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Review

Therapeutic benefits of H_2S in Alzheimer's disease

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ABSTRACT

Hydrogen sulfide (H_2S), an endogenously generated gaseous mediator, has been discovered to regulate a series of physiological and pathological processes in mammalian systems. In recent decades scientific interest has grown in the physiological and pathological implications of H_2S, specifically its role in the central nervous system (CNS). H_2S can work in the CNS as a neuromodulator to promote long-term potentiation and regulate intracellular calcium concentration and pH level in brain cells. H_2S may protect the nervous system from oxidative stress, apoptosis, or degeneration. The aim of this review is to present the current understanding of H_2S as a potential agent for the treatment of Alzheimer's disease (AD). Dysregulation of H_2S homeostasis is implicated in the pathological processes of AD. Substantial evidence from both *in vivo* and *in vitro* studies shows that H_2S prevents neuronal impairment and attenuates cognitive dysfunction in the experimental model of AD. The mechanisms underlying the protective role of H_2S in AD involve its antioxidant, anti-apoptotic, and anti-inflammatory effects. We conclude that H_2S has potential therapeutic value for the treatment of AD.

1. Introduction

For hundreds of years, people have thought that hydrogen sulfide (H_2S) is just a toxic gas with the smell of rotten eggs. However, recent studies have demonstrated that H_2S regulates a series of physiological and pathological processes in mammals [1]. H_2S is regarded as the third most abundant endogenous signaling gasotransmitter, following nitric oxide (NO) and carbon monoxide [1,2]. H_2S is primarily generated from L-cysteine and homocysteine (Hcy) by two enzymes: cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). CBS is mainly expressed in the central nervous system (CNS), while CSE is primarily expressed in the cardiovascular system [1,3,4]. Recently, it has been reported that the combined action of 3-mercaptopyruvate sulfurtransferase (3MST) and cysteine aminotransferase produce H_2S from cysteine in brain [5]. The physiological functions of H_2S in the CNS were first found in 1996 by Abe and Kimura [6]. They demonstrated that H_2S selectively improves N-methyl-D-aspartate receptor mediated function and is beneficial for the induction of long-term potentiation [6]. Subsequently, more and more physiological and pathological functions of H_2S in the CNS were discovered, and the neurobiology, neurochemistry, neurophysiology, neuropathology, and signaling properties of H_2S have been focused on in a number of outstanding articles [1–4,7]. This article provides an overview of the therapeutic benefits of H_2S in Alzheimer's disease (AD) and the underlying cellular and molecular mechanisms implicated.

2. Disturbance of endogenous H_2S generation in AD

AD is a progressive age-dependent neurodegenerative disease, affecting the cortex and hippocampus, and ultimately leading to cognitive dysfunction [8]. Neurofibrillary tangles and β-amyloid (Aβ) plaques in the cortex and hippocampus are the hallmarks of AD [9,10]. In both familial and sporadic AD, Aβ peptides, generated from amyloid precursor protein (APP) by β and γ-secretases, are considered to be pivotal factors in the pathology of the disease [11].

Increasing evidence has demonstrated that H_2S is relevant to AD pathogenesis. CBS is highly expressed in the brain and thus is believed to be the primary physiologic source of H_2S in the CNS [1,3,4]. In 1996, Morrison et al. first discovered that brain levels of S-adenosylmethionine, a CBS activator, are significantly decreased in AD patients [12]. It has been reported that the total serum level of Hcy is accumulative and increased in AD patients as the result of the disruption of the transsulfuration pathway linking Hcy and glutathione (GSH), which is mediated by CBS and CSE [13]. The dysfunction of CBS in the transsulfuration pathway may lead to a decrease in H_2S production in AD [14]. Moreover, our own research has shown that neurotoxicity of elevated Hcy is involved in inhibition of endogenous H_2S production and

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down-regulation of expression and activity of CBS in PC12 cells [15]. Recently, Liu et al. reported that levels of H_2S are decreased in AD patients and the change in H_2S level may be related to the severity of AD [16]. Based on these findings, it is logical to suggest that the generation of endogenous H_2S is disturbed in the AD brain, although more direct evidence is currently lacking.

3. Protective actions of H_2S in AD

Increasing evidence from both *in vivo* and *in vitro* studies suggest that H_2S has potential therapeutic value for treatment of AD.

3.1. H_2S protects against AD-related oxidative stress factors

It has been demonstrated that the level of hypochlorous acid (HOCl) is elevated in the temporal and frontal cortex of AD brains [17,18]. Whiteman et al. reported that sodium hydrosulfide (NaHS, the donor of H_2S) significantly inhibited HOCl-induced cytotoxicity, intracellular protein oxidation, and lipid peroxidation in SH-SY5Y cells (human neuroblastoma cells) [19], which implies the potential neuroprotective effect of H_2S against the pathological progression of AD.

Our data reveal that NaHS ameliorates Aβ-induced damage in PC12 cells through reducing the loss of mitochondrial membrane potential ($\Delta\psi_m$) and attenuating the increase of intracellular reactive oxygen species (ROS) [20]. Moreover, in cultured PC12 cells, recent research on the relationship of H_2S to β-site APP cleaving enzyme 1 (BACE-1) expression and Aβ secretion discovered that H_2S reduces BACE-1 mRNA and protein levels and $A\beta_{1-42}$ release [21]. Oxidative damage to lipids and proteins is an important early event in the pathogenesis of neurodegenerative diseases and malondialdehyde (MDA) and carbonyl proteins are regarded as useful oxidative markers in AD [22]. It has been demonstrated that H_2S reduces MDA levels in human umbilical vein endothelial cells exposed to hydrogen peroxide [23] and destroys lipid hydroperoxides in oxidized low-density lipoprotein [24]. Schreier et al. demonstrated that H_2S protect neuronal cells (SH-SY5Y) from the cytotoxic lipid oxidation product 4-hydroxynonenal (HNE) [25], which is markedly increased in the brains of patients with severe AD.

Based on the above, H_2S has a strong antioxidant capacity to resist AD-related oxidative stress factors such as HOCl, Aβ, MDA, and 4-HNE, suggesting a promising role for H_2S as a novel strategy to prevent AD.

3.2. H_2S resists AD by inhibiting Hcy-induced oxidative stress

Homocysteine (Hcy) is a thiol-containing amino acid derived from the metabolism of methionine. Both *in vitro* and *in vivo* studies have shown that Hcy is toxic to neuronal cells [26–32] and markedly enhances the vulnerability of neuronal cells to excitotoxic and oxidative injury [30]. Furthermore, Hcy changes hippocampus plasticity and synaptic transmission resulting in learning and memory deficits [33,34]. These unfavorable neuronal effects of Hcy are believed to be caused by the auto-oxidation of Hcy, which leads to cellular oxidative stress through the formation of ROS, including the superoxide anion and hydrogen peroxide [35,36]. Additional findings demonstrated that Hcy can induce lipid peroxidation and increase MDA and super oxide anion levels in rat brains [37,38]. These studies revealed that Hcy may be a marker of oxidative stress.

Elevated plasma Hcy levels, known as hyperhomocysteinemia (HHcy), cause neurological abnormalities such as mental retardation, cerebral atrophy, and seizures [39,40]. Elevated brain Hcy has been reported in AD [41]. It is now established that elevated plasma Hcy is a strong, independent risk factor of AD [13,14,42–44]. Therefore, Hcy is regarded as a novel therapeutic target for AD [14]. It has been shown that H_2S partly prevents HHcy-associated renal damage through its antioxidant properties [45] and protects against Hcy-induced cytotoxicity and oxidative stress in vascular smooth muscle cells [46]. Interestingly, our studies showed that H_2S protects PC12 cells against the increase in intracellular ROS induced by Hcy [47]. Additionally, we recently showed that ACS6, a novel H_2S-releasing sildenafil, results in prevention of Hcy-caused neurotoxicity and overproduction of ROS by upregulating paraoxonase-1 [48]. Moreover, H_2S significantly attenuates Hcy-induced oxidative stress, memory deficit, and neurodegeneration in mice [49]. In summary, H_2S has protective effects against Hcy-induced oxidative stress and neurotoxicity. Therefore, it is logical to assume that H_2S would be beneficial in the treatment of AD by inhibiting Hcy-induced oxidative stress.

3.3. H_2S protects against AD in animal models

Recently, Xuan et al. reported that pretreatment with NaHS ameliorates learning and memory deficits in an $A\beta_{1-40}$ rat model of AD [50]. Giuliani et al. found that H_2S significantly protected against learning and memory impairment in three experimental models of AD, including the rat models of AD induced by brain injection of $A\beta_{1-40}$ or streptozotocin, and an AD mouse model harboring human transgenes APP_{Swe}, $PS1_{M146V}$ and tau_{P301L} (3 × Tg-AD mice) [51]. Gong et al. reported that NaHS notably attenuates lipopolysaccharide (LPS)-induced neuroinflammation, neuronal ultrastructure impairment and cognitive defects [52], which suggest that H_2S is a potential agent for the treatment of neuroinflammation-related diseases, such as AD. Taken together, these findings from *in vivo* studies show the potential therapeutic value of H_2S for AD and lay the foundation for exploring a new H_2S-modulated agent for preventing or delaying the development of AD.

3.4. H_2S donors antagonize AD

H_2S can be produce non-enzymatically from polysulfides in garlic [53]. It is reported that garlic compounds containing S-allyl cysteine (SAC) attenuate Aβ-induced apoptosis [54] and decrease Aβ fibril production and defibrillate Aβ preformed fibrils *in vitro* [55]. Moreover, garlic extracts have been demonstrated to exert anti-amyloidogenic, anti-inflammatory and anti-tangle effects in AD transgenic models harboring the Swedish double mutation [56]. S-propargyl-cysteine (SPRC), which is an SAC structural analog that can be used to adjust endogenous H_2S levels [7,9], attenuates cognitive damage induced by LPS in rats [57]. Moreover, SPRC may inhibit $A\beta_{25-35}$-induced cognitive dysfunction and neuronal ultrastructure impairment in rats [58]. These findings indicate that appropriate treatments with H_2S-modulating agents, such as SAC and SPRC, represent a potential approach to treat AD.

4. Mechanisms of the protective effects of H_2S in AD

4.1. Antioxidation

Oxidative stress has significant implication in the pathogenesis of AD. Studies have shown that NaHS is capable of improving reducing activity in neurons and protects them against oxidative impairment induced by hydrogen peroxide, glutamate, and hypochlorous acid, mainly through increasing GSH levels but not directly working as an antioxidant [19,59]. Increased levels of GSH are brought about by enhancing the transporters of cystine/L-cysteine, the redistribution of GSH to mitochondria, the activity of γ-glutamylcysteine synthetase in neurons and the uptake of glutamate in astrocytes [59–61]. H_2S also can protect an immortalized mouse hippocampal