Editorial

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Protein persulfidation: The missing link in Alzheimer's disease defense mechanisms

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SUMMARY: Despite decades of research dominated by the amyloid-beta hypothesis, clinical treatment of Alzheimer's disease (AD) has yet to achieve a decisive breakthrough. This editorial advances an alternative pathological paradigm: the collapse of endogenous hydrogen sulfide (H_2S) signaling represents a central failure point in the brain's intrinsic defense mechanisms against AD. We dissect the molecular cascade triggered by cystathionine γ-lyase (CSE) deficiency, focusing on how reduced persulfidation of glycogen synthase kinase 3β (GSK3β) directly promotes Tau hyperphosphorylation and subsequent neuronal injury. A critical message of this commentary is the need to dispel the oversimplified notion that sulfide supplementation alone can confer neuroprotection. Because H_2S works within a narrow therapeutic window and has complex hormetic effects, untargeted dietary or environmental exposure cannot match the spatiotemporal precision of endogenous signaling. Instead, it may increase the risk of toxicity. By integrating analyses of transsulfuration metabolism, mitochondrial function, and nutritional status, we propose a precision medicine framework centered on brain-targeted delivery technologies and metabolic correction strategies to selectively restore compromised H_2S signaling networks. This conceptual shift marks a new direction in AD research, shifting the focus from clearing toxic protein aggregates to restoring endogenous neuronal resilience.

Keywords: gasotransmitter, thiol modification, neurofibrillary tangles, homocysteine metabolism, S-sulfhydration, blood-brain barrier

1. Introduction

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder worldwide, has proven far more mechanistically complex than early investigators anticipated (*1*). Although the amyloid-beta (Aβ) hypothesis has dominated the research agenda for the past three decades, recent immunotherapies targeting Aβ have achieved some notable advances. However, their clinical outcomes have remained underwhelming (*2*). This reality compels us to re-examine the pathological underpinnings of AD and to identify novel intervention targets (*3,4*). Against this backdrop, research into endogenous hydrogen sulfide (H_2S) signaling is uncovering a previously overlooked neuroprotective mechanism, offering fresh perspectives on both the fundamental nature of AD and potential therapeutic strategies.

2. A paradigm shift in our understanding of H_2S

For much of its history, H_2S was regarded simply as a foul-smelling toxic gas, and its neurotoxic properties were well documented (*5*). However, a series of landmark studies beginning in the early 2000s fundamentally transformed our view of this molecule. H_2S is now recognized as the third endogenous gasotransmitter, following nitric oxide (NO) and carbon monoxide (CO), and plays indispensable regulatory roles in the cardiovascular, nervous, and immune systems (*6*).

As a researcher with longstanding experience in neurodegenerative diseases, I believe the pivotal breakthrough in H_2S signaling has been the elucidation of its unique signal transduction mechanism: protein persulfidation. Unlike conventional post-translational modifications such as phosphorylation or acetylation (*7*), persulfidation reversibly converts the thiol group (-SH) of cysteine residues to a persulfide group (-SSH), thereby fine-tuning the activity and function of target proteins (*8*). The reversibility of this modification enables cells to

respond rapidly to environmental changes. Persulfides exhibit greater nucleophilicity and reducing capacity than thiols, which makes them a critical line of defense against oxidative stress.

3. The CSE-H_2S-GSK3β-Tau axis

As early as 2002, researchers reported that H_2S levels were significantly reduced in brain tissue of AD patients (*9*). However, the functional significance of this finding remained unclear for many years. In 2021, the research team led by Solomon H. Snyder at Johns Hopkins University published a landmark study in *Proceedings of the National Academy of Sciences*, which systematically elucidated the critical protective mechanisms of H_2S in AD from the perspective of enzyme activity regulation (*10*). This study delineated the molecular cascade linking protein persulfidation to the core pathological processes of AD, providing important theoretical insights into disease pathogenesis.

The key findings of this study can be summarized at three levels. At the level of enzyme activity regulation, wild-type Tau protein directly binds to cystathionine γ-lyase (CSE) and enhances its catalytic activity. In contrast, the AD-associated Tau P301L mutant lacks this binding capacity, leading to a marked reduction in local H_2S production. At the level of signal transduction, H_2S effectively inhibits glycogen synthase kinase 3β (GSK3β) activity by persulfidating critical cysteine residues. In cortical tissue from patients with AD, GSK3β persulfidation is markedly reduced, which in turn promotes Tau hyperphosphorylation, a central molecular event in neurofibrillary tangle formation. At the level of therapeutic intervention, long-term treatment with the slow-releasing H_2S donor Na-GYY4137 led to approximately 50% improvement in both cognitive and motor functions in 3xTg-AD transgenic mice. This treatment was accompanied by a restoration of overall brain persulfidation levels (*10*).

These findings clarify the fundamental nature of H_2S signaling abnormalities in AD. The abnormality does not reflect a simple deficiency of a signaling molecule, but instead indicates a systemic failure of endogenous protective mechanisms. Under normal physiological conditions, neurons continuously generate H_2S *via* CSE to maintain GSK3β in a persulfidated state, thereby suppressing Tau hyperphosphorylation. During the pathological progression of AD, multiple factors act in a coordinated manner, including CSE downregulation, dysfunction of the transsulfuration pathway, and oxidative stress-induced reversal of persulfidation. Together, these changes compromise the protective regulatory circuit and ultimately establish a vicious cycle (Figure 1).

4. Endogenous versus exogenous H_2S

Some have suggested that inhaling H_2S-containing gases or supplementing the diet with sulfur-containing compounds could prevent AD. As a neuroscience researcher, I must state unequivocally that this notion not

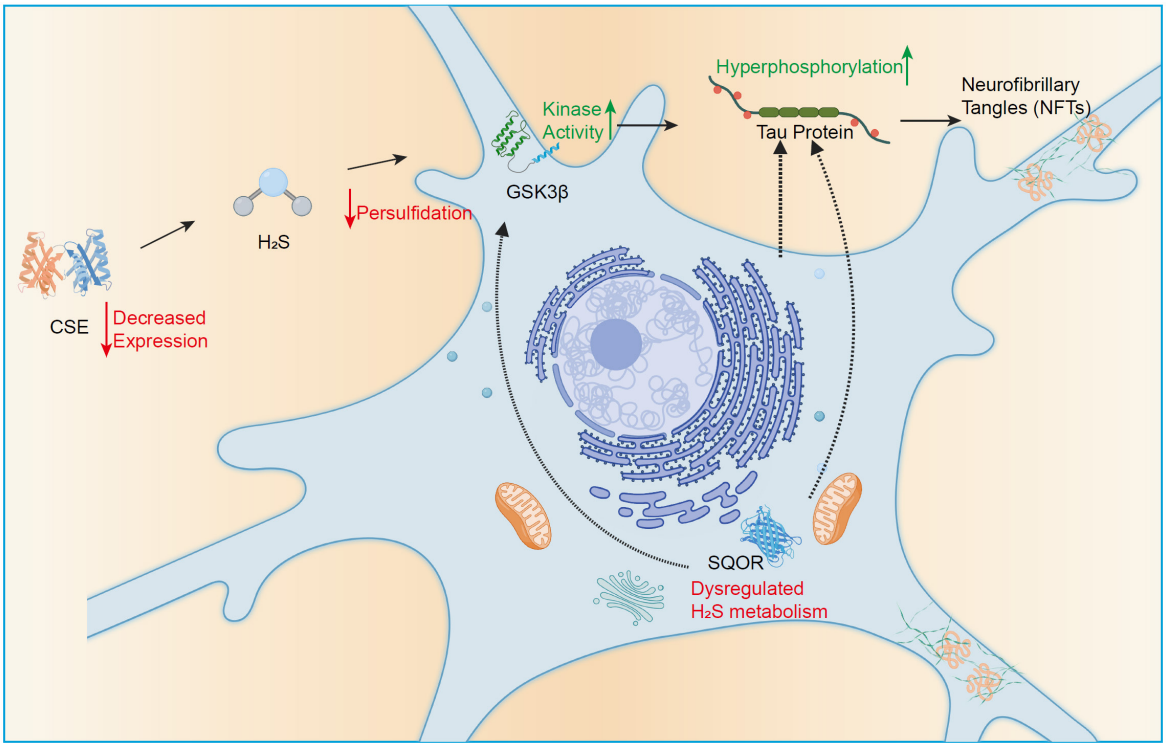

Figure 1. Molecular mechanisms underlying H_2S-mediated neuroprotection and its dysregulation in Alzheimer's disease. CSE: cystathionine γ-lyase; GSK3β, glycogen synthase kinase 3β; SQOR: Sulfide:quinone oxidoreductase.

only lacks scientific support but also risks endangering public safety through misinformation. A strict distinction must be drawn between uncontrolled environmental or dietary exposure and precisely engineered pharmacological donors. The former readily induces toxicity because of its unpredictable concentrations and lack of targeting. The latter, exemplified by GYY4137 and brain-targeted nanomedicines currently under development, is designed to restore endogenous signaling levels and represents an entirely different therapeutic strategy.

Endogenous and exogenous H_2S differ in fundamental ways. First, endogenous H_2S is produced by specific cell types at defined subcellular locations and acts directly on neighboring target proteins (*11,12*). The spatial proximity of CSE to GSK3β is a prerequisite for persulfidation to occur (*10*). Inhaled exogenous H_2S cannot be directionally delivered to specific intraneuronal sites, let alone replicate such precise molecular interactions. Second, H_2S exhibits classic hormesis. At physiological concentrations in the nanomolar to low micromolar range, it exerts robust cytoprotective effects, whereas at higher concentrations it exhibits neurotoxic effects (*13*). According to the U.S. Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR), exposure to 100–150 ppm H_2S causes olfactory fatigue, while concentrations above 500 ppm can induce unconsciousness or death within minutes (*14,15*). Inhalation exposure cannot finely control brain H_2S levels and readily exceeds the narrow physiological window. Third, endogenous H_2S production is dynamically coupled to neural activity and metabolic state, following precise temporal patterns that participate in synaptic plasticity and long-term potentiation (LTP) (*16*). Exogenous exposure cannot replicate this dynamic regulation matched to physiological demand.

Furthermore, it must be stressed that H_2S produced by intestinal sulfate-reducing bacteria is metabolically compartmentalized from brain H_2S signaling. The vast majority of gut-derived H_2S is cleared by sulfide oxidation pathways in the intestinal mucosa and liver; circulating free H_2S concentrations remain exceedingly low and are unlikely to cross the blood-brain barrier (BBB) effectively (*17*). While direct evidence that gut-derived gaseous molecules traverse the BBB into the parenchyma is lacking, whether they indirectly modulate brain function *via* the neuroimmune axis remains an open question. For now, intestinal H_2S should not be regarded as a direct source of cerebral H_2S signaling.

5. A metabolic bridge linking nutritional status to neuroprotection

The homeostasis of H_2S depends not only on local enzyme activity but also on the systemic supply of metabolic substrates. Endogenous H_2S synthesis relies on the transsulfuration pathway. This pathway converts homocysteine (Hcy) to cysteine, which serves as the direct substrate for H_2S production (*18*). Within the cerebrovascular system, multiple cell types utilize cysteine to generate H_2S. Cystathionine β-synthase (CBS) primarily catalyzes H_2S production in the brain parenchyma. CSE serves a similar role in the cerebral microvasculature. In addition, 3-mercaptopyruvate sulfurtransferase (MST) contributes to H_2S biosynthesis in neurons and mitochondria (*19*). Epidemiological evidence has established hyperhomocysteinemia as an independent risk factor for AD. The early Framingham Study reported that each 5 μmol/L increase in plasma Hcy was associated with an approximately 40% higher risk of AD (*20,21*). More recent meta-analyses, however, suggest a more modest risk increase of about 12%–15% (*22,23*).

From a metabolic integration perspective, the significance of this association extends well beyond statistical correlation. Efficient operation of the transsulfuration pathway requires the coordinated participation of several B vitamins. Folate and vitamin B(12) serve as essential cofactors for Hcy remethylation (*24*). Vitamin B6, in its active form pyridoxal 5'-phosphate, functions as a coenzyme for both CBS and CSE (*25*). It therefore directly participates in the enzymatic synthesis of H_2S (*26,27*). Consequently, reduced enzyme activity caused by nutritional deficiency leads to the accumulation of Hcy. It also impairs transsulfuration efficiency and thereby limits the capacity for H_2S production. Clinical intervention studies support this mechanism. In individuals with elevated Hcy levels, B vitamins supplementation effectively slows brain atrophy and cognitive decline (*28*). By contrast, such interventions show limited efficacy in those with normal Hcy levels. This seemingly paradoxical observation in fact reinforces a fundamental principle of precision medicine. Metabolic interventions should be tailored to individuals with demonstrable metabolic abnormalities rather than applied indiscriminately across populations.

6. Mitochondrial function and H_2S homeostasis

Mitochondria serve not only as the central hub of cellular energy metabolism but also as a critical node in H_2S metabolic regulation (*29,30*). Sulfide:quinone oxidoreductase (SQOR), located on the inner mitochondrial membrane, is the key enzyme catalyzing H_2S oxidation (*31*). Its reaction product, persulfide, possesses important endogenous antioxidant properties (*32*). Under physiological conditions, H_2S helps maintain mitochondrial membrane potential and suppresses excessive accumulation of reactive oxygen species (ROS). In doing so, it attenuates oxidative stress and bioenergetic impairment and preserves mitochondrial functional homeostasis (*33*).

Studies targeting mitochondrial H_2S delivery further support its protective role. Mitochondria-targeted H_2S

donors such as AP39 have been shown to enhance cellular energy production, improve cell viability, and exert protective effects on mitochondrial DNA (*34*). From a clinical genetics standpoint, mutations in the SQOR gene cause Leigh syndrome, a severe mitochondrial encephalopathy characterized by abnormal H_2S accumulation and pronounced mitochondrial dysfunction (*35*). This observation underscores that dysregulated H_2S oxidation per se can inflict serious damage on the nervous system.

The mitochondrial dysfunction prevalent in AD may affect SQOR activity and alter H_2S metabolic flux. These changes may disrupt H_2S clearance and utilization and thereby contribute to early pathological processes in the disease (*36*). This bidirectional interaction between mitochondrial function and H_2S metabolism likely represents an incompletely characterized metabolic node in neurodegeneration and warrants further systematic investigation.

7. Future research directions

At present, we lack reliable indicators capable of assessing individual "H_2S signaling status" at the clinical level. Developing biomarker panels in blood or cerebrospinal fluid that reflect cerebral H_2S metabolic status is a prerequisite for early diagnosis and precision intervention (*37*). Recent advances in persulfidome technologies have laid the methodological groundwork for achieving this goal (*38*). The precise transcriptional and translational regulators underlying CSE downregulation in AD remain unclear. Elucidating these mechanisms will not only deepen our understanding of pathological progression but may also reveal actionable nodes. For example, enabling the development of small-molecule CSE activators or expression inducers. Given the challenges associated with systemic administration of exogenous H_2S, including concentration control and targeted delivery, delivery systems targeted to the brain that enable slow release and can cross the BBB represent a promising translational strategy.. Existing donors such as GYY4137 have shown encouraging results in animal models, yet substantial work remains for translation from animals to humans (*39*). The preventive efficacy of metabolic interventions, including B vitamins and *N*-acetylcysteine (NAC), in high-risk populations urgently requires validation in large-scale clinical trials. Such interventions are low-cost and safe; if proven effective, they would carry major public health significance. Although this editorial focuses on Tau pathology, H_2S's potential interference with Aβ aggregation and its regulation of neuroinflammation mediated by microglia are equally worthy of attention (*40*). How does H_2S metabolism in neurons, astrocytes, and microglia change respectively in AD? How do their H_2S signaling networks interact? Answering these questions will require the application of emerging technologies such as single-cell omics and spatial omics (*41*).

8. Conclusion

Research on endogenous H_2S signaling pathways is revealing a previously neglected dimension of neuroprotective mechanisms. The essence of H_2S signaling dysregulation in AD is not a simple deficiency of a signaling molecule that can be corrected by exogenous supplementation; rather, it represents the systemic collapse of an endogenous protective apparatus. A scientifically accurate understanding of this fundamental distinction is critical for avoiding public misconceptions, safeguarding public health, and guiding research priorities. We propose adopting an integrative perspective that encompasses transsulfuration metabolism, mitochondrial function, and cell-type specificity. By combining this approach with novel methodologies such as persulfidome profiling and single-cell technologies, we anticipate breakthrough progress in the early intervention and prevention of AD. The establishment of this new paradigm not only expands the boundaries of our understanding of AD pathogenesis but also provides fresh strategic avenues for the prevention and treatment of neurodegenerative diseases in the era of precision medicine.

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