

Redox Effects of Molecular Hydrogen and Its Therapeutic Efficacy in the Treatment of Neurodegenerative Diseases

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Abstract:

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Review

Redox Effects of Molecular Hydrogen and Its Therapeutic Efficacy in the Treatment of Neurodegenerative Diseases

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Abstract: Oxidative stress (OS) and neuroinflammatory stress affect many neurological disorders. Despite the clinical significance of oxidative damage in neurological disorders, still, no effective and safe treatment methods for neuro diseases are available. With this, molecular hydrogen (H₂) has been recently reported as an antioxidant and anti-inflammatory agent to treat several oxidative stress-related diseases. In animal and human clinical trials, the routes for H₂ administration are mainly categorized into three types: H₂ gas inhalation, H₂ water dissolving, and H₂-dissolved saline injection. This review explores some significant progress in research on H₂ use in neurodegenerative diseases (NDs), including Alzheimer's disease, Parkinson's disease, neonatal disorders of the brain, and other NDs (retinal ischemia and traumatic brain injury). Even though most neurological problems are not currently curable, these studies have shown the therapeutic potential for prevention, treatment, and mitigation of H₂ administration. Several possible H₂-effectors, including cell signaling molecules and hormones, which prevent OS and inflammation, will also be addressed. However, more clinical and other related studies are required to evaluate the direct H₂ target molecule.

Keywords: molecular hydrogen; inflammation; neuroprotection; neurological disorder; oxidative stress; antioxidant



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1. Introduction

Neurodegenerative diseases (NDs) are groups of various aging disorders that generally lead to a gradual death and increase in neuronal cells, leading in affected persons to compromised motor and memory function [1]. The exact mechanism for the pathogenesis of NDs remains largely undefined; however, emerging evidence suggests that oxidative stress (OS) plays an important function in the pathogenesis of numerous brain-related disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), cerebral ischemia, and other brain injuries [2–4]. It is essential for our cells to maintain moderate levels of reactive oxygen species (ROS) to carry out normal biological functions. However, severe production of ROS is responsible for the cause of oxidative damage that may lead to apoptosis [5]. This excessive production of ROS appears to be a possible cause of structural and functional modifications of cellular biomolecules, including proteins, deoxyribonucleic acid (DNA), and lipids, and thus eventually confines neuronal function and survival and is commonly observed in the brains of patients with neurodegenerative conditions [3,4]. The central nervous system (CNS) utilizes large amounts of oxygen to perform physiological processes, resulting in the generation of abundant levels of free radicals [5]. Endogenous antioxidant systems, such as those comprising superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione, play an important role in the rescue of brain cells from

OS and preserve the correct redox balance in the brain tissue, by stimulating antioxidative defense mechanisms for counterbalance ROS. These enzymatic antioxidants are chain-breaking antioxidants that can scavenge radical species [6]. Manganese-containing SOD decreases the superoxide radical anion produced during the electron transport chain in the mitochondrial matrix, whereas CAT and/or GPx play key roles in decomposing hydrogen peroxide to water and oxygen [6,7]. Various studies have reported decreased levels of antioxidative enzyme activities, such as CAT and SOD, in neurological diseases including PD [8,9]. Interestingly, one study showed that impairment of SOD activity leads to possible pathogenesis related to OS in PD and AD [10]. Furthermore, research has shown that reticence of CAT activity results in elevated cytotoxicity and increased ROS, representing an essential role of CAT in maintaining the oxidative balance [11].

Emerging evidence clearly highlights and corroborates the role of OS in the pathogenesis of NDs [2–4]. As a result, in recent years, researchers have been interested in evaluating the role of antioxidants in preventing and alleviating these diseases. It is a well-accepted fact that natural antioxidants and antioxidative enzymes have a key role in the reduction of cellular ROS [12]. Recently, molecular hydrogen (H_2) has attracted great attention in the medical field as a nonfunctional gas that is safe and effective and attenuates OS by acting as a radical scavenger for hydroxyl radical ($\bullet OH$) and peroxynitrite ($ONOO^-$) [13]. Various studies have highlighted the beneficial effects of H_2 in reducing the pathophysiology of various diseases by reducing OS [13,14]. There are numerous convenient and effective routes for administering H_2 , such as inhalation, oral intake of hydrogen-rich water (HRW), injection of hydrogen-rich saline (HS), and direct incorporation (bath, eye drops, and others) [14,15]. H_2 has been reported as a therapeutic gas in a rat model of ischemia–reperfusion (IR) brain injury and reported to have a preventive effect on IR injury in optic nerves in a model of brain white matter [16]. Moreover, the protective effect of H_2 in drinking water through the antioxidative effects of dopaminergic neurons in the substantia nigra pars compacta (SNpc) has been studied in an animal model [17]. Further, interestingly, another study showed that drinking H_2 -dissolved water (HW) and intermittent H_2 exposure prevent PD neurotoxicity [18]. A clinical trial performed by Nagatani and colleagues showed that intravenous administration of HRW was found to be safe for patients suffering from acute cerebral infarction, including those treated with a tissue plasminogen activator [19]. Additionally, a study showed that inhalation of H_2 gas concealed brain damage-induced middle-cerebral occlusion in rats, enhanced cognitive scores, and lessened brain injury in patients with acute cerebral infarction [20]. H_2 was found to have remedial and ergogenic effects in different clinical and pre-clinical studies on mild cognitive impairment [21,22]. Most brain injuries in our nervous system respond to neuroinflammation, which is distinguished by phenotypical changes in microglia and astrocytes, and excessive production of free radicals, cytokines, and neurotrophins. Evidence indicates that regulation of microglial redox status plays an essential role in modulating the neuroinflammatory response [23]. Studies have shown that regular consumption of HW reduces the intensity of acute behavioral outcomes and promotes recovery from neuroinflammation [24]. H_2 can reduce the activation of proinflammatory cytokines, microglia, and 8-hydroxy-2-deoxyguanosine (8-OHdG) to reduce oxidative damage and neuroinflammation in the fetal brain in animal models [24,25]. In addition, a study showed that HW has a protective effect against neonatal hypoxic-ischemia encephalopathy by decreasing the levels of serum neuron-specific enolase, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) [26]. Therefore, this review article highlights the involvement of OS in NDs and the effect of H_2 in the treatment of these diseases.

2. Characteristics of Molecular Hydrogen

H_2 works as a moderate but efficient antioxidant [13,27]. Hydrogen is the world's most abundant element, accounting for about 75% of the world's mass. Hydrogen is present in water and in organic as well as inorganic compounds. H_2 gas is a colorless, odorless, fuel-intensive diatomic gas. There is less than 1 ppm hydrogen gas in the Earth's

atmosphere [28]. H₂ does not react with most compounds, including oxygen gas, at room temperature. H₂ gas is only inflammable at temperatures exceeding 537 °C. H₂ (4–75%, v/v) is explosive due to the rapid oxidation chain reaction. H₂ can be dissolved in water under atmospheric pressure to 0.8 mM (1.6 ppm, w/v) [28].

In recent years, various studies related to H₂ have attracted researchers' attention globally, owing to its protective and therapeutic effects [14,15]. Furthermore, hydrogen has a more significant advantage over other gases used for medical purposes, in terms of its toxicity; hydrogen remains non-toxic up to high concentrations and is even used in diving applications [29,30]. Studies have found that the effects of hydrogen inhalation are not apparent and do not affect blood pressure or other parameters, such as pH and temperature. Thus, in comparison, hydrogen has fewer side effects than other antioxidants, as it only decreases •OH [13,31].

3. Administration Routes of Hydrogen

H₂ may be administered or taken into the body via various routes. These routes may be divided into three types: H₂ gas inhalation, drinking HW, and HS injection. H₂ gas inhalation is the simplest and most commonly used method since the initial reports regarding the use of H₂ [13]. Inhaled H₂ diffuses into the lung alveoli and is transported to the entire body. This procedure can, however, be uncomfortable and even dangerous, since H₂ gas is explosive at concentrations above 4% in air [27]. Therefore, the mixed gas concentration of H₂ is usually maintained between 1% and 4%. Inhaling H₂ gas improves acute conditions such as ischemia–reperfusion injury (IRI) and several organ graft injuries. HRW is safer and more comfortable than H₂ gas inhalation. It has been reported that HW *ad libitum* prevents arteriosclerosis among mice with knockout apolipoprotein E, a model for atherosclerosis that develops spontaneously [32]. Consumption of H₂ prevents stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice [33]. Recently, the inhalation of H₂ and consuming HW showed different adjustments to signal and gene expression in mice [34]. Although the process is invasive, the neuroprotective efficacy in the brain following IRI intraperitoneal injection of HS has been similar to that of H₂ gas inhalation [35]. In the human gastrointestinal tract, H₂ is produced by intestinal bacteria and plays a key role in metabolic pathways. It functions as a distinctive antioxidant and prevents cardiovascular disorders [15]. One of the studies showed that gut bacteria plays a role in the progression of neurological disorders. In this regard, patients suffering from various CNS disorders were found to have increased intestinal permeability that creates a passage to harmful metabolites from the intestine to the blood which harmfully affect the CNS [36]. A study showed that oral administration of HW leads to protective effects in rat and mice models of PD [17]. These findings demonstrate the potential use of HRW for defense against NDs, as well as the possibility of using HRW to treat acute brain disorders, as shown in Figure 1.

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway act as a vital role in protecting cells against different stressors and its dysfunction is correlated with decreased tolerance to OS [37]. Nrf2 is an important defense mechanism of the brain against toxins in both, glial and neuronal cells [38,39]. The Nrf2 pathway targets various genes for instance heme oxygenase-1 (HO-1), glutathione S-transferase, SOD, CAT, NAD(P)H dehydrogenase(quinone)1, and others, thus, protecting the neurons of the CNS against OS [40,41]. Nrf2 and various antioxidant enzymes may also increase the expression of anti-inflammatory mediators, phase I and II drug-metabolizing enzymes, and mitochondrial pathways [42,43]. Recent research studies have shown that Nrf2 plays defensive action against the neurotoxins such as 6-hydroxydopamine and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), in both, in vitro and in vivo models of PD [44,45]. In this regard, oral administration of HRW has shown a neuroprotective effect against traumatic brain injury (TBI) by activating the Nrf2 signaling pathway. Furthermore, similar findings have been reported in various NDs such as PD, AD, IR, and hemorrhagic stroke, and the effects are attributed to the antioxidant properties of HRW [46–48].

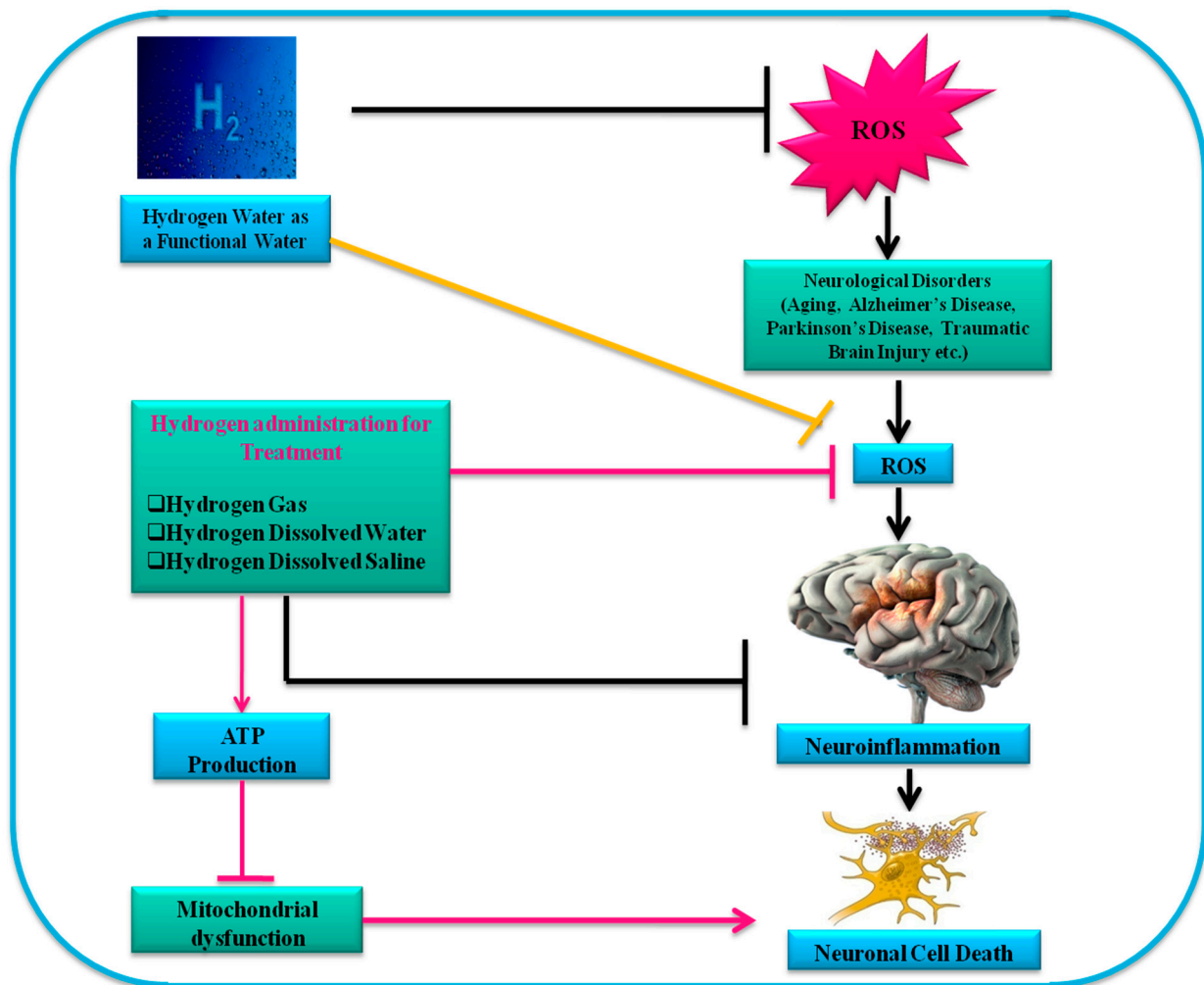


Figure 1. Beneficial effects of H₂ on different acute neuronal conditions.

4. H₂ Acts as an Antioxidant Agent

H₂ is highly reactive, protein denaturing, and promotes DNA breakdown. It can selectively reduce $\bullet\text{OH}$ and ONOO^- , causing a widespread reaction with proteins, lipids, and nucleic acids [49]. Based on animal models and clinical observations, an accumulated body of evidence has shown that H₂ can be efficiently used to protect against oxidative damage-associated diseases [50]. It decreases the amount of cytotoxic ROS ($\bullet\text{OH}$), successfully defending cells [50]. Other studies demonstrated similar protective effects of H₂ against IRI in organs, such as the liver, heart, and intestines [51]. In rat acute stroke models, 1% to 4% H₂ inhalation alleviates infarction dimensions [52]. H₂ inhalation prevents critical oxidative damage in 1% to 3% of the cases [53]. HRW intake attenuates learning and memory impairment in mice by reducing oxidative damage. Low-level (1, 3 v/100 v) gas respiration reportedly reduces OS, exceptional hypoxia-induced dyslipidemia, cardiomyocyte hypertrophy, and perivascular fibrosis in left ventricular in C57BL/6J mice [54]. Additionally, the ingestion of HRW triggers the Nrf2/antioxidant protection pathway and antioxidant gene expression to speed up the reduction in oral mucosal impairment in rats [55]. Similarly, the findings of another study showed that HRW had a beneficial effect on acute skin wounds in rats caused by radiation [56]. Several substitute pathways are currently being studied as main components of the energy moderating characteristics of H₂, including: (1) ghrelin-linked upregulation of ghrelin receptor (GHS-R1 α); (2) ghrelin-linked motivation of glucose transporter 1; (3) non-ghrelin linked stimulation of glucose transporter 4; and (4) non-ghrelin linked improved expression of fibroblast growth factor

21 (FGF21), a regulator of energy expenses [57,58]. HRW has shown neuroprotective properties in a murine MPTP-induced PD model [45,59,60]. Lin and colleagues reported that HRW reduces OS in patients with chronic hepatitis B and metabolic syndrome [61].

Studies have shown that H₂ may have benefits by activating the Nrf2 signaling pathway, thus improving antioxidant activity and reducing OS, apoptosis, and inflammation [46,62]. H₂ increases the antioxidant activities of enzymes in radiation and TBI through the upregulation of Nrf2 [63]. The basic anti-inflammatory mechanism of H₂ can even be used by macrophages via the Nrf2 signaling pathway [64]. Nrf2 is a transcription factor that combines antioxidant response elements to control the expression of antioxidants, protecting the body from injury and inflammations against oxidative damages [65].

5. Anti-Inflammatory Effects of H₂ in Different Neurodegenerative Disease Models

Numerous studies have reported the anti-inflammatory action of H₂ [63,64,66]. The rapid spread, high penetrability, and absence of clear side effects are some of its advantages. H₂ scavenges ROS radicals and is extremely effective in reducing inflammation in numerous tissues and organs, including the heart, brain, and lungs, and recognized to be a defender against oxidative damage [67,68]. HRW has been widely studied for its ability to inhibit inflammatory reactions and alleviate neuronal apoptosis [18,69]. Microglia is likely to cause neuroinflammation in the brain. Activated microglia and ROS produce pro-inflammatory cytokines. One of the studies showed that H₂ has a promising effect on prevention and inflammation related to perinatal brain injury in in vitro and in vivo models [70]. Furthermore, the same study reported that HW prevents lipopolysaccharide (LPS)-induced production of ROS by microglia and reduces LPS-induced microglial neurotoxicity [70]. Several studies have shown that HS can mitigate intestinal infections such as intestinal IR damage, ulcerative colitis, and colon inflammation [71,72]. Moreover, HRW has shown preventive effect against the superoxide ions formation in vitamin C-depleted SMP30/GNL-knockout mice during hypoxia–re-oxygenation conditions [73]. Additionally, one of the studies reported that the addition of H₂ to haemodialysis solutions had anti-inflammatory and anti-hypertensive action against the haemodialysis patients, suggesting it as a therapeutic option for uremia patients [74]. In another study, the role of reduction in athletes' muscle was enhanced by using H₂ in the case of intensive physical practice [21]. Domoki and colleagues reported that 2.1% air ventilation augmented by hydrogen substantially maintained cerebrovascular reactivity to hypercapnia and decreased neuronal damage caused by asphyxia-re-ventilation in a perinatal asphyxia newborn pig model [75]. In addition, HRW prevented endoplasmic stress and upregulated HO-1 expression [64]. HRW also ameliorates cognitive impairment in mice with accelerated senescence [53].

6. Effects of Molecular Hydrogen on Animal and Human Models of Neurodegenerative Diseases

PD is caused by the death of dopaminergic neurons at the SNpc of the midbrain and is the second most common ND after AD. PD is caused by two mechanisms: excessive OS and the abnormal ubiquitin–proteasome system [17,76]. Dopamine itself is a prooxidant and dopaminergic cells are intended for exposure to high levels of ROS. In the neuronal cell body, an irregular ubiquitin–proteasome system often induces accumulation of insoluble α -synuclein, resulting in neuronal cell death. By stereotactically injecting catecholaminergic neurotoxin 6-hydroxydopamine into the right striatum, a research group created a rat hemi-PD model, and H₂ was shown to have a positive impact [77]. Another study demonstrated a similar prominent effect of HRW on an MPTP-induced mouse model of PD [76]. It is interesting to note that the H₂ levels used for MPTP mice were only 5%, the second-lowest in all studies on rodents or humans that had previously been published.

AD is the most common ND and is characterized by irregular β -amyloid (A β) and tau accumulation, with large aggregates known as senile plaques and neurofibrillary tangles [78]. Various researches have demonstrated the effects of H₂ in different animal models of AD [17,33,46]. One research group reported that administration of HW prevented cognitive impairment and inhibited OS [33]. At the same time, they observed that HW restored

neural proliferation of the dentate gyrus after restraint stress [33]. Li and colleagues developed an intra-cerebroventricular injection rat model of A β (1–42) AD [79]. With HS treatment, they found that reduced learning and memory impairments and reduced A β caused neural inflammation [79]. HS also suppressed lipid peroxidation and inflammatory mediators, such as IL-6 and TNF- α [79]. Furthermore, Wang and colleagues reported that the protective effects of HS may be due to the activation of c-Jun N-terminal Kinase (JNK) and nuclear factor κ B (NF- κ B) pathways [80]. Additionally, a study in a dementia mouse model reported that administration of HW decreased OS and prevented the decline of memory and cognition while simultaneously increasing the lifespan in the mice. A clinical trial result showed that H₂ can notably improve cognition in the apolipoprotein E4 genotype carriers [53]. Studies have shown the relationship of apolipoprotein E in anti-inflammatory, antiapoptotic, and antioxidative effects during brain injuries [81]. In Table 1, the effects of H₂ on NDs, such as PD, AD, and other brain conditions are listed.

Table 1. Beneficial effects of H₂ against animal and human disease.

Diseases Category.	Species	Route of Administration	References
Alzheimer's disease	Animal	Saline	[79,80]
Parkinson's disease	Animal	Water	[76]
Corneal alkali-burn	Animal	Instillation	[82]
Spinal cord ischemia/reperfusion	Animal	Saline	[83]
Surgically induced brain injury	Animal	Gas	[84]
Spinal cord	Animal	Saline	[83,85]
Spinal cord injury	Animal	Saline	[85]
Senile dementia in senescence-accelerated mice	Animal	Water	[33,53]
Moderate to severe neonatal brain hypoxia	Animal	Gas	[86]
Cerebral infarction	Animal, Human	Gas, saline	[53,87]
Glaucoma	Animal	Instillation	[88]
Ear, hearing loss	Tissue, Animal	Medium, water	[89,90]
Radiation-induced lung injury	Animal	Saline	[91,92]
Lung transplantation	Animal	Gas	[93]
Burn-induced lung injury	Animal	Saline	[94]
Liver ischemia/reperfusion	Animal	Gas	[95]
Kidney transplantation	Animal	Water	[96]
Diabetes mellitus type I	Animal	Water	[97]
Diabetes mellitus type II	Human	Water	[98]

7. Hydrogen Therapy in Neonatal Brain Disorders

Brain disorders are the key factors in the development of autism, cerebral paralysis, mental delay, and various other impairments [99]. Perinatal asphyxia is one of the major causes of neonatal brain damage [99]. Inflammation and OS are major causes of neuronal apoptosis hypoxia–ischemia [100]. Cai and colleagues have reported the reduction of neuronal apoptosis from neonatal hypoxia in rats with H₂-gas inhalation [101]. Abnormal behavior in rats was improved 5 weeks after hypoxia–ischemia with HS administration in a study [102]. H₂ gas reduced neuronal damage caused by the cerebral cortex, hippocampus, basal ganglia, and hypoxia–ischemia brain ventilation in newborn pigs [75]. One study demonstrated that the inhalation of H₂ gas extended the after-asphyxia period from 4 h to 24 h in newborn pigs, highlighting the H₂ gas translation potential [103]. Administration of H₂ in neonates with ischemic brain injury was found to be highly effective in prognostic improvement. Mano and colleagues also reported the improvement of hippocampal damage caused by IRI, through maternal HRW administration by 4-hydro-xynonenal and 8-OHdG on day 7 after birth [25]. Furthermore, another study reported that H₂ improved fetal mouse brain injury caused by maternal exposure to LPS [70]. H₂ administration in

different forms, such as HRW, HS, or hydrogen inhalation, exhibits anti-inflammatory and antioxidant effects, as observed in many studies [33,79,80,84]. H₂ can also stimulate energy metabolism to reduce neuronal damage. For example, it could upregulate the expression of FGF21 [104]. These findings indicate that prenatal H₂ administration may be an effective approach for the treatment of inflammatory fetal response syndrome [104]. One study showed that sevoflurane exposure causes abnormal social behavior, similar to autism, in mice [105]. With this, Yonamine and colleagues reported that H₂ gas treatment eliminates the increased OS caused by sevoflurane in neonatal mice [106]. In addition, co-administration of H₂ prevented abnormal maternal behavior later in adulthood resulting from neonatal exposure to sevoflurane, which indicates a considerable H₂ gas potential in reducing adverse effects of anesthetic exposure [106,107].

8. Mechanisms of Hydrogen Treatment in Neurodegenerative Diseases

Understanding the mechanisms of action of H₂ in NDs is significant to fully explore the use of H₂ in clinical therapy. OS and inflammation mainly contribute to the pathogenesis of AD, PD, and other neurodegenerative disorders. AD is the most common ND that causes dementia [10,17,78]. In most cases, AD patients have decreased learning and memory, cognitive impairment, and social and emotional disorders [3,108]. Mitochondrial damage is also caused by tau protein, resulting in energy dysfunction, ROS production, and ultimately damage to synaptic properties. Tau protein also causes mitochondrial damage, leading to energy dysfunction, ROS production, and ultimately damage to synaptic properties. The overproduction of A β in the brain results in the dysfunction of mitochondrial complexes that contribute to ROS overproduction and adenosine triphosphate (ATP) depletion [80,108,109]. ATP is important for axonal transport and neurotransmission and contributes to the maintenance of ion channel function and ion balance, both internally and externally, in cells. The depletion of ATP is, therefore, the reason for mitochondrial damage. In addition, an increase in ROS causes a shift in the poles of the mitochondrial pore that causes ions of calcium to flow into mitochondria, thus aggravating mitochondrial damage [109]. ROS can also affect membrane function, leading to lipid peroxidation, encouraging apoptosis in cells, and a decrease in the number of neurons. In short, the pathogenic mechanistic systems of AD are known to include cholinergic function disorder, amyloid cascade, OS, inflammation, excitotoxicity, and steroidal hormone deficiencies [110]. In NDs, pro-inflammatory cytokines, such as NF- κ B, IL-1 β , IL-6, IL-10, TNF- α , C-C motif chemokine ligand 2 (CCL-2), interferon- γ , and intercellular adhesion molecule-1, are involved in the anti-inflammatory effects of H₂ [15,26,43]. The decrease in the nuclear-binding domain leucine-rich repeat and pyrin domain-containing protein-3 (NLRP3) in AD transgenic mouse models has been shown to inhibit memory impairment and A β deposition [111]. A study by Ren and colleagues showed that H₂ inhibits NLRP3 inflammatory activation in AD brains [112].

Additionally, Lin and colleagues reported that HRW can boost the AMP-activated protein kinase (AMPK). Sirt1-FoxO3a pathways may play a role in antioxidant stress, reduce mitochondrial damage, and act as a neuroprotective agent and neutralize ROS caused by AD [113]. Sirt1 may also induce autophagy that plays a neuronal role in many NDs [114]. Autophagy is an essential process to preserve cell homeostasis and, through the promotion of autophagy in AD [114], H₂ may also protect cells. Phospho-p38 and JNK participate in cell survival control as members of the mitogen-activated protein kinase (MAPK) [15,80]. Henderson and colleagues reported an improved Bax phosphorylation of the AD brains and mitochondrial translocation caused by OS and p38K [115]. The results in many animal models have shown that H₂ water can stop phospho-p38 and JNK activation [15,80,116].

Interestingly, Hou and colleagues reported that HRW improves the cognitive function in female AD mice by reducing brain estrogen levels, ER β , and brain-derived neurotrophic factor (BDNF) expression, but not in males, and without affecting the β -amyloid precursor protein treatment and A β clearance [117]. In addition, inflammation and OS were more

pronounced in female AD mice than in males. This suggests that hydrogen can also be involved in the pathogenesis of AD by affecting the ER β -BDNF estrogen signaling pathway [117]. MAPK and the signaling pathway of protein kinase C can inhibit AD and neuronal damage [70]. It was also thought that BDNF and tyrosine kinase recipient B were designed to regulate the expression of neuronally related genes. Finally, synaptic plasticity, learning, and the ability to remember are enhanced by H₂ treatment [70]. In addition, the estrogen ER β -BDNF signaling pathway was related to the antioxidant and anti-inflammatory effects in AD [118]. In pathological AD prevention, the activation of ER β signaling also involves ROS scavenging [118]. Therefore, the main mechanisms of action of H₂ include anti-inflammatory, antioxidative, and antiapoptotic properties, and autophagy regulation and the hormone signal pathway [15].

9. Studies Related to Hydrogen Therapy in Neurodegenerative Diseases

Numerous studies have investigated the potential use of H₂ treatment in various NDs. In addition, HW was observed to increase malondialdehyde and 4-hydroxy-2-nonenal, and OS markers enriched by chronic restriction. In addition, an increase in malondialdehyde and 4-hydroxy-2-nonenal and OS markers enriched by chronic restriction was observed by HW. At the same time, the decrease in the number of proliferating cells in the dentate gyrus, after restraining stress, was restored [33]. Neurogenesis continues to change in the adult hippocampus, which is important in learning, memory, and plasticity. A reduction in hippocampal neurogenesis may cause cognitive impairments and pathologic tau aggregations, which are characteristic of AD [119]. One report stated that HW can reduce memory and learning impairment and A β inflammation, and significantly improve memory and long-term potentiation (LTP), and synaptic plasticity, which has implications in learning and memory [79].

Moreover, another study revealed that HS protection might be caused by the inhibition of JNK and NF- κ B activation [80]. Similarly, one study revealed that age-related impairment of learning capacity and memory in senescence-accelerated mouse prone 8 strains could be improved in 30-day HW consumption [120]. Numerous studies have demonstrated that apolipoprotein E has anti-inflammatory, antioxidant, and anti-apoptotic effects during brain injury [53,81]. However, apolipoprotein E4 is thought to play an active role in the pathological process of AD to promote oxidation, phosphorylation, and A β production [121]. Table 2 lists the various experimental studies related to NDs. However, there are still numerous ongoing studies and clinical trials all over the world.

Table 2. Experimental studies related to H₂ in Alzheimer's disease (AD).

Author	Animals/Cells	Model	Results	References
Nagata et al.	Mice	Dementia induced by chronic physical restraint stress	Molecular hydrogen inhibited memory and learning from stress	[33]
Lin et al.	Human neuroblastoma SK-N-MC cells	AD	AMPK-Sirt1-FoxO3a pathway and excessive ROS neutralization to protect the neuron is not regulated by hydrogen-rich water	[113]
Nishimaki et al.	Mice	Dementia	In apolipoprotein genotype carriers, molecular hydrogen enhances cognition	[53]
Hou et al.	Mice	AD	Water-rich in hydrogen inhibits NLRP3 and diminishes the signal pathway of estrogen-ER β -BDNF	[117]
Li et al.	Rats	AD	The saline-rich hydrogen enhances the memory by inhibiting OS and reducing interleukin-6 and TNF- α and activating astrocytes	[79]

10. Other Neurological Disorders

Numerous studies have shown a high occurrence of CNS disorders, including retinal ischemia [82,88,121]. Topical HS eye drops have been administered on a regular basis during ischemia periods, and the drops have been found to suppress an increment of $\bullet\text{OH}$. Furthermore, HS reduces the number of apoptotic and oxidative cells with retinal stress, and prevent retinal dilution with associated activation of Muller glia, astrocytes, and microglia [122]. Moreover, it has been reported that H_2 protected itself against antimycin A and a cisplatin-causing strain in auditory tissue cultures, suggesting that H_2 prevented hair cell destruction, partly by reducing ROS production [123–125]. When the ear is exposed to loud sounds, the over-stimulation of the hair cells leads to ROS development that causes cell death [90,123]. Intraperitoneal HS injection has recently been shown to protect guinea pigs against noise-induced hearing loss [125].

In addition, in developing countries, TBI and spinal cord injury cause most deaths and disabilities. There are an estimated 200–600 injuries per 100,000 people in different regions for CNS injuries [126]. Ji and colleagues reported that H_2 administration protected the animal TBI model against neuronal cell death [127]. H_2 gas inhalation prevents the growth of oxidative products and improves enzyme activity in the brain tissue of endogenous antioxidants (SOD and CAT), resulting in a rat TBI model [127]. Moreover, Dohi and colleagues have reported that the use of HRW inhibited TBI edema and completely blocked the expression of pathologic tau in mice [128]. Additionally, H_2 treatments have also been used to prevent sepsis and LPS inflammation in the brain and to protect carbon monoxide rodents from toxicity [52,129].

11. Therapeutic Efficacy of H_2 Molecule

H_2 has extensive and numerous effects on NDs including PD. Moreover, due to its beneficial efficacy with no adverse effects has been reported to date. The brain can be provided with detectable H_2 amounts through the inhalation of H_2 gas as well as HS injection [28]. On the other hand, the H_2 concentration is too low to detect using a conventional hydrogen sensor after HRW administration. Interestingly, HRW has shown better results than H_2 gas in an animal PD model [18]. Matsumoto and colleagues reported that HRW increased gastric expression and ghrelin secretion in mouse models [130]. Interestingly, the neurological impact of HRW was negated by a growth hormone secretagogue receptor (GHSR) (ghrelin receptor antagonist) and ghrelin-secretion antagonist [130]. Ghrelin was found to encourage the release of growth hormones and food intake, and GHSRs are manifested in substantia nigra dopaminergic neurons. Ghrelin is neuroprotective in PD as it inhibits microglia-related neuroinflammation [131]. Based on these results, higher levels of H_2 in HRW are expected to directly affect gastric cells producing ghrelin and regulate intracellular signaling secretions of ghrelin [130].

In addition, one of the studies has shown that HO-1 and its enzyme products are associated with ischemic brain damage. However, a similar study showed that H_2 gas inhalation does not improve lung hyperoxia in Nrf2-knockout mice and does not inhalation during hyperoxia has been reported by Kawamura and colleagues to increase blood oxygenation, reduce inflammation, and induce the expression of HO-1 in the lung [132]. HO-1 functions in carbon monoxide, free ions, and biliverdin production in enzymatic heme, and is monitored in transcription through Nrf2. Therefore, HO-1 is involved in the defense of cells against OS, and it has been hypothesized that HO-1 could be a neuroprotective therapeutic target. HO-1 mutations have been related to a high risk of triggering HO-1 expression [53,55,132].

In addition, Iuchi and colleagues have shown that H_2 even at lower levels (approximately 1% *v/v*) modulates the Ca^{2+} signals and regulates gene expression by changing the production of oxidized phospholipids [133]. As H_2 is the smallest and the non-polar molecule, some protein mediators are unlikely to be binding. Further research is needed to identify the direct target molecule of H_2 . H_2 regulates the cell response to OS, inflammation, and apoptosis [27].

Humans are innocuous when exposed to hydrogen. The risk of explosion at concentrations above 4% is a limiting factor in using H₂ gas studies. Safer storage technologies, especially hydrides, are being developed [27,134]. The risk of explosion can also be eliminated by the dissolution of H₂ in water or normal saline, either orally or intravenously [134].

12. Novel Advantages of H₂ Molecule

To date, there is insufficient information about the pharmacodynamics and toxicity of H₂. The therapeutic effect of H₂ is already recognized in the medical field. However, before recognition as an innocuous and effective remedial gas, numerous issues must be resolved [27,135]. As a valuable treatment agent in clinical medicine, H₂ has numerous potential benefits. Its physical characteristics and a low molecular mass enable its rapid dispersion into the cytosol, other target cells, and the sub-cellular compartments through the plasma membrane [14,15,27]. H₂ delivery does not influence physiological parameters including oxygen saturation, temperature, pH, and blood pressure [27,31].

In the biomedical sciences, the outcome of H₂ appears to be similar to other types of therapeutic gas families, such as nitric oxide, hydrogen sulfide, and carbon monoxide. H₂ was seriously considered only 10 years ago as an unreactive gas; scientists now see H₂ as a healing agent and a preferred treatment course [136]. Although existing information on H₂ remains insufficient, the promising characteristics of H₂ therapy, as established through some pilot studies, are the motivation for future research; appreciation of the activities of H₂ could guide us towards new forms of H₂ therapy for many conditions and human diseases.

13. Concluding Remarks

Although several NDs are currently incurable, the therapeutic potential action of H₂ administration for the prevention, treatment and mitigation of these disorders is indicated by numerous studies. Although some NDs are currently not curable, several studies indicate the therapeutic action. Potential of H₂ administration to prevent, treat and alleviate certain disorders. To date, no reports of adverse effects of H₂ have been illustrated. H₂ is relatively easy to implement, inexpensive, and efficient in everyday health practice. However, the optimal route and dose of H₂ administration for each disease remain to be established. This review summarizes current evidence on the preventive and therapeutic roles of H₂ in different animal models and the human pathologies of OS-related NDs, inflammation and apoptosis. More studies are required to expand the basic concepts and understanding of H₂ for its optimal clinical use.

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Abbreviations

OH	Hydroxyl radical
AD	Alzheimer’s disease
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
A β	Amyloid beta
BDNF	Brain-derived neurotrophic factor
CAT	Catalase
CCL-2	C-C motif chemokine ligand 2
CNS	Central nervous system
FGF21	Fibroblast growth factor 21
FIRS	Inflammatory fetal response syndrome
GHSR	Growth hormone secretagogue receptor
GPx	Glutathione peroxidase
HD	Hemodialysis
HO-1	Heme oxygenase-1
HRW	Hydrogen-rich water
HS	Hydrogen dissolved saline
HW	H ₂ -dissolved water (or H ₂ -water)
IL	Interleukin
IR	Ischemia-reperfusion
IRI	Ischemia-reperfusion injury
JNK	c-Jun N-terminal Kinase
LPS	Lipopolysaccharides
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MTTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
ND	Neurodegenerative disease
NF- κ B	Nuclear factor κ B
NLRP3	NLR Family Pyrin Domain Containing 3
Nrf2	Nuclear factor-E2-related factor 2
ONOO-	Peroxynitrite
OS	Oxidative stress
PD	Parkinson’s disease
ROS	Reactive oxygen species
SNpc	Substantia nigra pars compacta
SOD	Superoxide dismutase
TBI	Traumatic brain injury
TNF- α	Tumor necrosis factor- α

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