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Molecular Hydrogen: an Emerging Therapeutic Medical Gas for Brain Disorders

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Abstract

Oxidative stress and neuroinflammation are the main physiopathological changes involved in the initiation and progression of various neurodegenerative disorders or brain injuries. Since the landmark finding reported in 2007 found that hydrogen reduced the levels of peroxynitrite anions and hydroxyl free radicals in ischemic stroke, molecular hydrogen's antioxidative and anti-inflammatory effects have aroused widespread interest. Due to its excellent antioxidant and anti-inflammatory properties, hydrogen therapy via different routes of administration exhibits great therapeutic potential for a wide range of brain disorders, including Alzheimer's disease, neonatal hypoxic-ischemic encephalopathy, depression, anxiety, traumatic brain injury, ischemic stroke, Parkinson's disease, and multiple sclerosis. This paper reviews the routes for hydrogen administration, the effects of hydrogen on the previously mentioned brain disorders, and the primary mechanism underlying hydrogen's neuroprotection. Finally, we discuss hydrogen therapy's remaining issues and challenges in brain disorders. We conclude that understanding the exact molecular target, finding novel routes, and determining the optimal dosage for hydrogen administration is critical for future studies and applications.

Keywords Hydrogen · Medical gas · Neuroinflammation · Oxidative stress · Alzheimer's disease · Brain disorders

Background

As the smallest gas molecule and the world's most abundant element, molecular hydrogen comprises two electrons and two protons held together by a non-polar covalent molecule [1]. Hydrogen first showed its therapeutic effects in a mouse squamous cell carcinoma model after 2 weeks of hyperbaric hydrogen therapy [2]. In 2007, the antioxidative effect of hydrogen was demonstrated and aroused increasing concern by reducing cytotoxic oxygen radicals [3]. In the same study, the brain injury was significantly attenuated by inhaled hydrogen through buffering the cytotoxic oxidative stress-induced oxidative damage in an acute ischemia/reperfusion injury rat model [3]. Following this important finding, extensive work reported excellent anti-inflammatory effects and antioxidative stress of hydrogen in various brain disorders [1].

Oxidative stress is indispensable in aging and various neurological disorders [4]. In Alzheimer's disease (AD), oxidative stress has been considered an early and essential pathogenic operator of AD [5]. In both transgenic and non-transgenic AD animal models, the reactive oxygen species (ROS) induce oxidative damage to proteins, lipids, and nucleic acids generating protein carbonyls, lipid peroxides, and DNA/RNA modifications [5–7]. ROS-induced oxidative damage contributes to neuronal degeneration in the cortex and hippocampus [5–7]. Similarly, oxidative stress contributes to the damage and degeneration of dopaminergic neurons in Parkinson's disease (PD) [8]. The dysfunction of redox potential disrupts the normal function of essentially biological processes and finally leads to the loss of dopaminergic neurons [8, 9]. Additionally, substantial evidence suggests that oxidative stress is implicated in multiple brain injuries, including ischemic stroke, traumatic brain injury (TBI), and neonatal hypoxic-ischemic encephalopathy (HIE) [7, 10, 11]. For instance, excessive ROS contributes to secondary injury after TBI, and targeting the ROS generation attenuates secondary brain injury and inhibits epilepsy [12,

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13]. Similar results are found in HIE and global cerebral ischemia [10, 14]. These findings suggest that oxidative stress constitutes essential pathophysiology in multiple brain diseases and is recognized as an important target for the prevention and treatment of brain disorders [7].

Neuroinflammation and oxidative stress are intimately related [15]. The excessive release of ROS and reactive nitrogen species (RNS) activates the signaling pathways that induce the activation of glial cells, including microglia and astrocytes [16]. The inflammatory cytokines released by excessively activated glial cells further increase oxidative stress and damage mitochondria. This process induces vicious cycles and maintains the increased or high secretion of proinflammatory cytokines [17, 18]. Like oxidative stress, neuroinflammation is a typical pathology that contributes to the initiation and progression of multiple neurodegenerative diseases and brain injury [10, 11, 19, 20]. According to previous studies, microglia mediate Aβ propagation at the early stage of AD and contribute to the accumulation of Aβ at the following stage [21–23]. Additionally, astrocyte, another primary glial cell type, mediates myelin phagocytosis and is implicated in the pathogenesis of ischemic neuronal death [24–26]. In the photothrombotic stroke model, the neuroinflammation-induced harsh microenvironment enhances stroke development and inhibits post-stroke recovery [11, 27]. Notably, anti-inflammatory therapy show promise in slowing down the disease progression in the animal model of multiple sclerosis (MS), a neurodegenerative disease characterized by neuroinflammation [28].

In a nutshell, oxidative stress and neuroinflammation are prominent traits of various neurodegenerative diseases and brain injuries [29, 30]. The excellent anti-inflammatory effects and antioxidative stress of hydrogen suggest that hydrogen is a promising therapeutic medical gas for brain disorders [1]. Although hydrogen therapy's effectiveness and underlying mechanism have witnessed tremendous progress since 2007, the current understanding of the exact underlying mechanism and the optimal administration of hydrogen in neurodegeneration and brain injuries is still limited. This review summarizes the existing routes for hydrogen administration, provides an extensive review of hydrogen in various brain disorders, and discusses the remaining issues and challenges in future studies and applications.

Routes for Hydrogen Administration

Hydrogen Gas Inhalation Inhalation of hydrogen gas is one of the most commonly utilized hydrogen administration methods [31]. In previous studies, hydrogen in various concentrations has been employed, including 1% [3], 1.3% [32], 2% [3, 33], 2.1% [34], 4% [3], and 66.7% [35]. Inhaled hydrogen gas enters the lungs, diffuses into the alveoli, and then transfers throughout the body via the vascular system [36]. For safety concerns, the most widely studied hydrogen is maintained within 1–4% [36]. The inhaled hydrogen diffuses, transfers rapidly, and responds efficiently to defend against acute oxidative stress [36]. In terms of safety, eight healthy adult participants underwent 2.4% hydrogen for 72 h via a high-flow nasal cannula in a previous study [36]. Promisingly, hydrogen inhalation does not cause adverse effects, suggesting that hydrogen administration via gas inhalation is safe and well tolerated. However, a protocol with a higher concentration and longer time should be analyzed in the future [36].

Hydrogen-Rich Water Drinking Although gas inhalation is one of the most straightforward approaches for hydrogen administration, it is not practical for continuous hydrogen therapy or preventive use [37]. Therefore, in previous studies, hydrogen-rich water has gained much attention [38]. Hydrogen administration via drinking hydrogen-rich water is more portable and safer than hydrogen gas inhalation for preventive use in daily life. The solubility of molecular hydrogen in water is up to 0.8 mM at room temperature under atmospheric pressure [37]. Because molecular hydrogen is a neutral molecule, its solubility is relatively low. Therefore, as reported previously, hydrogen with high pressure (0.4 MPa) was applied to increase the concentration of hydrogen to a supersaturated level and stored in an aluminum bag without dead volume [39]. Notably, the hydrogen-rich water should be stored in an aluminum container rather than a glass or plastic one because hydrogen penetrates the glass or plastic walls of the container rapidly and almost disappears around 8 h [37]. In addition, hydrogen-rich water can be made by electrolysis or by placing a magnesium metal or hydride into drinking water [40]. Although only 41% of hydrogen in hydrogen-rich water can be utilized within the body [41], water with a low concentration of hydrogen is also effective in improving cellular and metabolic processes [39].

Hydrogen-Dissolved Saline Injection Although hydrogen administration via inhalation and drinking is portable, safe, and easy to use, the intake dose to a specific target area is limited [42]. Hydrogen-dissolved saline injection is an approach that can provide a substantial amount of hydrogen to the affected area. In previous animal studies, intraperitoneal injections of hydrogen-rich saline showed neuroprotective potential in multiple brain disorders [43, 44]. However, because the hydrogen-dissolved saline injection is invasive, it is challenging to be accepted as a way for preventive use or daily hydrogen treatment [42]. Furthermore, frequent injections of hydrogen-dissolved saline have the risk of cross-infection and would be very dangerous if hydrogen-dissolved saline were injected directly into the vein [42].

Primary Mechanism of the Neuroprotective Effect of Hydrogen

Anti-inflammatory Properties The anti-inflammatory effect of hydrogen is one of the primary reasons for the application of molecular hydrogen in various brain diseases [45–48]. Usually, inflammation is considered a defense mechanism that protects the tissue from infection and damage and is involved in activating immune cells and releasing inflammatory cytokines [42]. In the brain, neuroinflammation is prevalent in neurodegenerative diseases and a common feature in brain injuries [7]. The overactivation of glial cells and excessive release of inflammatory factors contribute to the initiation of several neurodegenerative diseases (e.g., multiple sclerosis) [7]. They are also essential factors that affect the pathogenesis and progression of brain injury [7]. The anti-inflammatory effects of hydrogen have been widely studied [45–48]. For example, the increased proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, and the reactive astrogliosis induced by spinal cord injury are attenuated by hydrogen-rich saline injection [49]. In addition, the overactivation of microglia is attenuated, and the microglia polarization is promoted toward the anti-inflammatory M2 phenotype in a middle cerebral artery occlusion model [50]. Similar phenotypes (A1 and A2 astrocytes) are also observed in astrocytes [51]. The M1/M2 microglial polarization affects the transformation of A1/A2 astrocytes [51], indicating that hydrogen has the potential to regulate A1/A2 transformation.

Antioxidant Properties Since the discovery of hydrogen's cytoprotective and antioxidant effects in a focal stroke model [3], molecular hydrogen has been widely studied in neuroscience due to its ability to scavenge powerful oxidants in brain diseases [52]. The disequilibrium between the production of free radicals and the endogenous antioxidant defense system is considered one of the essential pathological processes in most brain diseases [7, 10]. The hydrogen worked as an electron donor for RNS and ROS to scavenge ONOO- and ·OH [3]. In most cases, hydrogen only selectively scavenges the excessive hydroxyl radical by reaction of $H_2 + \bullet OH = H_2O + \bullet H$. The produced •H is removed by another reaction of $\bullet H + O_2^- = HO_2^-$ [53]. It is also possible that •H reacts with •OH to form H_2O [54]. Other necessary ROS and RNS for normal signaling regulation are preserved [53]. In addition, the regulation of the KEAP1/NRF2/ARE signaling pathway contributes to the antioxidative effects of hydrogen [55]. Under normal physiological conditions, the KEAP1 binds to NRF2 and modulates NRF2 levels by ubiquitination and proteasomal degradation within the cytoplasm [56]. In response to oxidative stress, the cysteine modification-induced conformational changes in KEAP1 allow NRF2 to evade degradation and escape from KEAP1 trapping [5]. The phosphorylated NRF2 moves from the cytoplasm to the nucleus and binds to ARE, promoting the transcription of detoxification and cytoprotective genes [5]. Hydrogen-rich water, hydrogen gas, and the injection of hydrogen-rich saline activate the KEAP1/NRF2/ARE pathway and promote the antioxidant capacity in various brain diseases, including TBI [57], depression [58], and anxiety [58].

Endogenous Hydrogen Produced by Gut Microbiota

Gut bacteria are one of the primary sources of endogenous hydrogen [59]. Members of the Enterobacteriaceae family, strains of the genus Clostridium, and anaerobic cocci contribute to the most percentage of hydrogen production released by gut bacteria [59]. As mentioned previously, hydrogen gas can reduce the expression of proinflammatory cytokines, neutralize hydroxyl radicals, and exerts cytoprotective effects [3, 51]. The role of endogenous hydrogen in brain disorders has been investigated in neurodegenerative disorders. For example, a previous study found that PD patients lacked Prevotella and Clostridium (hydrogen-releasing bacteria) and compromised gut microbiota was always accompanied by a worse motor ability [59, 60]. This finding indicates that endogenous hydrogen released by gut microbiota is involved in the progression of PD. Similarly, endobacteria-produced hydrogen is fundamental for proper neuronal function, and the changes in endobacteria-produced hydrogen also contribute to AD pathogenesis [61]. Although there are relatively few studies regarding the role of endogenous hydrogen produced by gut microbiota in brain disorders, the findings mentioned previously suggest that exogenous hydrogen may represent a potential agent for neurodegenerative diseases and brain injury.

The solubility of hydrogen depends on temperature and pressure. As mentioned previously, the solubility of molecular hydrogen in water is up to 0.8 mM at room temperature under atmospheric pressure [37]. The hydrogen solubility in the plasma and the blood is around 6.44 μmol/L/kPa at 37 °C [62]. The hydrogen solubility and the half-life of hydrogen in the body fluids are significant for the endogenous/exogenous hydrogen conferring its neuroprotective and practical application. However, the hydrogen solubility in cerebrospinal fluid and the half-life of hydrogen in various body fluids remain unclear and deserve further investigation.

Molecular Hydrogen Therapy in Alzheimer's Disease

As one of the most common forms of dementia in the elderly, AD affects more than 6 million individuals in the USA and more than 50 million worldwide [6, 63]. It is characterized

by progressive cognitive decline, extracellular β-amyloid plaques, intracellular neurofibrillary tangles, neuroinflammation, mitochondrial dysfunction, and oxidative stress [6]. In AD, the Aβ accumulation and tau pathology contribute to mitochondrial function, leading to the excessive production of reactive oxidative species and ATP depletion, which promote Aβ deposition and tau hyperphosphorylation [6]. Evidence indicates that maintaining the cellular redox balance is essential for AD prevention and therapy [6, 64].

A growing number of studies reveal that hydrogen possesses antioxidant and anti-inflammatory effects, indicating its therapeutic potential in AD [1, 65]. In a rat model of Aβ intracerebroventricular injection-induced AD, hydrogen-rich saline exhibited its beneficial effect by significantly improving spatial learning and memory [66]. Moreover, long-term potentiation, an essential process in the context of synaptic plasticity supporting learning and memory functions, was impaired in the Aβ-treated group. However, interestingly, hydrogen-rich saline significantly enhanced long-term potentiation and improved the synaptic information storage processes [66]. Hydrogen's beneficial role in AD is inseparable from its antioxidant and anti-inflammatory effects. For instance, Aβ intracerebroventricular injection induces pronounced lipid peroxidation, oxidative DNA damage, and neuroinflammation, which were alleviated by hydrogen-rich saline treatment [66, 67]. Furthermore, previous studies have indicated that inhibiting the c-Jun N-terminal kinases signaling pathway, an imperative in stress signaling pathways implicated in neuronal plasticity, neuronal degeneration regeneration, and cellular apoptosis, is a potential approach for AD treatment [68]. Intriguingly, the hydrogen inhibits the JNKs pathway, indicating that the therapeutic effects of hydrogen in AD may be mediated by the inhibition JNK pathway [68].

Moreover, the gender-dependent neuroprotective effect is found in a transgenic AD mouse model. As reported by a previous study, hydrogen-rich water administration only improves cognitive function in the female APP/PS1 mice without affecting male transgenic AD mice [69]. Consistent with this finding, the hydrogen-rich water attenuated oxidative stress and neuroinflammation. However, these effects are more profound in female AD mice than males [69]. Further analysis suggested that the sex-specific effects of hydrogen may rely on the changes in brain estrogen levels, estrogen receptor beta (ERβ), and the brain-derived neurotrophic factor (BDNF) [69]. The estrogen levels, Erβ, and BDNF levels in the female AD mice decreased, but no apparent changes are detected in male AD mice [69]. Although the change of BDNF in the male AD mice is inconsistent with other studies and needs further analysis in this mouse model [70, 71], the hydrogen reverses the changes in estrogen levels, Erβ, and BDNF levels. These findings suggest that the gender-dependent neuroprotective effect of hydrogen may partly depend on the activation of ERβ-BDNF signaling in AD pathogenesis [69].

Furthermore, an in vitro study using cultured human neuronal cells confirms the neuroprotective role of hydrogen [72]. For example, H_2O_2 exposure induces excessive hydroxyl radicals in human neuroblastoma, which is ameliorated prominently by hydrogen [72]. Notably, in the in vitro model of AD, the Aβ-induced cellular apoptosis is significantly attenuated in the hydrogen-rich cell culture medium [72]. The mechanistic study found that the activation of the AMPK/SIRT1/FOXO3a signaling pathway contributes to the protective effect of hydrogen [72]. Worked as a critical molecular sensor and modulator, AMPK is involved in the anti-aging signaling network. Similar to AMPK, the Sirt1-FoxO3a axis is a well-studied pathway that responds to oxidative stress and favors cell survival [72, 73].

Molecular Hydrogen Therapy in Neonatal Hypoxic-Ischemic Encephalopathy

Neonatal hypoxic-ischemic encephalopathy (HIE) is one of the most common but severe brain injuries that result in a high morbidity and mortality rate [10]. The HIE occurs when the neonatal brain is deprived of the blood and oxygen [10]. The impaired cerebral blood flow and oxygen deprivation lead to mitochondrial dysfunction, ATP depletion, oxidative stress, cellular damage, and neuronal apoptosis [74]. The progression of HI injury can be divided into primary and secondary energy failure [75]. The primary energy failure occurs when the hypoxic-ischemic insults initiate. When the ATP is deprived rapidly due to the decreased oxidative phosphorylation, the neurons change to anaerobic metabolism, resulting in lactic acid and hypoxanthine accumulation [75]. The rapid depletion of ATP causes the failure of numerous essential process that maintains cellular integrity, particularly the failure of sodium/potassium pumps. Next, the failure of Na/K pumps and the accumulation of metabolites induce depolarization of neurons, followed by excessive release of excitatory amino acids on the extracellular side and an additional influx of sodium and calcium [75, 76]. These changes finally induced cellular edema and early cell apoptosis.

Moreover, the primary energy failure-induced changes contribute to the secondary energy failure phase several hours to days after ischemia and hypoxia after the initial injury. During this process, mitochondrial dysfunction, excessive production of free radicals, and increased inflammation are involved in secondary energy failure and contribute to late cell death [75, 76]. Mitochondrial dysfunction and oxidative stress are crucial in brain damage following hypoxia and ischemia [77]. Although the low concentrations of reactive oxygen species ROS and RNS worked as

signaling molecules under physiological conditions, excessive free radicals induced oxidative damage to DNA, protein, and lipids during hypoxic-ischemic injury [77]. However, the mitochondria changes and oxidative damage contribute to the secondary phase of injury after ischemia and hypoxia, which induces persistent inflammation and mitochondrial dysfunction, exacerbating the neuronal injury [78].

Evidence suggests antioxidant treatments may alleviate neuronal damage following hypoxia–ischemia [78]. As mentioned previously, molecular hydrogen is one such antioxidant therapy for HIE [79]. In a neonatal HIE rat model, hydrogen therapy with 2% hydrogen is employed immediately following the hypoxic-ischemic insult. Intriguingly, hydrogen inhalation significantly reduced the infarct brain area and alleviated neuronal apoptosis time dependently in the cortex and hippocampus [80]. The neuroprotective effects of the hydrogen can be detected even with 30-min hydrogen inhalation [80]. As reported in the same study, 30-min hydrogen therapy significantly inhibits the activity of caspase-3 and caspase-12. Notably, caspase-12 is a vital regulator of ER stress-induced cellular apoptosis. It is proteolytically activated under ER stress-induced cellular apoptosis [81]. Therefore, the inhibitive effect of hydrogen on caspase-12 suggests the potential role of hydrogen in alleviating ER stress-induced apoptosis [80]. Another work using 3% hydrogen supports the neuroprotective effects of hydrogen in neonatal rats following HI insults [82]. The motor deficits and impaired learning and memory function were significantly attenuated by 3% hydrogen [82]. Moreover, similar to hydrogen therapy with 2% hydrogen, hydrogen therapy with 3% also exhibited a time-dependent neuroprotective effect, showing the most significant protective result with 90-min hydrogen inhalation, compared to 30-min and 60-min therapy immediately after HI insults [82]. Notably, hydrogen therapy may have a neuroprotective time window in HIE treatment [82]. For example, the protective effect of 90-min hydrogen therapy decreased if the treatment is initiated 12 h after HI insults and nearly disappeared 24 h following injury [82]. In vitro study further confirmed the neuroprotective role of hydrogen in the oxygen–glucose deprivation/reperfusion (OGD/R) model using cultured PC12 cells [82]. The OGD/R-induced PC12 apoptosis was prominently attenuated by 90 min H_2 therapy, and the protective role of hydrogen is abolished by heme oxygenase-1 (HO-1) knockdown. HO-1 is a critical enzyme in protecting against oxidative stress [83]. A further mechanistic study supports the MAPK/HO-1/PGC-1α pathway as one of the possible molecular mechanisms underlying hydrogen therapy's anti-inflammatory, anti-apoptotic, and antioxidative effects [82].

Therapeutic hypothermia is a standard treatment for HIE. However, hypothermia has limited efficacy, and nearly 50% of the neonates receiving the treatment still suffer from severe disability and death [10]. However, hydrogen can enhance the therapeutic benefits of hypothermia therapy against HI insults [84]. In a neonatal HI piglet model, hydrogen ventilation combined with mild hypothermia is administered 24 h after HI insults [84]. Interestingly, the combination therapy with hypothermia and hydrogen significantly alleviates the neurological deficits, and animals with hypothermia therapy alone only displayed a tendency for improvement [84]. Although hypothermia therapy alone cannot alleviate cellular apoptosis in the dorsal cortex, combination therapy with hypothermia and hydrogen ventilation significantly reduced the cellular apoptosis induced by HI insults [84].

However, hydrogen does not always show its neuroprotective effect in HIE. In addition to the treatment duration and therapeutic time window, the results of hydrogen therapy may also depend on the disease severity. For example, a previous study finds that post-hydrogen treatment with 2.9% hydrogen inhalation is ineffective in protecting neonates against moderate and severe neonatal HIE [85]. No significant changes are detected in the infarct volume and the lipid peroxidation marker following hydrogen therapy in HIE [85]. Unlike other preconditioning or pretreatment regimens, hydrogen preconditioning exacerbates the HI insult-induced brain damage, suggesting hydrogen therapy may only work as a treatment rather than a pretreatment approach to improve resistance to hypoxic-ischemic insults [85].

Molecular Hydrogen Therapy in Depression and Anxiety

Growing evidence suggests that oxidative stress and neuroinflammation are pivotal in the pathogenesis of depression and anxiety [86]. Patients or animals with depression or anxiety display increased neuroinflammation and oxidative stress in the brain and the periphery systems [87–89]. Consistent with this, studies found that pharmacological agents that induce oxidative stress in rats cause anxiety-like behavior and depression [90–92], suggesting that antioxidants may be a potential treatment approach for depression and anxiety [91, 93].

Hydrogen is a potential therapeutic gas for depression and anxiety due to its antioxidative, anti-inflammatory, and anti-apoptotic effects [42]. In a previous study, water or hydrogen-rich water is supplied to the animal at the commencement of the chronic unpredictable mild stress (CUMS) procedure [94]. Rats receiving a 4-week CUMS procedure exhibited apparent depressive-like behavior, including decreased sucrose preference and extended immobility [94]. Interestingly, hydrogen-rich water significantly prevents the CUMS-induced depressive-like behavior [94]. Further studies found significantly decreased IL-1β levels, caspase-1 activity, and ROS production in the hippocampus

and prefrontal cortex [94]. The caspase-1 is a cysteine protease that promotes the secretion of proinflammatory, including IL-1β [95]. The inhibited activation of caspase-1 in the hydrogen-treated group alleviates neuroinflammation and contributes to the attenuation of oxidative stress [94].

Repeated inhaling of high concentrations of hydrogen can also increase stress resilience [58]. For example, the mice receiving 1-h or 3-h daily hydrogen treatment with high concentrations (67%) for 14 days exhibit increased resilience to acute and chronic stress-induced anxious-depressive-like behavior [58], as evidenced by decreased immobility in the tail suspension and forced swimming test, improved novelty-suppressed feeding, and increased time spent in the central zone assed by the open field test [58]. Consistent with the previously mentioned time-dependent neuroprotective effect in HIE, mice receiving 3-h daily hydrogen are more resilient to acute stress [58]. The hypothalamic–pituitary–adrenal (HPA) axis is an indispensable adaptive neuroendocrine system in stress resilience and vulnerability [48]. Repeated inhalation of hydrogen significantly inhibited the chronic stress-induced changes of corticosterone and adrenocorticotropic hormone [48], the major hormones contributing to the HPA axis's response to stress [96, 97]. In line with the previous study, chronic stress-induced neuroinflammation is alleviated by hydrogen inhalation [48]. More interestingly, hydrogen inhalation-induced resilience to acute stress in adolescence can be detected in early adulthood, suggesting the benefits of hydrogen have long-lasting effects [48].

Molecular Hydrogen Therapy in Multiple Sclerosis

MS is a chronic and progressive inflammatory disease characterized by mistaken attacks of reactive inflammatory cells against the brain tissue, resulting in pronounced demyelination, axonal degeneration, and extensive inflammation [98]. Indeed, multiple inflammatory cells play a pathogenic role in MS, including CD4 and CD8 T lymphocytes, macrophages, and microglia [99]. Currently, the most widely accepted concept of MS lesion formation is that acute demyelination is induced by phagocytes that internalize and degrade myelin sheaths with infiltrating T cells. The recruitment of inflammatory cells is an early or initial event in MS progression. Other studies proposed that extensive apoptosis of oligodendrocytes and excessive activation of glial cells are the major pathological changes in the newly formed MS lesion [100, 101]. Therefore, inflammation-related changes play a central role in the initiation and progression of MS [100]. The inflammatory changes in MS also induce the exaggerated expression and release of reactive oxygen species [100]. For example, the activation of microglia and infiltration of macrophages can contribute to the release of large amounts of oxidative stress-related molecules, including superoxides, nitric oxide, hydrogen peroxide, and hydroxyl radicals [100]. In addition, numerous studies revealed the association between oxidative stress and MS lesion formation [100]. For example, prominent immunoreactivity for oxidized DNA and lipids was found in the area of initial demyelination, suggesting the essential role of oxidative stress in the early stages of MS [102]. Notably, in an animal model of MS, experimental autoimmune encephalomyelitis (EAE) rats treated with ROS scavengers significantly alleviated the autoimmune inflammatory lesions, indicating that therapeutic manipulation of oxidative stress may be a potential approach for the treatment of MS [103]. Many currently used MS medications are expensive and often have side effects [104], which prompted efforts to identify novel therapies for MS patients.

Molecular hydrogen's anti-inflammatory and antioxidant properties have attracted increased research attention and interest in MS prevention and treatment [104]. In the experimental autoimmune encephalomyelitis model, one of the most widely used animal models for MS, hydrogen-rich water orally twice a day significantly delayed the initiation and attenuated the severity EAE and attenuated the severity of EAE, as evidenced by prominently improved clinical scores in the hydrogen-treated group [104]. Further analysis confirmed the prophylactic and therapeutic effects of hydrogen on demyelination following hydrogen administration [104]. Notably, the effects of hydrogen on the disease severity are exhibited in a dose-dependent manner within a specific range [104]. Consistent with the previous study, another study using the EAE animal model also found the effects of hydrogen on alleviating the severity of EAE and demyelination [46]. Intriguingly, the expression of CNPase, a myelin-associated enzyme, is preserved by hydrogen treatment, indicating that hydrogen administration inhibited myelin-associated changes in EAE [46]. In addition, hydrogen-rich saline inhibits glial activation and reduces the levels of inflammatory cytokines (i.e., TNF-α, IL-1β, IL-6, and HMGB1), suggesting that the anti-inflammatory effects were involved in alleviating disease severity [46]. Furthermore, the antioxidant capacity also contributed to the beneficial effects of the hydrogen in MS [46]. Hydrogen-rich saline improved the activity of antioxidant enzymes and reduced the generation of oxidative stress-induced lipid peroxidation and oxidative DNA damage, confirming the antioxidant effect of hydrogen in MS [46]. Further analysis found that the activation of the NRF2-ARE signaling pathway was responsible for the upregulated antioxidant capacity, and the NRF2 inhibitor abolished the improved antioxidant capacity [46].

Molecular Hydrogen Therapy in Parkinson's Disease

As the second most common neurodegenerative disease, Parkinson's disease (PD) is characterized by motor dysfunction and non-motor symptoms, including sleep disturbances, depression, and constipation [105]. The pathological hallmarks of PD include the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the abnormal intracellular accumulation of misfolded and aggregated α-synuclein-induced Lewy bodies [106]. Like other neurodegenerative diseases, oxidative stress and inflammation play an indispensable role in PD's generation and progression [7]. Several lines of evidence suggest that pathological changes in dopamine metabolism, inflammation, and mitochondrial dysfunction contribute to oxidative stress and damage in PD [107].

According to previous studies, dopamine metabolism disruption is one of the sources of oxidative stress in PD [108]. Under normal conditions, dopamine is generated from tyrosine by aromatic amino acid decarboxylase and tyrosine hydroxylase and then stored in synaptic vesicles. However, under pathological changes, the cytosolic dopamine in damaged neurons is metabolized by auto-oxidation and monoamine oxidase, generating excessive ROS [108, 109]. Mitochondria dysfunction is another primary source of oxidative stress in PD. For example, complex I deficiency has been detected in the substantia nigra pars compacta of PD patients and results in unfavorable neuronal apoptosis [110]. As one of the most widely used neurotoxicant inducers of PD, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a complex I inhibitor [107]. MPTP can be transferred into MPP^+ by monoamine oxidase-B and accumulated in the dopaminergic neurons of SNc, which result in ROS release by the mitochondria, including hydroxyl radicals, hydrogen peroxide, nitric oxide, and superoxide anion [108]. Moreover, mitochondria-associated gene mutations affect mitochondrial function and structure [111]. For example, parkin mutations impair mitochondrial complex I activity [112]. However, parkin overexpression attenuates dopamine neuronal loss induced by MPTP through mitochondrial protection and alleviates α-synuclein aggregation [113]. These findings indicate that mitochondria-related changes and excessive oxidative stress are essential in neuronal dopamine loss and PD progression [108].

Due to the prominent role of excessive oxidative stress in the pathological changes of PD, increasing studies detected the potential therapeutic effects of antioxidants in PD treatment [114]. As mentioned previously, hydrogen is one of the most potent natural antioxidants. It has recently garnered heightened attention due to its antioxidant and anti-inflammatory properties [115, 116]. In an MPTP-induced PD model, hydrogen-rich water alleviated acute MPTP administration-induced neurotoxicity, as evidenced by a significant attenuation in the loss of dopaminergic neurons in substantia nigra pars [115]. Moreover, hydrogen-rich water significantly improved chronic MPTP administration-induced behavioral deficits [115]. Notably, the mechanism underlying the beneficial effects of hydrogen-rich water is involved in alleviating oxidative stress. For example, the ROS-derived oxidative products, including 8-oxoguanine (a marker of DNA damage) and 4-hydroxynonenal (a marker of lipid peroxidation), were inhibited by hydrogen-rich water, confirming the antioxidant effects of hydrogen in the PD [115]. Similarly, the effect of hydrogen-rich water in the PD animal model was also dose dependent, with a better effect at a lower concentration than the saturated concentration [115]. The dose-dependent effects of hydrogen are also confirmed in clinical trials. For example, PD patients who received 1000 mL of hydrogen water per day for 48 weeks significantly improved Parkinson's features [117]. However, a more extended hydrogen water treatment did not show any effects in patients with PD [118]. The negative results of hydrogen therapy are also found in one of the clinical trials using inhaled hydrogen [119], indicating that the duration, concentration, and routes for hydrogen administration are essential in hydrogen therapy. Interestingly, a Si-based agent that can generate hydrogen continually further enriched the routes of hydrogen therapy [120]. In a 6-hydroxydopamine (6-OHDA)-induced PD mouse model, Si-based agent treatment alleviated dopaminergic neurodegeneration and ameliorated 6-OHDA-induced behavioral impairment, suggesting Si-based agent that continues generating molecule hydrogen may be a potential approach to treat PD [120].

Molecular Hydrogen Therapy in Ischemic Stroke

Stroke is one of the most common cerebrovascular diseases with high morbidity and disability rate [121]. It can be divided into ischemic and hemorrhagic strokes [121]. Ischemic stroke accounts for 85% of total strokes and occurs when blood vessels are blocked by a blood clot or other particles [122]. When an ischemic stroke occurs, initial inflammation is triggered by cellular debris and dying cells in the ischemic area [123]. Increasing evidence indicates that postischemic inflammation exacerbates brain injury and contributes to the secondary damage of neurons [124].

Oxidative damage is another specific change induced by ischemic insults [125]. Rapid production of ROS following acute ischemic stroke overwhelms the antioxidant

capacity, causing further brain damage [125]. Excessive oxidative stress damaged cellular macromolecules and led to autophagy, cellular apoptosis, and necrosis [125]. Furthermore, the rapid and prolonged reperfusion leads to the second burst of ROS generation and contributes to reperfusion-induced secondary neuronal damage [7, 125]. Neuroinflammation and oxidative stress in ischemic stroke are interactive and play an essential role in ischemic/reperfusion-induced injury [126]. Substantial evidence suggests that approaches targeting neuroinflammation and oxidative stress are potential treatment options for ischemic stroke [126].

The antioxidative and anti-inflammatory effects of molecular hydrogen have attracted increasing attention in ischemic stroke over the past few years [127]. In a previous study, the primary culture of neocortical cells underwent oxygen–glucose deprivation (OGD) followed by reperfusion with a cell medium containing normal O_2 and glucose was employed to mimic ischemia–reperfusion injury [3]. The cell culture model with ischemia–reperfusion induced prominently increased hydroxyl radicals (·OH), the most reactive oxygen species [3]. Intriguingly, the cell culture medium with dissolved molecular hydrogen notably alleviated this increase and promoted neuronal vitality and survival, indicating that molecular hydrogen protects neurons against oxidative stress-induced neuronal death [3]. Furthermore, ROS was generated in a rat model of focal ischemic stroke and caused apparent brain injury. Notably, hydrogen inhalation exhibited concentration-dependent protection on this brain injury, as evidenced by the most substantial reduction in infarct volume with hydrogen inhalation at 2–4% [3]. Of particular interest, hydrogen only exhibited its neuroprotective effect when the treatment is employed during reperfusion and had no significant effect on infarct volume during ischemia, indicating that hydrogen therapy has its "therapeutic window" [3]. In addition, the protective effects of hydrogen on the brain injury were not only limited to the initial stage (ischemia and perfusion). After the ischemic-perfusion insults, hydrogen also alleviated its progressive damage, as evidenced by significant improvement in the functional behavioral assessment and suppression of oxidative stress and inflammation [3]. Similar findings are found in the global cerebral ischemia and reperfusion mouse model [32]. Mice subjected to global cerebral ischemia and reperfusion exhibited neurological deficits and severe neuronal injury in the hippocampal CA1 region, which are significantly reduced in the hydrogen treatment group [32]. This neuroprotection of hydrogen involvs the alleviation of oxidative DNA damage, lipid peroxidation, and postischemic autophagy in the CA1 region [32].

Another study clarified another possible mechanism underlying hydrogen neuroprotection using OGD/reperfusion damaged hippocampal neurons [128]. Similarly, the study found that hydrogen significantly alleviated ROS levels and cellular apoptosis following OGD/R insults. However, the hydrogen was provided by a cell culture incubator consisting of 60% hydrogen, suggesting neuroprotection of hydrogen can be achieved through different hydrogen administration routes [128]. Notably, the decreased mitochondrial membrane potential induced by OGD/R insults was attenuated by hydrogen therapy, indicating that hydrogen protects against mitochondrial dysfunction [128]. However, the neuroprotective effect of hydrogen is lost entirely when the mitophagy inhibitor is added, suggesting that mitophagy may mediate the improved mitochondrial function and the neuroprotective effects of hydrogen [128]. Further analysis detects the activation of the PINK1/Parkin pathway, a well-understood mitophagy-associated pathway, which confirmed the essential role of mitophagy in hydrogen therapy [128]. Although further studies are still needed on how hydrogen affects the expressions of mitophagy-related proteins, these findings provided one of the possible mechanisms underlying the neuroprotection of hydrogen.

Molecular Hydrogen Therapy in Traumatic Brain Injury

Traumatic brain injury (TBI) is one of the leading causes of disability and mortality among people of all age groups [129]. More than 50 million people suffer from TBI yearly, and almost 50% of the world's population will experience mild TBI more than once [130]. TBI occurs when an external force causes damage to the head, including closed head injury induced by a blow, jolt, or bump to the head and penetrating injury induced by objects penetrating the skull [131]. TBI-induced injury includes primary and secondary injuries [132]. Primary injury after TBI includes direct mechanical damage to brain tissue and blood vessels, causing neuronal loss and necrotic cell death [133]. Following the primary injury, the secondary injury further damages the brain tissue, which occurs seconds to minutes following the primary injury, involving various biochemical processes, including oxidative stress, inflammation, mitochondrial dysfunction, and blood–brain barrier (BBB) disruption [133].

Mitochondrial dysfunction and oxidative stress are typical changes contributing to secondary cell injury in TBI [7]. Excessive release of ROS and RNS following TBI causes oxidative damage to the cell, including lipoperoxidation of the cell membranes, various organelles, and microstructures within neurons. These changes result in widespread neuronal injury and death [134]. Notably, the oxidative stress-induced lipid peroxidation of mitochondrial membranes led to the disruption of mitochondrial function [134]. In addition to serving as the powerhouse of the neurons, mitochondria are essential in maintaining calcium homeostasis [135]. The impaired mitochondrial function and disrupted intracellular

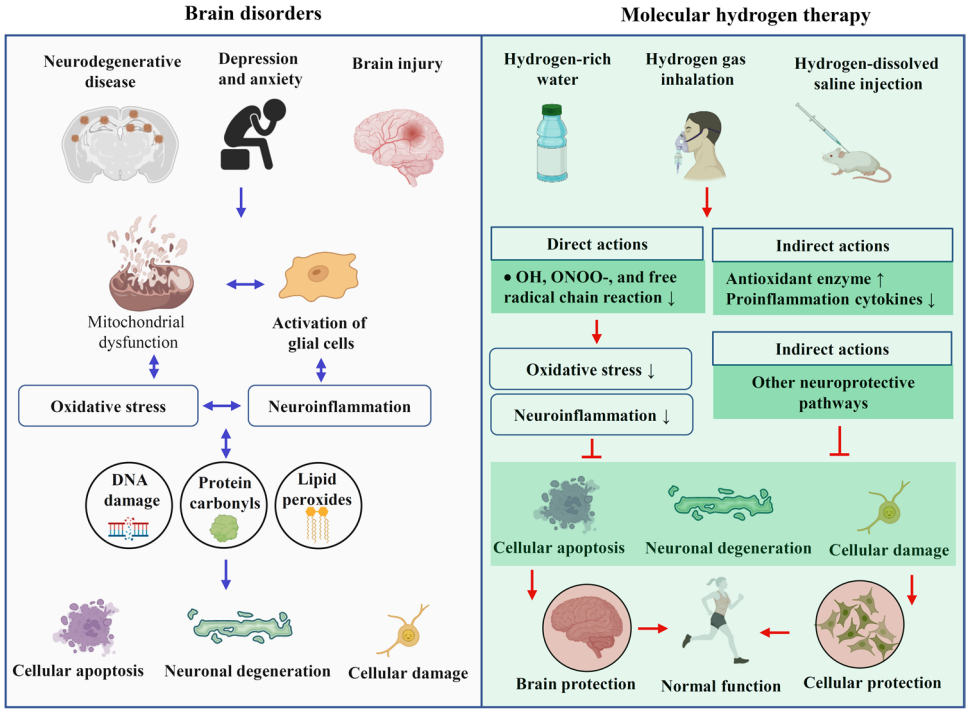

Fig. 1 Primary mechanisms of molecular hydrogen therapies in brain disorders. Nearly all neurodegenerative diseases, brain injuries, and mood disorders are characterized by mitochondrial function and neuroinflammation. The dysfunction of mitochondria induces excessive production of ROS and the excessively released inflammatory cytokines, which further damage mitochondria and active glial cells. All these changes induce oxidative damage to DNA, protein, and lipids, which finally induce cellular damage, neuronal degeneration, and neuronal loss. However, hydrogen works as an electron donor to selectively scavenge the excessive hydroxyl radical to reduce oxidative stress directly. Additionally, hydrogen enhances the activity of antioxidant enzymes, reduces the release of proinflammatory factors, and activates other neuroprotective pathways

calcium homeostasis contribute significantly to the pathophysiology of delayed neuronal damage and death following TBI [136]. Therefore, mitochondria-targeted antioxidants or antioxidant therapies have attracted considerable efforts in TBI studies [7, 137].

Several studies have reported that hydrogen's anti-inflammatory and antioxidative effects are implicated in protecting against TBI [45, 47]. In a controlled cortical impact model, 2% hydrogen therapy was employed from 30 min to 5 h following TBI [47]. Interestingly, TBI animals with hydrogen therapy exhibited a better neurological outcome, improving BBB integrity, and attenuating cerebral lesion volume and brain edema [47]. Further analysis found that hydrogen significantly enhanced the activities of antioxidant enzymes and alleviated the release of oxidative products [47]. Notably, the microRNA-21 inhibitor inhibited these beneficial changes, indicating that miR-21 is critical in hydrogen therapy following TBI [47]. Another study demonstrated the beneficial effects of hydrogen-rich saline in ameliorating early brain injury in a TBI animal model [57]. The hydrogen-rich saline is administered for 72 h following TBI. Intriguingly, neurological deficits, brain edema, neuronal necroptosis, neuroinflammation, and oxidative stress are significantly alleviated in the hydrogen-treated groups [57]. Notably, hydrogen modulated necroptosis via the regulation of the ROS/HO-1 signaling pathway, suggesting the neuroprotective effects of hydrogen partly depend on ROS/heme oxygenase 1 (HO-1) signaling pathway-regulated necroptosis [57]. The HO-1 is an antioxidant enzyme downstream of the Nrf2 pathway [138]. In the TBI animal model, hydrogen-rich water promotes the disassociation of Nrf2 from Keap1, resulting in the Nrf2 nuclear translocation followed by binding to the antioxidant response element (ARE) and producing endogenous antioxidant enzyme, including HO-1 [55]. This finding suggests that the modulation of the Keap1/Nrf2/ARE signaling pathway contributes to the antioxidative effects of hydrogen and is imperative to protect against TBI [55]. Similar to the findings in other brain diseases, the beneficial effects of hydrogen on TBI are also concentration-dependent [139]. For example, hydrogen therapy alleviated cerebral lesions following TBI in a concentration-dependent manner, wherein 4% hydrogen exhibites better effects in preserving brain tissue than 1% and 2% hydrogen [139], suggesting hydrogen therapy exists the optimal dosage, which needs more study.

Table 1 Experimental studies of hydrogen therapy in brain disorders

Animal/cellular model	Routes for hydrogen administration	Effect of treatment with hydrogen	Mechanisms
3xTg-AD mice [140]	Hydrogen-rich water	• Prevents synaptic loss and neuronal death • Inhibits senile plaques • Reduces hyperphosphorylated tau and neurofibrillary tangles	• Reduces neuroinflammation • Regulates intestinal microbiota
Aβ-injection rat model [66]	Hydrogen-rich saline injection	• Improves memory function • Improves synaptic plasticity	• Prevents Aβ-induced neuroinflammation and oxidative stress
Aβ-injection rat model [67]	Hydrogen-rich saline injection	• Prevents Aβ-induced neuroinflammation and oxidative stress	• Attenuates activation of JNK and NF-κB
APP/PS1 mice [69]	Hydrogen-rich water	• Improved cognitive behaviors in female transgenic AD mice	• Reverses the brain estrogen level, ERβ, and brain-derived neurotrophic factor expressions
Aβ-induced cytotoxicity on SK-N-MC cells [72]	Hydrogen-rich water	• Protects cultured cells against Aβ-induced neuronal apoptosis	• Reduces intracellular ROS levels • Improves levels of antioxidative enzymes • Preserves mitochondrial function • Activates the AMPK/SIRT1/FOXO3a signaling pathway
Neonatal hypoxia–ischemia rat model [80]	Hydrogen gas inhalation	• Reduces neuronal apoptosis and infarct volume	• N/A
Neonatal hypoxia–ischemia rat model [82]	Hydrogen gas inhalation	• Improves early neurological outcomes and learning and memory in adults • Reduces the area of infarction and neuronal loss	• MAPK/HO-1/PGC-1α pathway • Anti-inflammation • Antioxidant
Depressive-like behavior [94]	Hydrogen-rich water	• Prevents chronic unpredictable mild stress-induced depressive-like behavior	• Suppress the inflammasome activation • Reduces reactive oxygen species
The chronic mild stress model [58]	Hydrogen gas inhalation	• Decreases both the acute and chronic stress-induced depressive- and anxiety-like behaviors	• Inhibits the hypothalamic–pituitary–adrenal axis and the inflammatory responses
EAE mouse model [104]	Hydrogen-rich water	• Reduces the clinical score of EAE • Inhibits inflammatory infiltration and demyelination	• Regulates the CD4 + population • Inhibits Th17 cell differentiation
EAE mouse model [46]	Hydrogen-rich saline injection	• Reduces the severity of EAE • Inhibits the loss of oligodendrocytes	• Ameliorates inflammation and oxidative stress • Activates the Nrf2-ARE signaling pathway
MPTP-mouse parkinsonian model [115]	Hydrogen in drinking water	• Reduced loss of dopaminergic neurons in substantia nigra • Protects the neurons against acute MPTP neurotoxicity	• Reduces oxidative damage
6-OHDA-induced PD mouse model [120]	Si-based agent generates hydrogen	• Alleviates the degeneration of dopaminergic neurons • Improves the ability in the motor balance and coordination	• Decrease oxidative stress
OGD/R model [3]	Hydrogen-rich DMEM medium	• Protects neurons from oxygen–glucose deprivation and reperfusion	• Reduces ·OH in cultured cells
Cerebral ischemia and reperfusion [3]	Hydrogen gas inhalation	• Protects brain injury by reperfusion and suppresses the progression of damage	• Decreases oxidative stress and inflammation

Table 1 (continued)

Animal/cellular model	Routes for hydrogen administration	Effect of treatment with hydrogen	Mechanisms
Global cerebral ischemia/reperfusion [32]	Hydrogen gas inhalation	• Improves survival rate • Alleviates neurological deficit • Reduces neuronal injury	• Attenuates oxidative stress
In vitro ischemic models OGD/R [128]	Hydrogen gas inhalation	• Improves cell viability and reduces neuronal apoptosis induced by OGD/R injury	• Decreases ROS production • Preserves mitochondrial membrane potential • Promotes mitophagy and activates PINK1/Parkin signaling pathway
Rat TBI model [47]	Hydrogen gas inhalation	• Improves the neurological performance and BBB integrity • Reduces the brain edema and cerebral lesion volume	• Improves antioxidant enzymes activities • Increases miR-21 expression
Rat TBI model [57]	Hydrogen-rich saline injection	• Attenuates TBI-induced neurological deficits and brain edema • Reduces neuronal necroptosis	• Alleviates neuroinflammation and oxidative stress • Modulates necroptosis via the ROS/HO-1 pathway
Rat TBI model [55]	Hydrogen-rich water	• Promotes the survival rate and reduces neurologic deficits	• Alleviates oxidative stress • Promotes nuclear translocation of the Nrf2

EAE, experimental autoimmune encephalomyelitis; *MPTP*, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; *OGD/R*, oxygen–glucose deprivation (OGD)/reperfusion; *TBI*, traumatic brain injury; *BBB*, blood–brain barrier

Remaining Issues and Challenges

As mentioned previously, hydrogen therapy with various administration routes has shown great potential for neuroprotection in brain disorders, including neurodegenerative diseases [66, 67, 140], brain injury [32, 57, 82], and mental diseases [58, 94] (Fig. 1). However, several unresolved issues still need to be addressed.

The Exact Molecular Targets and Mechanisms Remain Unclear Although hydrogen's antioxidant and anti-inflammatory properties have been widely studied in various brain disorders [32, 57, 66, 67, 82, 140], the crosstalk among anti-inflammation, anti-oxidation, and other pathways are still unclear. Additionally, although studies have found the protective effects of hydrogen on mitochondria and the regulation of various genes and proteins, further investigation is needed to determine whether these modulations are the cause or the results of the hydrogen's anti-inflammatory and antioxidant effects [141].

No Consensus on Hydrogen Administration and Dose Regimes As mentioned previously, various routes of hydrogen administration have shown their preventive and therapeutic effects in various brain diseases [32, 57, 66, 67, 82, 140]. The neuroprotective effects of hydrogen therapy in brain disorders are displayed in a dose-dependent, gender-dependent, and time-dependent manner [69, 80, 104]. However, there is no consensus on the optimal hydrogen administration and dose regimes [142]. Therefore, more studies are needed to further our understanding of the optimal routes for hydrogen administration, dosage, pharmacokinetics, toxicity, and biology in animal and clinical studies [142].

New Routes for Hydrogen Administration Are Needed Although hydrogen administration via drinking or injection has shown its advantages in various brain diseases [32, 57, 66, 67, 82, 140], the solubility of molecular hydrogen in water and saline is relatively low [37]. Additionally, the storage of hydrogen-rich water or saline needs a specific container. For example, aluminum containers retain hydrogen longer than glass and plastic containers [37]. Moreover, the daily hydrogen-rich saline injection has the risk of infection and would be very dangerous if hydrogen-dissolved saline were injected directly into the vein [42]. Therefore, new routes for hydrogen administration are needed. For example, in previous studies, a Si-based agent that continues generating molecule hydrogen has been developed and exerts neuroprotective effects in a mouse model of Parkinson's disease [120]. The new routes for hydrogen administration should have the following advantages: portable, easy to store, and reach a specific target area with expected

concentration and release hydrogen continuously. Nanoparticles for hydrogen generation may hold great potential for hydrogen utilization in preventing or treating brain diseases [143].

The Effects of Hydrogen on Neurovascular Coupling Remains Unclear, and the Half-Life of Hydrogen in Bio-fluids Deserves Further Investigation Neurovascular coupling is defined as a tight coupling between cerebral blood flow and neural activity, which is intrinsically regulated by a complex interplay between neurophysiological and hemodynamic signals [144]. The impaired neurovascular coupling has been detected in various brain disorders, including neurodegenerative disease, brain injury, and psychiatric disorders [145–147]. However, the effects of hydrogen on neurovascular coupling in physiology and pathological conditions remain unclear. Additionally, to investigate the effects of hydrogen in physiology and pathological conditions, we should know the half-life of hydrogen in the bio-fluids, including blood, plasma, and cerebrospinal fluid. Therefore, this issue should also be addressed in future studies.

Conclusions

As mentioned previously, the biological properties of hydrogen, especially the antioxidant and anti-inflammatory effects, make it a promising candidate for various neurodegenerative diseases and brain injuries (Table 1) [45–47, 114, 127]. However, the short biological half-life and the low saturation make the administration complex [37, 42]. Additionally, the mechanisms underlying the neuroprotection of hydrogen, especially the exact molecular targets and mechanism, remain unclear [141]. Therefore, more preclinical studies are needed to understand the pathways and the biological changes impacted by molecular hydrogen therapy. Moreover, the optimal concentration, the mode of administration, pharmacokinetics, biology, and the clinical application of hydrogen are still lacking [45]. Nevertheless, it has been suggested that hydrogen has great therapeutic potential in treating various brain disorders [141].

Abbreviations *AD*: Alzheimer's disease; *PD*: Parkinson's disease; *TBI*: Traumatic brain injury; *HIE*: Neonatal hypoxic-ischemic encephalopathy; *ROS*: Reactive oxygen species; *RNS*: Reactive nitrogen species; *EAE*: Experimental autoimmune encephalomyelitis; *MPTP*: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; *OGD/R*: Oxygen-glucose deprivation (OGD)/reperfusion; *BBB*: Blood-brain barrier

Author Contribution C. W. reviewed the literature and drafted the manuscript. C. W. and P. Z. drew the figures and tables. L. D. Y. supervised the writing and edited the manuscript. All authors read and approved the final manuscript.

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Data Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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