Research progress of hydrogen sulfide in Alzheimer's disease from laboratory to hospital: a narrative review

Song-Yang Peng#, Xin Wu#, Ting Lu*, Gang Cui*, Gang Chen
Department of Neurosurgery & Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China

*Correspondence to: Ting Lu, MM, 22339090@qq.com; Gang Cui, MD, cgsz_neurosurgery@163.com.
#These authors contributed equally to this work.
orcid: 0000-0001-5391-2079 (Ting Lu); 0000-0002-4788-8057 (Gang Cui)

Abstract

Alzheimer's disease is a neurodegenerative disease that mainly occurs in old age and early stages. Its main manifestations are memory impairment, aphasia, apraxia, loss of identity, abstract thinking and impairment of computing power, personality and behavior changes, etc. At present, the treatment of Alzheimer's disease only stays on reducing the disease and delaying the development, which is also a difficult problem to overcome in clinical practice. Hydrogen sulfide, as a third gaseous signal molecule after carbon monoxide and nitrogen monoxide, has become very popular in recent years. It shows very promising prospects in the Alzheimer's disease model. It can protect the nerve function and prevent the progress of the disease by affecting the amyloid precursor protein metabolism, anti-apoptosis, anti-inflammatory, and antioxidant pathways. Therefore, this article summarizes the relevant basic and clinical research of hydrogen sulfide in Alzheimer's disease, and discusses its progress and findings and mechanism characteristics.

Key words: Alzheimer's disease; amyloid precursor protein metabolism; anti-apoptosis; anti-inflammation; antioxidation; hydrogen sulfide; synthesis and metabolism; therapy

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Introduction

Degenerative diseases of the nervous system are a group of diseases of the central and peripheral nervous systems characterized by chronic neurological dysfunction and neuronal inactivation.[1,2] Today, the classification of neurological deformities is based largely on clinical syndromes, of which Alzheimer's disease (AD) is one. AD is a degenerative disease of the central nervous system, signed by progressive cognitive dysfunction and behavioral impairment, that occurs mostly in the elderly and early elderly.[3,4] The clinical manifestations include memory loss, aphasia, behavioral variation, epilepsy, apraxia, agnosia, impaired visuospatial ability, abstract thinking and computational power. AD risk factors include mutations in the apolipoprotein E-4 allele, low education, lack of exercise, high blood sugar, hypertension, and vascular risk factors.[5] For the pathogenesis of AD, there are currently many theories. Among them, the amyloid-cascade hypothesis is the most classic. It is believed that the accumulation of amyloid-β (Aβ) is a key link leading to neuronal deformation and dementia.[6,7] Typical pathological changes include amyloid plaques, neurofibrillary tangles, loss of neurons, and glial cell proliferation.[8]

Hydrogen sulfide (H_2S) is a colorless, flammable, toxic gas with odorous eggs.[9] In the past 25 years, with the continuous deepening of research, it has been found that H_2S plays an important role in the nervous system, cardiovascular system, respiratory system, etc., making it the third gaseous signal molecule after nitrogen monoxide and carbon monoxide.[10] Low-dose H_2S (80 ppm) can reduce acute lung injury by inhibiting mitochondrial-related enzyme activity, relaxing blood vessels and anti-inflammatory.[11] Lin et al.[12] reviewed the literature and found that taking drugs that release H_2S may help improve renal damage after obstruction. H_2S activates adenosine triphosphate-sensitive potassium channels, which in turn dilates blood vessels and lowers blood pressure, while improving myocardial ischemia-reperfusion injury.[13,14] Saito et al.[15] conducted a retrospective analysis of 23 clinical data and found that H_2S can also be used as an indicator to evaluate asthma-related phenotypes. de Pascual et al.[16] found that H_2S can increase the release of catecholamines by enhancing the depolarization of adrenal chromaffin cells, and speculated that this effect may be related to the regulation of intracellular Ca^{2+}, and proposed that the use of H_2S donor drugs for neurodegenerative diseases can improve synaptic transmission neurotransmitter exocytosis. Zhao et al.[17-19] up-regulated endogenous and exogenous H_2S in experimental rats, and observed the effect of H_2S on the activation of the inflammatory factor NOD-, LRR- and pyrin domain-containing 3 (NLRP3) *in vivo* and *in vitro*, and obtained inflammatory cell infiltration, microglia aggregation and cell damage after intracerebral hemorrhage, activation of NLRP3 inflammatory bodies was inhibited. H_2S exerts protective effects through different pathways in a variety of injuries, and AD also has similar pathophysiological mechanisms as those mentioned above. It is speculated that H_2S may have a certain protective effect on AD. This review focuses on H_2S as a protective gaseous signaling molecule in the development of AD. An electronic search of databases includes PubMed and Google Scholar was searched up to March 2020. Some reference materials may not appear in any database because they are outdated, so I need to consult my personal experience and knowledge in

this field. The term "hydrogen sulfide" as a medical subject heading (MeSH) and key word, was combined with the term "Alzheimer's disease" as a medical subject heading (MeSH) and key word.

Mechanisms of Endogenous Hydrogen Sulfide Synthesis and Metabolism

Four pathways for endogenous H_2S generation have been identified. The process involves cystathionine-β-synthase (CBS), cystathionine-gamma-lyase, 3-mercaptopruvate sulfurtransferase (3-MST), and cysteine aminotransferase.[20,21] CBS is found in liver, kidney, brain and other tissues, mainly in the cytoplasm, but can also be found in the nucleus and mitochondria, which is through the cysteine β condensation reaction, and β substitution reaction of replacing cysteine with homocysteine to generate H_2S. Studies have shown that adenoxylmethionine, a CBS structure activator, can promote the production of H_2S from CBS, while nitrogen monoxide and carbon monoxide can inhibit it.[22-24] Cystathionine-gamma-lyase is mainly expressed in liver, kidney, thoracic aorta and other tissues, and its expression is low in the brain. Cystathionine-gamma-lyase mainly produces H_2S through alpha and beta elimination of cysteine. In hyperhomocysteinemia, high concentrations of homocysteine in the body can make alpha elimination response and gamma replacement reaction of homocysteine the main pathway of H_2S production.[25,26] In addition, 3-MST and cysteine aminotransferase can also be used to synthesize H_2S with cysteine as the substrate. 3-MST produces H_2S through 3-mercaptopyruvate, while cysteine aminotransferase produces H_2S through cysteine and α-ketoglutarate.[27-29] In preclinical experiments, H_2S is used as a preventive and treatment method for related diseases, and its administration methods are few. There are two kinds of exogenous H_2S donors sodium sulfide (NaHS)[30-32] and H_2S inhalation.[33] The former is the most commonly used.

The mechanism of H_2S metabolism has not yet been fully elucidated. Olson et al.[34] found that catalase may be a key enzyme in the metabolism of H_2S, which can convert H_2S into sulfide, thereby achieving scavenging effect. Olson et al.[35] established a model of intracellular H_2S concentration distribution to predict two ways that H_2S can be reduced-mitochondrial oxidation and simple gas diffusion, the former being more effective. Relevant research reports that SULFIDE: Quinone oxidoreductase is a catalytic enzyme with redox activity located on mitochondria.[36] After combining H_2S with the SULFIDE: Quinone oxidoreductase-cysteine complex, it can transfer electrons in H_2S to the oxidative respiratory chain and participate in the generation of adenosine triphosphate. At the same time, sulfides are formed.[37] According to the literature summary, there are some unconventional forms of H_2S metabolism, which often involve signal transduction or redox reactions of related substances, such as O_2, O_2^-, HClO, H_2O_2, etc.[38,39]

Experimental Research of Hydrogen Sulfide in Alzheimer's Disease

Amyloid precursor protein (APP) metabolism

Nagpure et al.[40] Established an AD cell model (SH-SY5Y cells transfected with APPswe) and found that NaHS can interfere with three nodes in the cell to inhibit the production of $A\beta_{42}$. First, the mature APP, the immature APP in the Golgi complex O-glycosylation generates mature APP, which forms the raw material for $A\beta_{42}$ production; second, γ secretase is activated, and mAPP is cleaved by activated γ secretase to produce $A\beta_{42}$; third, cyclic adenosine monophosphate production, adenosine triphosphate in the adenylyl cyclase complex. It can be converted into cyclic adenosine monophosphate under the action of serotonin and enter the cascade reaction to generate β-CREB, thereby enhancing the cleavage of γ secretase.[41] Zhang et al.[42-44] further explored the mechanism by which NaHS affects beta-secretase 1 (Aβ-producing key enzyme; plays an initial cleavage effect on APP) mRNA and protein levels. The authors treated PC12 with 50 μM NaHS and analyzed the resulting lysates by Western blot. It was found that H_2S passed phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase/extracellular-signal-regulated kinase pathway affects beta-secretase 1 expression and Aβ secretion. He et al.[45,46] evaluated the levels of $A\beta_{40}$ and $A\beta_{42}$ by using western blot and enzyme-linked immunosorbent assay immunological techniques by administering NaHS at concentrations of 10, 20, and 50 μmol/kg. $A\beta_{40}$ and $A\beta_{42}$ were significantly reduced ($P < 0.01$), and it was suggested that 50 μmol/kg of NaHS was the best choice for the efficacy and toxicity trade-offs for their AD mouse model. In addition, the study has shown that a certain concentration of exogenous H_2S can promote APP's non-amyloid metabolic pathway and reduce Aβ production.

Anti-inflammation

Inflammation has been found to be an important pathophysiological process in many neurodegenerative diseases, such as AD, Parkinson's disease, ischemic stroke, multiple sclerosis, and amyotrophic lateral sclerosis.[47] Components related to AD neuroinflammation include microglia and astrocytes, classical and alternative pathways of the complement system, angiotensin, acute phase proteins, neuronal nicotinic acetylcholine receptors, peroxisomes Proliferation-activated receptors and "pro-inflammatory" cytokines and chemokines.[48,49] Among them, the excessive activation of microglia is particularly obvious, which can produce iron, reactive oxygen species and inflammatory mediators, such as tumor necrosis factor-α and interleukin 1β, leading to neuroinflammation and neurodegenerative diseases. At the same time, damaged or necrotic neurons form a vicious cycle with over-activated microglia, accelerating the process of neuro-inflammation.[50] Lipopolysaccharide is a bacterial endotoxin that can cause neuroinflammation.[51] In related studies, by injecting lipopolysaccharides (LPS) into the hippocampus and observing the expression and learning and memory functions of rat microglia, it was found that the activation of microglia in the hippocampus. The performance is obvious, indicating that LPS can also affect the hippocampus to participate in the pathogenesis of AD. At the same time, the hippocampal function of learning and memory is also reduced to varying degrees.[52,53] Gong et al.[54] observed the effects of S-propargyl-cysteine (an analog of S-allylcysteine which has cardioprotective and neuroprotective

effects and can regulate endogenous H_2S) on spatial memory and learning disorders in rats induced by LPS, through the Morris water maze experiment. The spatial memory and learning ability were evaluated, and it was found that the LPS operation group had significant dysfunction compared with the sham operation group, but the S-propargyl-cysteine intervention group had significant improvement in dysfunction ($P < 0.01$), and was 40 and 80 mg/kg. The drug dose was the most significant. After measuring the H_2S concentration in the hippocampus, it was found that the concentration in the LPS surgery group was significantly lower than that in the sham operation group ($P < 0.01$). At the same time, compared with the LPS surgery group, in the H_2S in the intervention group given S-propargyl-cysteine the level was increasing ($P < 0.01$). It is speculated that there is a correlation between the level of H_2S and spatial memory and learning dysfunction caused by LPS. The authors also observed the expression of tumor necrosis factor-α, tumor necrosis factor receptor 1 and Aβ protein precursor mRNA, and found that the expression was significantly increased in the LPS surgery group, but S-propargyl-cysteine exerted an inhibitory effect ($P < 0.01$), indicating that S-propargyl-cysteine may improve spatial memory and learning disabilities by reducing the production of the above inflammatory factors.[55]

Anti-apoptosis

Cui et al.[56] reviewed the literature and found that Aβ is an important pathophysiological basis of AD. Changes in phosphatase and tensin homolog may be related to neuronal apoptosis.[57] H_2S may have a certain therapeutic effect on the neurological damage caused by Aβ. Later, Aβ was used as the culture condition and co-treated with NaHS. It was found through pre-experiment that 50 mM NaHS apoptosis inhibitory effect was the most significant. After the above methods were processed, PTEN, Bax, phospho-Akt, Akt and other related indicators to evaluate. It was found that H_2S has an important inhibitory effect on the apoptosis of neurons induced by Aβ, which may be achieved by preventing the migration of phosphatase and tensin homologs deleted by PTEN from cytoplasm to mitochondria with the participation of phosphoinositide 3-kinase/Akt pathway.[58,59] Wei et al.[60] reviewed the literature and found that homocysteine can cause a variety of neuronal cell death, and epidemiological studies have concluded that high homocysteine may be an important independent risk factor for AD.[61,62] Endoplasmic reticulum stress is very important in the pathophysiology of AD. The brain-derived neurotrophic factor-TrkB pathway is a neurotrophic pathway. It may function through anti-inflammatory in depression. It is speculated that in AD, high homocysteine may cause endoplasmic reticulum stress, and the presence of H_2S may up-regulate brain-derived neurotrophic factor-TrkB pathway to suppress the stress of the endoplasmic reticulum, and then experiments were performed, and the above inferences were verified.[60,63] Kamat et al.[64] discovered by terminal deoxynucleotidyl transferase dUTP nick-end labeling staining that NaHS is of great significance in inhibiting apoptosis. Tang et al.[65] induced the apoptosis of PC12 cells by $A\beta_{25-35}$ and treated them with H_2S. It was found that $A\beta_{25-35}$ can induce apoptosis by inducing mitochondrial membrane potential dissipation and generating excess reactive oxygen species. However, H_2S can reverse the above effects and inhibit apoptosis.

Antioxidation

A review of the literature found that extensive oxidative stress and damage exist in the brains of AD patients, appearing in the form of oxidation of proteins, lipids, and DNA. There are many mechanisms, such as H_2O_2 and hydroxyl radicals, reactive nitrogen (nitrogen monoxide and peroxynitrite), HOCl (produced by myeloperoxidase/myeloperoxidase). Epidemiological evidence indicates that 3-chlorotyrosine, a marker of HOCl formation *in vivo*, is significantly increased in patients with AD. Whiteman et al.[66] conducted experiments using mature *in vitro* and cell culture models and found that H_2S has a significant inhibitory effect on HOCl-mediated SH-SY5Y cell damage and is not different from GSH; *in vivo*, H_2S also has the potential to inhibit HOCl oxidation. At the same time, it can be observed that there is a correlation between increased HOCl production in microglia and neurons and H_2S consumption. Whiteman et al.[67] later studied oxidative stress in AD patients from the perspective of active nitrogen. Previous research has shown that the generation of H_2S in the brain may involve changes in at least two types of ionic glutamate receptors. In degenerative diseases, peroxynitrite (ONOO-) is widely found and can be evaluated by the measurement of 3-nitrotyrosine. Multiple experiments have found the presence of 3-nitrotyrosine in AD brain. The above evidence suggests that there must be some connection between H_2S and ONNO- in the body. Therefore, through the same model construction method, it was found that H_2S may be one of the scavengers of ONOO-, and ONOO-mediated 3-nitrotyrosine formation is an important pathway leading to neuronal oxidation, and thus effectively prevents oxidation, delay the progress of AD.[68] Gao et al.[69] reviewed the literature and found that active nitrogen plays an important role in cell signal transduction through redox effect, and sodium azide (NaN_3) can irreversibly bind to the heme cofactor, thereby inhibiting cytochrome oxidase (a kind of Enzymes; play a role in aerobic energy metabolism and mitochondrial function), which leads to mitochondrial dysfunction and produces excess reactive oxygen species. Their previous research found that the expression and activity of CBS and 3-MST in PC12 cells treated with NaN_3 decreased (data not shown). Therefore, it is speculated whether the decrease in H_2S is related to the cell damage caused by NaN_3. It constructs a NaN_3-PC12 cell model to simulate the pathophysiology of AD. Studies have shown that PC12 cells treated with NaN_3 show a significant oxidative stress response, which is dependent on concentration and time; after pretreatment with NaHS on PC12 cells, it was found that the cytotoxicity of NaN_3 was significantly weakened, specifically by protecting mitochondria membrane potential dissipation, reducing intracellular reactive oxygen species accumulation, and reducing lipid peroxidation.[70]

Clinical Research of Hydrogen Sulfide in Alzheimer's Disease

Liu et al.[71] collected 31 patients with AD as the experimental

group and 23 normal persons as the control group to measure the plasma H_2S content, and performed a related scale test on all subjects, and then used the Comprehensive Decline Scale graded assessment. It was found that the plasma H_2S level in AD patients was significantly lower than that in the normal control group, and the plasma H_2S level was negatively correlated with the severity of AD patients. Eto et al.[72] obtained cadaver brain tissue samples from 13 AD patients and 6 normal people, and measured H_2S in the brain by gas chromatography. It was found that the endogenous H_2S level in the brain of AD patients was significantly lower than that of normal people. The CBS level in the brain was measured by blot, and there was no significant difference in the CBS content in the brains of AD and normal people. Previous studies have shown that the CBS-related enzyme CBS can convert homocysteine to cysteine, and CBS is activated by S-adenosyl-L-methionine (SAM). Analysis of cysteine, SAM, and homocysteine by HPLC found that homocysteine content was higher in AD patients than normal people, and a rough estimate of the SAM content was low. The H_2S content in AD patients decreased, and may be related to the decrease in CBS activity. McCarty and others[73] proposed to improve the neurological dysfunction of AD patients through dietary adjustment. A cysteine-rich diet or supplementation with an appropriate amount of N-acetylcysteine is beneficial to the synthesis of H_2S in the brain; taurine can be enhanced by enhancing CBS activity and angiogenesis lead to increased H_2S levels; folic acid, vitamin B12 and betaine in the diet promote the remethylation of homocysteine, resynthesis of methionine and promote the production of SAM. Related research shows effective nutritional and health measures can promote the synthesis of H_2S and thus play a neuroprotective role. It may be effective not only in the field of AD but also in Parkinson's disease, cerebral hemorrhagic disease and craniocerebral trauma (**Table 1**).

Conclusion

H_2S is well known as a toxic gas. As research continues, it has become the third gaseous signal molecule after nitrogen monoxide and carbon monoxide. According to the above introduction, H_2S has been found to have a negligible role in the progression of AD. H_2S works by interfering with APP metabolism, anti-inflammatory, anti-apoptosis and anti-oxidation, but the clinical research progress of H_2S is still relatively limited, and may be restricted for many reasons. Therefore, the function of H_2S in AD is becoming increasingly important. It is believed that a large number of basic and clinical research will emerge to provide some new schemes for the prevention and treatment of AD.

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Conflicts of interest
The authors have no conflicts of interest to declare.
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Table 1: Main experimental studies of hydrogen sulfide in AD

Study	Model	Animals/cells	Experimental results
Nagpure et al.[40]	AD	SH-SY5Y cells	NaHS interferes with the three nodes of $A\beta_{42}$ production: amyloid precursor protein maturation; gamma secretase activation; cyclic adenosine monophosphate production.
Zhang et al.[42]	AD	PC12 cells	H_2S affects beta-secretase 1 expression and Aβ secretion through phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase/extracellular-signal-regulated kinase pathways.
Gong et al.[52]	AD	Rats	Regulation of H_2S generation may improve spatial memory and learning dysfunction.
Cui et al.[56]	AD	Neuronal cells	H_2S may inhibit apoptosis by preventing the transfer of phosphatase and tensin homologs deleted by phosphatase and tensin homolog.
Tang et al.[65]	AD	PC12 cells	H_2S inhibits apoptosis by reversing mitochondrial membrane potential dissipation and reactive oxygen species overproduction.
Whiteman et al.[66,67]	AD	SH-SY5Y cells	H_2S exerts antioxidant functions by acting on HOCl and ONOO-, thereby protecting neural functions.
Eto et al.[72]	AD	Human	The H_2S content in the brain of AD patients is lower than that in normal people, and may be related to the decrease in cystathionine beta synthase activity.

Note: AD: Alzheimer's disease; Aβ: amyloid-β; H_2S: hydrogen sulfide.

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