low molecular weight disulfides in the cytosol are quite low. As a result, the formation of polysulfides may be predominantly located in the endoplasmic reticulum rather than the cytosol [67].

A negative correlation is identified between cysteine residue activities and their acid dissociation constant (pKa) [23]. Typically, the S-Persulfidation sites are demonstrated to exist at cysteine residue sites with low pKa, albeit some S-Persulfidation modifications occur on cysteine residue sites with higher pKa [23]. In other words, the cysteine residue sites with low pKa seem to be more reactive with S-Persulfidation since they are present in the form of thiolate anions (S^-) under physiological circumstances. However, the low pKa cysteines are more susceptible to oxidants such as hydrogen peroxide (H_2O_2) that are responsible for the formation of sulfenic acid (SOH), sulfinic acid (SO_2H), or sulfonic acid (SO_3H) derivatives [68-70]. Under the H_2O_2 challenge, the intracellular persulfide contents are upregulated; this rise could be prevented by inhibition of CBS or CSE [71]. In this process, the production of protein sulfenic acids (P-SOH) could be further oxidized to sulfinic acids (P-SO_2H) and sulfonic acids (P-SO_3H), which are irreversible oxidized products of the original protein cysteine adducts [72, 73]. S-Persulfidation of target proteins might induce the formation of P-SSO_2H (perthiosulfinic) and P-SSO_3H (perthiosulfonic) under an oxidative environment [71]. Both of them could be reduced to thiols, thereby recovering their physiological functions in cells [31, 74]. Polysulfide species (such as H_2S_n or RS_nSH) are important molecules that could deliver the sulfur atom to the specific cysteine residues, causing protein S-Persulfidation and consecutive signal transduction events [18, 67, 75]. Kimura and colleagues have suggested that the endogenous polysulfides are primarily generated from 3-MP by 3-MST [76]. The same group further demonstrated that the endogenous polysulfides could be produced from H_2S by 3-MST and rhodanese [77]. Besides 3-MST, other sulfur transfer enzymes are also responsible for the production of endogenous persulfide species; such enzymes include sulfide quinone oxidoreductase (SQR), CSE, CBS, and cysteine desulfurase [31, 78, 79]. The cysteine could also be catalyzed by prokaryotic and mammalian cysteinyl-tRNA synthetases (CARSs), contributing to the formation of cysteine persulfide and polysulfides [80]. The production of polysulfides by CARSs could act as central mediators to induce endogenous protein S-Persulfidation.

In addition to S-Persulfidation, the cysteine residues might undergo other modifications, such as glutathionylation, palmitoylation, and nitrosylation. Therefore, it is of utmost importance to effectively distinguish the distinct post--translational modifications. Despite that, it is still a challenge to differentiate the persulfide group from the thiol group due to their analogous reactivity. There are several strategies for the detection of S-Persulfidation, such as modified biotin switch assay, maleimide assay, tag-switch method, or mass spectrometry assay, and these methods are well-reviewed [1, 6, 12, 50, 81-83]. As of yet, the specificity and sensitivity of the currently available methods for detecting S-Persulfidation might be questionable. Hence, it is needed to develop more novel and specific approaches for the ex-

act identification of S-Persulfidation. To date, it is highly possible that a combination of the currently available methods, together with mass spectrometry may provide accurate avenues for the detection of target protein S-Persulfidation.

4. S-PERSULFIDATION BY H_2S IN THE CNS

A variety of high-quality review papers have documented that H_2S protects against neurologic disorders, including traumatic brain injury, ischemia-reperfusion injury, stroke, AD, PD, Huntington's disease (HD), and Down syndrome [84-91]. It is expected that H_2S therapy might become a potential treatment regimen in the near future on the basis of pre-clinic and clinical studies. The favorable effects of H_2S on neurological diseases might be dependent on various mechanisms involving anti-oxidative, anti-inflammatory and anti-apoptotic effects, inhibition of endoplasmic reticulum stress and calcium overload [50]. Also, S-Persulfidation is recommended as an important model of action of H_2S where H_2S adds a sulfur atom to the cysteine residues of target proteins, which is being employed to investigate H_2S-mediated signaling pathways in various brain disorders [82]. Therefore, we will next focus on the roles of H_2S-mediated S-Persulfidation of target proteins in neuropathology.

4.1. S-Persulfidation by H_2S in PD

PD, a neurodegenerative disorder in the middle-elderly population, is manifested by motor system abnormalities [92, 93]. A growing number of studies have identified that the pathologies of PD involve dopamine neuron degeneration in the substantia nigra, early reduction of dopaminergic uptake in the frontal lobes, the cholinergic disturbance in both brainstem and corticostriatal pathways [94-97]. However, to date, there is no consensus on the etiopathogenesis of PD [98]. The ambiguous pathogenesis of PD leads to limited clinical treatment options, thus causing immeasurable socioeconomic burdens and family suffering [99, 100]. Therefore, it is urgent to investigate the potential mechanisms that underlie the evolution of PD, and it is essential to establish more standardized management of PD.

Accumulating lines of evidence demonstrate a favorable role of H_2S in the pathologies of PD, suggesting that H_2S may be a new frontier for the treatment of PD [8, 81, 101, 102]. The endogenous levels of H_2S are found to be down-regulated in the substantia nigra from 6-hydroxydopamine (6-OHDA)-induced PD rats or 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice [102, 103]. The decreased H_2S production may be ascribed to the diminished H_2S generating enzyme, CBS, in the substantia nigra of PD models [102]. Evidence for H_2S-mediated therapies against PD is achieved from the exogenous administration of H_2S-releasing donors [8, 81, 101, 102, 104-108]. Multiple mechanisms are speculated to be responsible for the therapeutic roles of H_2S in PD [107, 109, 110]. Among which, dysregulation of protein S-Persulfidation contributes to the pathogenesis of PD [12, 81]. As such, treatment with H_2S donors may be beneficial in the treatment of PD by stimulating the transsulfuration pattern [8]. As an E3 ligase, parkin is able to ubiquitinate the target proteins for proteasome-induced degradation; mutations of parkin lead to dopaminergic cell death during the progression of PD [111, 112]. Snyder and coworkers have confirmed that S-Persulfidated parkin is remarkably depleted in the brain tissues from PD patients [29], implying that disrupted parkin activities might be pathogenic in the development of PD. Its S-Persulfidation is associated with its normal catalytic activity, whereas nitrosylated parkin impairs its activity [29, 113]. It can be proposed that the restored S-Persulfidation of parkin by H_2S enhances its catalytic activity, thus exerting neuroprotective effects against PD (Fig. **2**) [29]. The protein p66Shc acts as a critical modulator in mitochondrial redox signaling, and its dysregulation is involved in the pathophysiology of PD [114-116]. Our group found that H_2S inhibited overproduction of mitochondrial reactive oxygen species (ROS) in H_2O_2/D-galactose-incubated SH-SY5Y cells by S-Persulfidation of p66Shc as mutation of cystein-59 within p66Shc abolished the antagonistic effects of H_2S on mitochondrial ROS production [117]. Given the importance of oxidative stress in the evolution of PD [118], our results suggest that p66Shc S-Persulfidation mediates the antioxidant actions of H_2S, thus protecting against the development of PD. Although the roles of H_2S-mediated protein S-Persulfidation in the pathogenesis of PD are still in its early stage, it is believed that intensive investigations will be inspired by such findings.

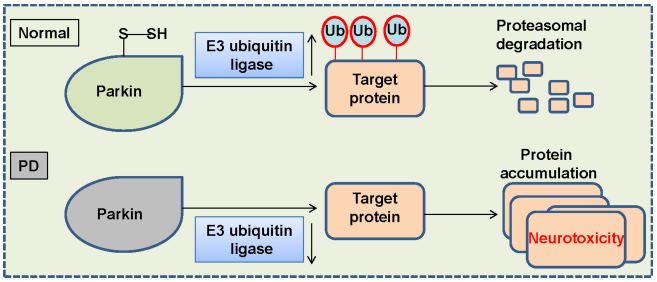

Fig. (2). Effects of S-Persulfidation on parkin in PD. Under healthy conditions, an E3 ubiquitin ligase, the parkin activity is enhanced by S-Persulfidation and induces target protein degradation caused by ubiquitination. In PD, the activity of parkin is decreased by S-Persulfidation of reactive cysteine residues within parkin, thus causing accumulation of target protein, such as a-synuclein, and subsequent neurotoxicity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.2. S-Persulfidation by H_2S in HD

HD is characterized by the expansion of polyglutamine repeats in the protein huntingtin within the corpus striatum [119, 120]. Mutant huntingtin triggers its aggregates, leading to disrupted cognitive and motor functions along with psychiatric disturbances [121]. The transcriptional factor specificity protein 1 (Sp1) is a potent regulator of CSE [122, 123], and this transcriptional factor is sequestered and inactivated by mutant huntingtin in early HD [124], resulting in cell redox imbalance because of depleted cysteine biosynthe-

sis. Indeed, the expression of CSE is diminished in HD brain tissues, indicating that H_2S might play an essential role in the pathophysiology of HD [125, 126]. Aside from the deficiency of cysteine biosynthesis, the dysfunction of cysteine and cystine transporters is also observed in HD, all of which are responsible for elevated ROS production in cells due to a cysteine deficit [127, 128]. In response to amino acid limitation and endoplasmic reticulum stress, CSE is also modulated by activating transcription factor 4 (ATF4), this signaling pathway is impaired in HD as aberrant cysteine biosynthesis and transport contribute to oxidative stress-induced neurotoxicity [129]. In addition, the expression of CSE, a critical enzyme in the metabolism of cysteine, is downregulated in brain tissues of spinocerebellar ataxia type 3 patients, whereas thevoverexpression of CSE suppresses the detrimental effects of spinocerebellar ataxia type 3, a disease that is caused by a CAG repeat expansion in the ataxin-3 (ATXN3) gene [130]. Most importantly, CSE overexpression recovers protein S-Persulfidation and inhibits oxidative stress, thereby improving spinocerebellar ataxia type 3-associated tissue degeneration [130]. On the basis of these observations, we speculated that appropriate regulation of the reverse transsulfuration pathway is essential for the maintenance of cellular redox homeostasis, thus conferring neuroprotection. Although not conducted experimentally, S-Persulfidation of cysteine residues within the target proteins, such as huntingtin and ATXN3, most likely mediates the protective effects of H_2S against HD, which may merit further investigation.

4.3. S-Persulfidation by H_2S in AD

AD is a prevalent neurodegenerative disease that leads to cognitive dysfunction and memory loss in affected individuals [131, 132]. The pathophysiology of AD is closely associated with the generation of neurofibrillary tangles and accumulation of amyloid plaques, especially in the cerebral cortex and the hippocampus [133, 134]. Aggregation of β-amyloid (Aβ) and Tau proteins could induce the formation of amyloid plaques and neurofibrillary tangles, respectively [135, 136]. Mutations of the amyloid precursor protein (APP), presenilin-1 and 2 are frequently encountered in AD [137]. APP undergoes sequential proteolysis with the aid of proteases (also termed secretases), including α, β and γ secretases [138]. Similar to other several neurodegenerative diseases, AD is also tightly associated with elevated oxidative stress [139-141]. Increased lipid peroxidation, DNA damage and protein nitration are found to be engaged in the progression of AD [142-145]. Besides, mitochondrial dysfunction, transcriptional dysregulation, and aberrant nitrosylation occur at multiple levels in the progression of AD [33]. Regardless of the intensive research on the underlying mechanisms of AD, its etiologies are not fully elucidated.

H_2S is proposed to be an important contributor to the development of AD [146-148]. It is reported that the high levels of homocysteine (a precursor of cysteine when acted on by CBS and CSE) are taken as a high risk factor for AD progression. It is reasonable that the decreased CBS activity accounts for the abnormal homocysteine deposition [149, 150]. The CBS-mediated homocysteine transsulfuration pathway is responsible for the development of AD [151], and the formation of H_2S is actually hampered because of the disturbed CBS-mediated homocysteine transsulfuration in patients with AD [149, 152, 153]. As a matter of fact, the plasma level of H_2S tends to be lower in AD patients and the decreased H_2S level may be correlated with the severity of AD [151]. A number of studies have confirmed that H_2S plays a protective role in the management of AD. Schreier *et al.*, have found that H_2S exerts a strong ability to counteract the cytotoxic lipid oxidation product 4-hydroxynonenal (HNE) in SH-SY5Y neuronal cells [154], an elevated cytotoxic in the brain tissues of severe AD patients [155, 156]. H_2S donor sodium hydrosulfide (NaHS) is documented to improve spatial learning and memory impairment in a mouse model of AD [157]. Furthermore, the administration of NaHS slows down the development of experimental AD models *via*regulation of oxidative and nitrosative stress, inflammation and apoptosis [158]. A myriad of studies have also demonstrated that H_2S influences Aβ formation and toxicity through various ways, such as APP glycosylation, γ secretase, cell cycle re-entry, inflammation response, and mitochondrial member potential [52, 159-162]. Thus, H_2S might represent a new entity to delay AD progression through numerous signaling pathways. Nevertheless, it is noteworthy to mention that the precise roles of H_2S in the pathogenesis of AD remain largely uncertain. Therefore, more studies are needed before its transformation to a clinical therapy for AD.

Neuroinflammation and excessive Aβ deposition synergistically contribute to the development and progression of AD [163]. The intervention, neuroinflammation and Aβ accumulation might provide a potential approach for AD therapy [163, 164]. Signal transducer and activator of transcription 3 (STAT3) is revealed to participate in neuroinflammation and Aβ pathogenesis during the progression of AD [165, 166]. Cathepsin S (Cat S) is predominantly expressed in the microglial cells and its inhibition produces neuroprotective effects in AD [167, 168]. We recently found that H_2S attenuated adenosine triphosphate (ATP)-induced ROS production, inflammation response, and Aβ1-42 generation *via*inactivation of STAT3 and Cat S in both BV-2 and primary cultured microglial cells [169]. Moreover, we demonstrated that the S-Persulfidation of Cat S at cysteine-25 was required for H_2S-mediated effects in the context of ATP [169]. Our results provided a novel understanding of the possible contribution S-Persulfidation of Cat S to the neuroprotective effects of H_2S. In addition to the direct S-Persulfidation of Cat S, the Akt is S-Persulfidated at cysteine-77 by H_2S, and Akt S-Persulfidation is also detected in the postmortem brains from AD patients [170]. Very recently, in a transgenic knockin mouse that lacked sulfhydrated Akt, decreased dendritic spine loss and improved cognitive dysfunctions were observed by reducing dendritic localization of human Tau is phosphorylated at S199 [170], representing a novel posttranslational modification of Akt, which primarily

contributes to synaptic dysfunction in AD. These above findings suggest that S-Persulfidated proteins, such as Cat S and Akt, might exert a vital role in the pathological functions of AD.

A common feature of AD is aggravated oxidative burden in neuronal cells, and supplementation of H_2S donor prevents neuronal cell death induced by oxidative stress [47, 171, 172]. H_2S is also able to relieve oxidative injury by stimulating glutathione biosynthesis and aldehyde dehydrogenase 2 expressions [173, 174]. Additionally, the upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) by H_2S plays a vital role in the maintenance of cellular redox balance [175, 176]. As described earlier, H_2S induces the increased Nrf2 activation by inducing S-Persulfidation of Keap1 and subsequent Keap1/Nrf2 disassociation [177-182]. However, whether Keap1 S-Persulfidation by H_2S could be extrapolated to the treatment of AD requires in-depth research.

The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) are key elements for fast excitatory synaptic transmission, and their dynamic regulation is majorly responsible for adaption of the CNS to environment stimulations [183, 184]. The dysfunction of AMPARs is one of the pathological factors for the development of AD [185]. A downregulation of AMPAR GluR1 subunit expression is a hallmark in pathological molecular alterations in AD [186]. Restoration of AMPAR GluR1 subunit or inhibition of AMPAR endocytosis may be promising new strategies to improve spatial memory deficits in the Tg2576 AD mouse model [187, 188]. Bath application of H_2S and Na_2S_4 obviously promotes the surface insertion of AMPAR GluR1 subunit in the hippocampal tissues, and this is abolished in the presence of dithiothreitol (DTT), hinting an involvement of the S-Persulfidation-dependent mechanism [189]. However, AMPAR is not directly S-Persulfidated by H_2S, but the phosphorylation levels of GluR1 at serine-831 and serine-845 sites are activated by H_2S [189]. Despite this, H_2S could directly increase the S-Persulfidation levels of postsynaptic signal molecules that control GluR1 phosphorylation, including protein phosphatase type 2A (PP2A), protein kinase A (PKA), protein kinase C, and calcium/calmodulin-dependent protein kinases II (CaMKII) [189]. This observation suggests that H_2S promotes the surface delivery of AMPARs *via*S-Persulfidation-mediated mechanisms. In this regard, H_2S-mediated S-Persulfidation of specific reactive thiols in target postsynaptic proteins indirectly regulates AMPARs in the hippocampus area, which may provide a new perspective of the pathophysiological functions of H_2S in AD. Although the mechanisms that underlie S-Persulfidation-dependent regulation of kinase activity remain unclear, H_2S may stimulate phosphorylation of these kinases *via*S-Persulfidation of themselves.

4.4. S-Persulfidation by H_2S in Brain Memory Functions

Memory impairment is present in several neurodegenerative disorders, which is induced by numerous pathophysiological mechanisms, including neuroinflammation and aging [190-193]. IL-1β, a well-known pro-inflammatory cytokine, is widely observed in the brain [194, 195], and brain-derived IL-1β plays a dispensable role in the process of learning and memory *via*regulation of postsynaptic density 95 (PSD95), a critical scaffold protein that regulates synaptic stability, strength, and plasticity [196-199]. The brain memory impairment in response to IL-1β is mediated by CBS-generated H_2S production as gene ablation of CBS ameliorates IL-1β-induced neurological impairments in mice [200]. At the molecular level, the induction of H_2S by IL-1β modifies glyceraldehyde- 3-phosphate dehydrogenase (GAPDH) essentially *via*S-Persulfidation at cysteine-150, which enhances the binding of the E3 ligase Siah to the S-Persulfidated GAPDH, thereby inducing ubiquitination-mediated degradation of PSD95 in IL-1β-induced cognitive dysfunction [200]. GAPDH can not be S-Persulfidated by IL-1β when CBS is absent; the degradation of PSD95 will be less and IL-1β-triggered synaptic dysfunction and memory impairment are markedly relieved [200]. This study establishes a novel signaling pathway whereby IL-1β evokes the degradation of neuronal PSD95 by GAPDH S-Persulfidation in an H_2S-dependent manner (Fig. **3**). The S-Persulfidation of GAPDH by H_2S may provide a therapeutic strategy for the prevention and treatment of neurological disorders-related memory impairment whereby the overproduction of IL-1β manifests the pathologies of such diseases.

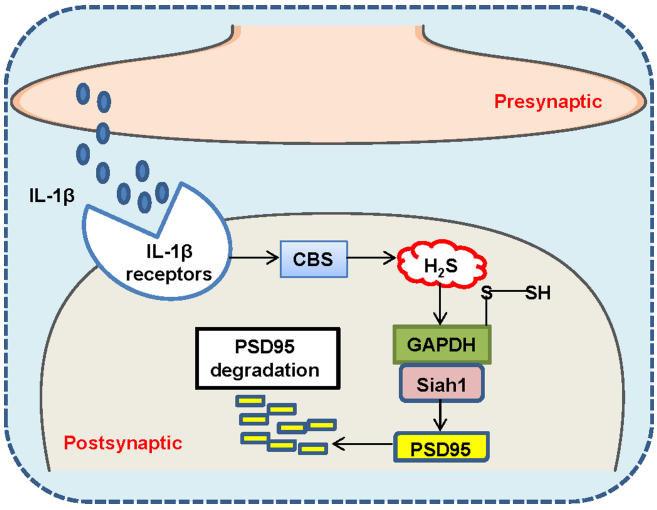

Fig. (3). S-Persulfidation of GAPDH mediates synaptic function. The proinflammtory cytokine IL-1β upregulates CBS-generating H_2S production, and leads to S-Persulfidation of GAPDH. This event results in the binding of GAPDH to siah1, an E3 ubiquitin ligase, which triggers PSD95 toward for degradation. The dysregulation of PSD95 plays an important role in learning and memory dysfunction. CBS, cystathionine β-synthase; IL-1β: interleukin-1β; GAPDH: glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase; PSD95: post-synaptic density 95 protein; Siah1: seven in absentia homolog-1. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

LTP, a cellular model for memory, is regulated by various redox signaling molecules in which they act as dou-

ble-edged swords [201-203]. In the presence of several thiol agents, such as DTT and glutathione, the LTP is increased and the aging-associated synaptic dysfunctions are enormously reversed [204-206], suggesting that the endogenous reducing agents might serve as a physiological mediator in synaptic plasticity. The D-serine released from astrocytes is one of the governing coagonists of synaptic NMDARs by stimulating its glycine modulatory sites [207-209]. Serine racemase (SR) is one of the main synthetases of D-serine [210]. The sulfide generation and protein S-Persulfidation are induced after high-frequency stimulation, which are necessary for NMDARs-dependent induction of LTP *via*the maintenance of D-serine [211]. The S-Persulfidation and disinhibition of SR by both H_2S and polysulfides stimulate NMDARs-dependent LTP; this may be beneficial for hippocampus-dependent memory (Fig. **4**) [211]. Actually, the levels of H_2S and SR S-Persulfidation are diminished significantly in aged rats, and exogenous administration of H_2S restores the S-Persulfidation of SR, followed by upregulation of D-serine and improvement of age-related deficits in hippocampus LTP [211]. In summary, this study suggests that H_2S-induced posttranslational modification of SR appears to play a pivotal role in NMDARs-dependent synaptic plasticity, and H_2S-based therapies may be effective for the management of memory loss in aging animals (Fig. **4**). Excepting the S-Persulfidation of SR, other mechanisms underlying H_2S-mediated regulation of D-serine await in-depth research. For example, activation of TRPA1 by polysulfides may promote the release of D-serine and NMDARs-dependent LTP [18, 212, 213]. These findings allow us to suppose a possible role for H_2S-linked TRPA1 S-Persulfidation in synaptic plasticity and memory function; this hypothesis is further confirmed by a finding that polysulfides activate the TRPA1 channels by S-Persulfidating cysteine residues within the channels, thereby inducing Ca^{2+} influx in rat astrocytes (Fig. **4**) [18, 28, 44].

4.5. Roles of H_2S in other Neurological Disease

Amyotrophic lateral sclerosis (ALS), a detrimental neurodegenerative disease, is an important cause of the selective degeneration of upper and lower motor neurons [214]. Recently published results have revealed that abnormal autophagy, vesicle trafficking, RNA metabolism, and cytoskeleton dynamics act as functional pathways in ALS pathogenesis [215]. Human genetic studies have demonstrated that mutation of Cu/Zn superoxide dismutase (SOD1) gene mainly aggregates and causes motor neurons death in the process of ALS [216, 217]. The levels of H_2S are higher in the spinal fluid of ALS patients, and the upregulated levels of H_2S are also observed in the tissues from mice bearing the familial ALS mutation SOD1G93A [218]. In spinal cord cultures, H_2S is toxic for motor neurons through increasing intracellular Ca^{2+} levels [218]. Interestingly, pharmacological inhibition of H_2S obviously enhances the lifespan of female mice bearing the familial ALS mutation SOD1G93A, but not in male ALS mice [219]. This observation suggests that the relationship between gender and H_2S needs to be adequately considered in the development of ALS. These studies unravel H_2S as an important mediator of motor neuron damage in the setting of ALS.

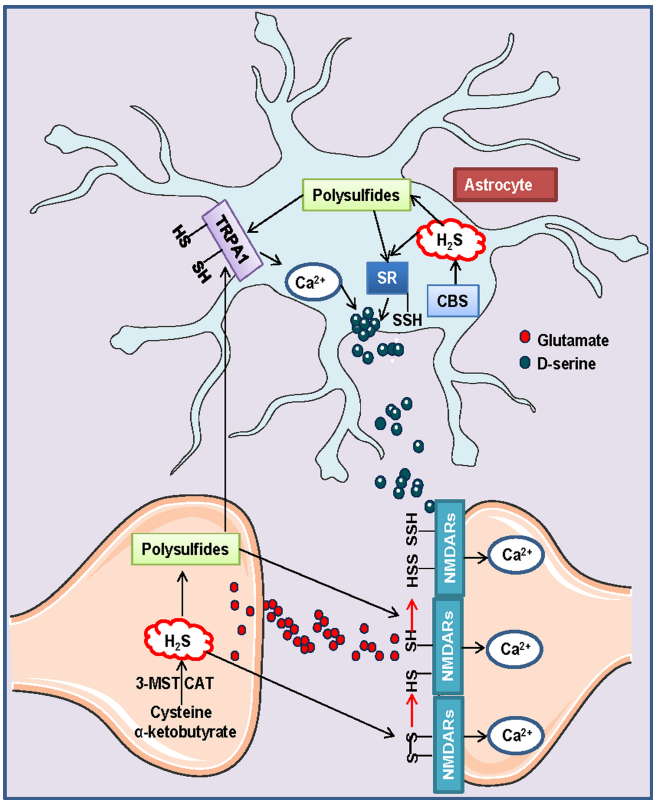

Fig. (4). A putative mechanism of H_2S/polysulfides involving in the induction of LTP. The cysteine disulfide bond of NMDARs is reduced by H_2S, thus enhancing its activity. Polysulfides derived from H_2S further induce the formation of bound sulfane sulfur in the cysteine residues of NMDARs and further facilitate NMDARs-dependent induction of LTP. In astrocyte, activation of TRPA1 by polysulfides derived from H_2S may promote the release of D-serine and NMDARs-dependent LTP, this effect may be mediated by S-Persulfidating the cysteine-422 and cysteine-622 of TRPA1. Also, the S-Persulfidation and disinhibition of SR by both H_2S and polysulfides stimulate NMDARs-dependent induction of LTP, and SR is one of the main synthetases of D-serine. NMDARs: N-methyl-D-aspartate subtype glutamate receptors; TRPA1: transient receptor potential cation channel subfamily A member 1; CBS, cystathionine β-synthase; 3-MST, 3-mercaptopyruvate-sulfurtransferase; CAT, cysteine aminotransferase; SR: serine racemase; LTP: long-term potentiation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In accordance with the results obtained from ALS, the elevated H_2S generation is also detected in Down syndrome, a disease manifested by trisomy of chromosome 21 (a chromosome on which CBS is located) [220]. The levels of urine thiosulfate, a catabolic product of H_2S, are also upregulated in subjects with Down syndrome [221]. The expression of CBS is localized in astrocytes adjacent to the senile plaques,

indicating involvement of H_2S in this disease process [220]. A recent report has shown that overproduction of H_2S disrupts Complex IV activity, mitochondrial electron transport, ATP synthesis and fibroblasts cell proliferation, inducing significant destruction in mitochondrial function of Down syndrome [222]. As a consequence, inhibition of CBS-derived H_2S offers an attractive approach for the pharmacological treatment of Down syndrome-associated mitochondrial dysfunction. It is concluded that higher concentrations of H_2S may be detrimental in both ALS and Down syndrome. However, the S-Persulfidation-related mechanisms by H_2S are scarce in both diseases. At the molecular level, we should develop proteomic approaches to solve the sites of H_2S-mediated S-Persulfidation and its interplay with the pathogenesis of ALS and Down syndrome.

It has been accepted that H_2S promotes tumor proliferation in some types of cancer, while it inhibits tumor cell growth in other cancer types [61]. Glioblastoma is a malignant brain tumor type with a poor prognosis [223]. Currently, effective and sufficient therapeutic strategies for glioblastoma are unavailable due to the poor understanding of its pathological mechanisms [224]. The roles of H_2S in glioblastoma development and progression are recently disclosed by cell and animal experiments. Injection of H_2S donor NaHS aggravates the physical symptoms of glioma-bearing rats *via*upregulating hypoxia-inducible factor 1α (HIF-1α) expression and neovascular formation [225]. Incubation of C6 glioma cells with NaHS (400 μM) facilitates the cell proliferation and inhibits cell apoptosis, and this may be mediated by the p38 MAPK/ERK1/2-COX-2 pathway [226]. The tumor-promoting effects of H_2S are challenged by a finding that the administration of NaHS inhibits cell proliferation and induces apoptosis of C6 gliomas cells through the p38 MAPK signaling pathway [227]. In accordance, the silencing of CBS, a major H_2S-generating enzyme in the brain, promotes the growth of human glioma tumor cells [228]. However, whether the level of CBS is altered in human glioma tissues is not examined. Considering that 3-MST expression is obviously enhanced in gliomas tissue [229], we can not exclude a possibility that 3-MST, a crucial enzyme for H_2S production in the brain system, may be upregulated on CBS silencing, thus compensatory H_2S from 3-MST might promote the growth of glioma cells in the absence of CBS. However, the direct effects of 3-MST on glioma behaviors are unknown. Therefore, the exact roles of CBS and 3-MST in glioma development will be an interesting field to explore in the near future. Doxorubicin exerts cytotoxicity toward rat C6 glioma cells [230], this effect may be attributed to an elevation of H_2S contents as the pro-apoptotic effects of H_2S at high millimolar doses are accompanied by an increase in the generation of ROS and a decrease in the gluthatione concentration, leading to activation of the caspase 3-mediated apoptotic pathway [231-233]. All in all, the effects of H_2S on glioma biology remain controversial, and these unsolved matters need to be answered in further studies. Overwhelming evidence suggests that H_2S-mediated S-Persulfidation of target proteins are demonstrated to be involved in a plethora of signaling transduction during the development and progression of different types of cancer [61]. Unfortunately, this post-translational modification paradigm is unexplored in H_2S-mediated effects on glioblastoma. Consequently, H_2S-mediated protein S-Persulfidation that is relevant to glioblastoma biology will become a focus of future research.

In agreement with the above findings, although H_2S is an important dominator in the pathologies of stroke and traumatic brain injury from accumulative studies [10, 52, 88], no extensive investigations are performed to determine the possible effects of H_2S-mediated S-Persulfidation of target proteins in both neurodegenerative diseases. It is shown that sulfane sulfur in astrocytes is obviously lower in stroke-prone spontaneously hypertensive rats, and this decrease is further diminished by CBS inhibitor [234], implying that the formation of S-Persulfidation by H_2S may be involved in this disease development. More original experiments are warranted to provide novel insights into how potential S-Persulfidation on specific cysteine residues by H_2S could induce benefits to the pathological changes in stroke and traumatic brain injury.

5. S-PERSULFIDATION BY POLYSULFIDES IN THE CNS

Polysulfides are identified to be abundantly expressed in the brain, and exhibit a higher oxidation capability than the sulfur atom in H_2S as they contain sulfane sulfur [25, 65]. The levels of polysulfides in the brain are found to be in micromolar concentrations using high-performance liquid chromatography (HPLC) analysis, this dose of polysulfides is enough to activate the TRPA1 channels [18]. Even though it is still unclear whether polysulfides are actively transported into cells, polysulfides are known to easily pass through the plasma membranes [18, 23]. Similar to H_2S, polysulfides are also involved in neurodegenerative diseases, including PD, HD, ethylmalonyl encephalopathy, and even in brain cancer [29, 235, 236].

Studies have established that polysulfides may directly target several molecules, such as Keap1/Nrf2 complex [237], a tumor suppresser PTEN [23], GAPDH, an enzyme that catalyzes glycolysis [238], and a vascular tension regulator protein kinase G1α [239]. Apart from being important signaling molecules, polysulfides also function as a neuroprotective modulator by activating the channels, enzymes, and transcription factors through S-Persulfidation of the target proteins [28, 42, 50, 240]. Polysulfides activate the TRPA1 channels by S-Persulfidated cysteine residues within the channels, thereby inducing Ca^{2+} influx in rat astrocytes (Fig. **4**) [18]. The actions of polysulfides are attenuated by inhibitors of TRPA1 or silencing of TRPA1, implying that the responses of polysulfides are attributed to TRPA1 activation. Once activated in astrocytes, the release of D-serine to the synapse enhances the activity of NMDARs and facilitates the induction of LTP [212, 241].

The imbalance in cellular redox state is an important reason for oxidative stress, which is also a common etiological

factor in neurological diseases [242, 243]. Under normal homeostatic conditions, Keap1 is a redox-sensitive ubiquitin ligase substrate adaptor that represses the activity of the transcription factor Nrf2 [178, 181, 244]. Upon oxidative stress, Keap1 S-sulfhydration by polysulfides induces Nrf2 dissociation from Keap1, which upregulates the nuclear translocation of Nrf2 and the subsequent expressions of antioxidant genes [237], thus conferring beneficial effects against oxidative injury in Neuro2A cells. In addition, the activation of the PI3K/Akt pathway is necessary for polysulfides for the translocation of Nrf2 to the nucleus [237]. With the growing identification of anti-oxidative protein, S-sulfhydration, by polysulfides, significant advancements in the roles and mechanisms of polysulfides in modulating cellular responses to oxidative stress in the neurodegenerative process will be made.

A recent study has detected the higher levels of polysulfides in glioblastoma-bearing ipsilateral hemispheres, but not in glioblastoma-free control hemispheres using surface-enhanced Raman spectroscopy [235]. Although it is still unknown, for the accurate molecular entities of polysulfides in glioma cells, they might be involved in the pathologies of glioma. GAPDH is an enzyme that catalyzes glycolysis, an orchestrated process in the development of chemotherapy resistance in some types of malignancies, including glioma [245-248]. For this reason, inhibition of GAPDH activity has gained considerable attention as an attractive strategy for cancer therapy [249, 250]. Interestingly, polysulfides treatment significantly inhibits the activity of GAPDH, by S-Persulfidation of GAPDH at cysteine-156 and cysteine-247 [238]. Accordingly, it will be exciting to know whether targeting S-Persulfidation of GAPDH by polysulfides alters the glycolysis process in brain gliomas. This hypothesis, therefore, requires further research. Furthermore, polysulfides are shown to inhibit the activity of PTEN by inducing the generation of a cysteine disulfide bond [23]. The development and progression of glioblastoma are intimately related to abnormal PTEN expression [251], as dysregulated PTEN may participate in glioma initiation, progression, and treatment resistance [252, 253]. On these grounds, the protein S-Persulfidation by polysulfides may be an attractive therapeutic avenue for the prevention of brain gliomas. Further investigations are needed to verify this assumption.

CONCLUSION AND FUTURE PERSPECTIVES

Over the last decade, an important post-translational modification induced by H_2S and polysulfides, named S-Persulfidation, has been well accepted. S-Persulfidation is a novel redox pathway to exhibit diverse biological processes in H_2S/polysulfides signaling. There is no doubt that the studies on protein S-Persulfidation are increasingly proposed as the future research direction in the field of gasotransmitters for the coming years. However, there are still several issues to be resolved. (1) The production and metabolism pathways of polysulfides in the brain are largely unknown. Solving this problem might provide novel insights into the biochemistry of H_2S and facilitate the therapeutic application of H_2S-derived compounds. (2) In the process of protein S-Persulfidation, both small-molecule based persulfides and protein persulfides are correspondingly generated, and such species are highly reactive. The metabolic regulation of these species is largely unknown. (3) It is interestingly to know how brain cells differentially use H_2S and polysulfides at the appropriate time points. (4) More scientific approaches with higher specificity and sensitivity are urgently required to detect protein S-Persulfidation. (5) More protein cysteine sites of S-Persulfidation are necessary to be clarified in the CNS. (6) The interactions of S-Persulfidation with other post-translational modifications, such as S-nitrosylation, deserve to be elucidated in neuropathy. (7) The clinical relevance of S-Persulfidation in neurological disorders needs to be explored in detail.

It is anticipated that a comprehensive understanding of protein S-Persulfidation will be helpful in identifying the underlying mechanisms in which S-Persulfidation could benefit various neurological disorders. Importantly, the S-Persulfidated proteins could serve as potential targets for the therapeutic intervention of neurological disorders, thus advancing the development of H2S/polysulfides-based agents in the near future.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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