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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 (H_2) 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 H_2 administration are mainly categorized into three types: H_2 gas inhalation, H_2 water dissolving, and H_2-dissolved saline injection. This review explores some significant progress in research on H_2 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 H_2 administration. Several possible H_2-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 H_2 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 thatgenerally 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 decomposinghydrogen 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 (•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 studyshowed 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]. H_2 does not react with most compounds, including oxygen gas, at room temperature. H_2 gas is only inflammable at temperatures exceeding 537 °C. H_2 (4–75%, *v/v*) is explosive due to the rapid oxidation chain reaction. H_2 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 H_2 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

H_2 may be administered or taken into the body via various routes. These routes may be divided into three types: H_2 gas inhalation, drinking HW, and HS injection. H_2 gas inhalation is the simplest and most commonly used method since the initial reports regarding the use of H_2 [13]. Inhaled H_2 diffuses into the lung alveoli and is transported to the entire body. This procedure can, however, be uncomfortable and even dangerous, since H_2 gas is explosive at concentrations above 4% in air [27]. Therefore, the mixed gas concentration of H_2 is usually maintained between 1% and 4%. Inhaling H_2 gas improves acute conditions such as ischemia–reperfusion injury (IRI) and several organ graft injuries. HRW is safer and more comfortable than H_2 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 H_2 prevents stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice [33]. Recently, the inhalation of H_2 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 H_2 gas inhalation [35]. In the human gastrointestinal tract, H_2 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 whichharmfully 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 theneurotoxins 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, similarfindings 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].

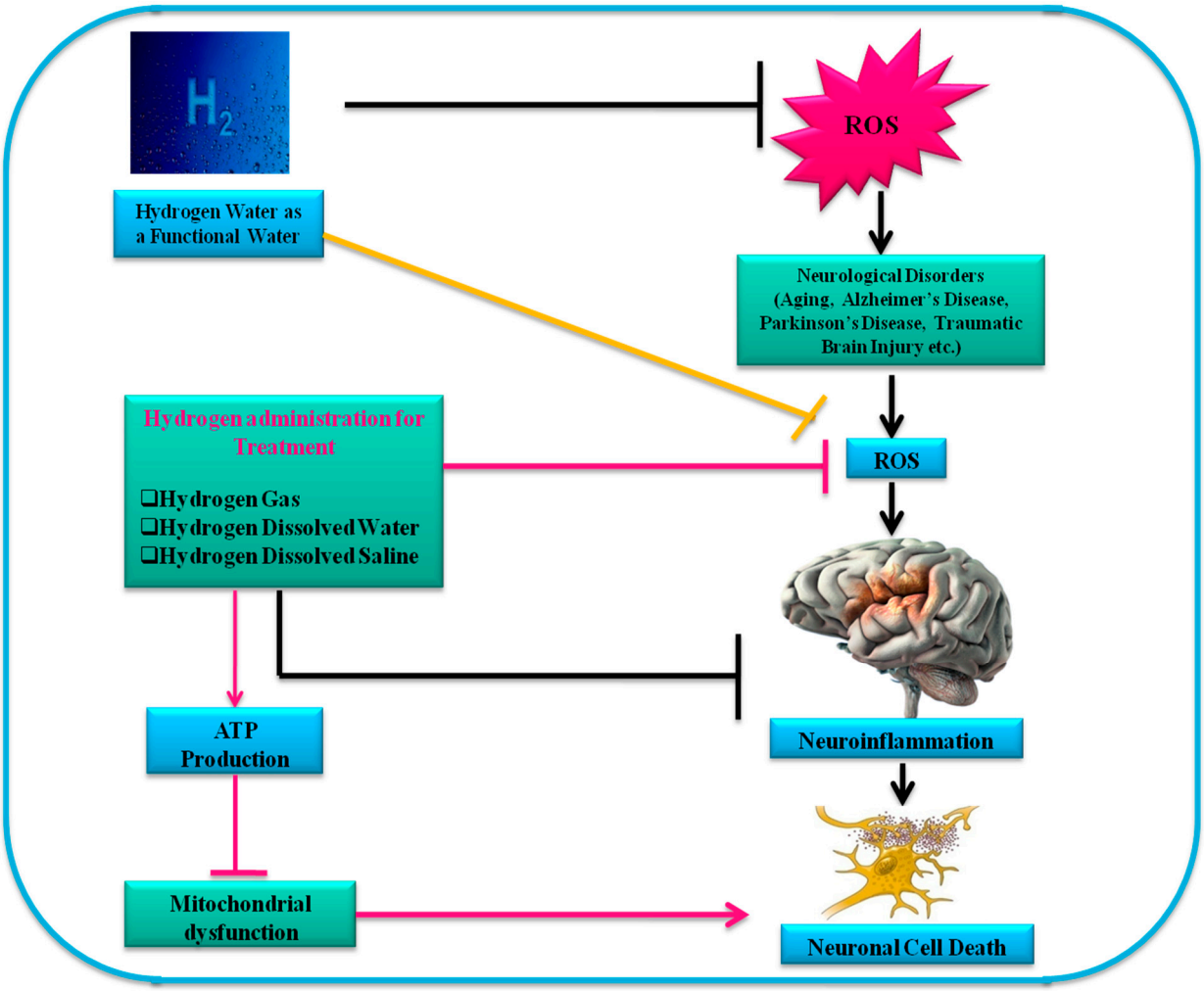

Figure 1. Beneficial effects of H_2 on different acute neuronal conditions.

4. H_2 Acts as an Antioxidant Agent

H_2 is highly reactive, protein denaturing, and promotes DNA breakdown. It can selectively reduce •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 H_2 can be efficiently used to protect against oxidative damage-associated diseases [50]. It decreases the amount of cytotoxic ROS (•OH), successfully defending cells [50]. Other studies demonstrated similar protective effects of H_2 against IRI in organs, such as the liver, heart, and intestines [51]. In rat acute stroke models, 1% to 4% H_2 inhalation alleviates infarction dimensions [52]. H_2 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 H_2, including: (1) ghrelin-linked upregulation of ghrelin receptor (GHS-R1α); (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 MTTP-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 H_2 may have benefits by activating the Nrf2 signaling pathway, thus improving antioxidant activity and reducing OS, apoptosis, and inflammation [46,62]. H_2 increases the antioxidant activities of enzymes in radiation and TBI through the upregulation of Nrf2 [63]. The basic anti-inflammatory mechanism of H_2 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 H_2 in Different Neurodegenerative Disease Models

Numerous studies have reported the anti-inflammatory action of H_2 [63,64,66]. The rapid spread, high penetrability, and absence of clear side effects are some of its advantages. H_2 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 studiesshowed that H_2 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 studiesreported that the addition of H_2 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 H_2 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 H_2 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 H_2 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 (Aβ) and tau accumulation, with large aggregates known as senile plaques and neurofibrillary tangles [78]. Various researches have demonstrated the effects of H_2 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 Aβ (1–42) AD [79]. With HS treatment, they found that reduced learning and memory impairments and reduced Aβ 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 κB (NF-κB) 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 H_2 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 H_2 on NDs, such as PD, AD, and other brain conditions are listed.

Table 1. Beneficial effects of H_2 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 H_2-gas inhalation [101]. Abnormal behavior in rats was improved 5 weeks after hypoxia–ischemia with HS administration in a study [102]. H_2 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 H_2 gas extended the after-asphyxia period from 4 h to 24 h in newborn pigs, highlighting the H_2 gas translation potential [103].Administration of H_2 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 H_2 improved fetal mouse brain injury caused by maternal exposure to LPS [70]. H_2 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]. H_2 can also stimulate energy metabolism to reduce neuronal damage. For example, it could upregulate the expression of FGF21 [104]. These findings indicate that prenatal H_2 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 H_2 gas treatment eliminates the increased OS caused by sevoflurane in neonatal mice [106]. In addition, co-administration of H_2 prevented abnormal maternal behavior later in adulthood resulting from neonatal exposure to sevoflurane, which indicates a considerable H_2 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 H_2 in NDs is significant to fully explore the use of H_2 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 Aβ 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-κB, IL-1β, 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 H_2 [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 Aβ deposition [111]. A study by Ren and colleagues showed that H_2 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], H_2 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 H_2 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, ERβ, and brain-derived neurotrophic factor (BDNF) expression, but not in males, and without affecting the β-amyloid precursor protein treatment and Aβ 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 ERβ-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 H_2 treatment [70]. In addition, the estrogen ERβ-BDNF signaling pathway was related to the antioxidant and anti-inflammatory effects in AD [118]. In pathological AD prevention, the activation of ERβ signaling also involves ROS scavenging [118]. Therefore, the main mechanisms of action of H_2 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 H_2 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 Aβ 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-κB 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 Aβ 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 H_2 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-ERβ-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 •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-1expression [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 H_2 gas studies. Safer storage technologies, especially hydrides, are being developed [27,134]. The risk of explosion can also be eliminated by the dissolution of H_2 in water or normal saline, either orally or intravenously [134].

12. Novel Advantages of H_2 Molecule

To date, there is insufficient information about the pharmacodynamics and toxicity of H_2. The therapeutic effect of H_2 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, H_2 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]. H_2 delivery does not influence physiological parameters including oxygen saturation, temperature, pH, and blood pressure [27,31].

In the biomedical sciences, the outcome of H_2 appears to be similar to other types of therapeutic gas families, such as nitric oxide, hydrogen sulfide, and carbon monoxide. H_2 was seriously considered only 10 years ago as an unreactive gas; scientists now see H_2 as a healing agent and a preferred treatment course [136]. Although existing information on H_2 remains insufficient, the promising characteristics of H_2 therapy, as established through some pilot studies, are the motivation for future research; appreciation of the activities of H_2 could guide us towards new forms of H_2 therapy for many conditions and human diseases.

13. Concluding Remarks

Although several NDs are currently incurable, the therapeutic potential action of H_2 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 H_2 have been illustrated. H_2 is relatively easy to implement, inexpensive, and efficient in everyday health practice. However, the optimal route and dose of H_2 administration for each disease remain to be established. This review summarizes current evidence on the preventive and therapeutic roles of H_2 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 H_2 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
Aβ	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-κB	Nuclear factor κB
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

References

1. Tarozzi, A. Oxidative stress in neurodegenerative diseases: From preclinical studies to clinical applications. *J. Clin. Med.* **2020**, *9*, 1223. [CrossRef] [PubMed]
2. Hannan, M.A.; Dash, R.; Sohag, A.A.M.; Haque, M.; Moon, I.S. Neuroprotection against oxidative stress: Phytochemicals targeting TrkB signaling and the Nrf2-ARE antioxidant system. *Front. Mol. Neurosci.* **2020**, *13*, 116. [CrossRef]
3. Singh, E.; Devasahayam, G. Neurodegeneration by oxidative stress: A review on prospective use of small molecules for neuroprotection. *Mol. Biol. Rep.* **2020**, 1–8. [CrossRef]
4. Yeung, A.W.; Tzvetkov, N.T.; Georgieva, M.G.; Ognyanov, I.V.; Kordos, K.; Jóźwik, A.; Kühl, T.; Perry, G.; Petralia, M.C.; Mazzon, E.; et al. Reactive oxygen species and their impact in neurodegenerative diseases: Literature landscape analysis. *Antioxid. Redox Signal.* **2021**, *34*, 402–420. [CrossRef] [PubMed]
5. Schieber, M.; Chandel, N.S. ROS function in redox signaling and oxidative stress. *Curr. Biol.* **2014**, *24*, R453–R462. [CrossRef]
6. Lee, K.H.; Cha, M.; Lee, B.H. Neuroprotective effect of antioxidants in the brain. *Int. J. Mol. Sci.* **2020**, *21*, 7152. [CrossRef] [PubMed]
7. Guan, Y.; Hickey, M.J.; Borgstahl, G.E.; Hallewell, R.A.; Lepock, J.R.; O'Connor, D.; Hsieh, Y.; Nick, H.S.; Silverman, D.N.; Tainer, J.A. Crystal structure of Y34F mutant human mitochondrial manganese superoxide dismutase and the functional role of tyrosine 34. *Biochemistry* **1998**, *37*, 4722–4730. [CrossRef]

8. Bošković, M.; Grabnar, I.; Terzič, T.; Plesničar, B.K.; Vovk, T. Oxidative stress in schizophrenia patients treated with long-acting haloperidol decanoate. *Psychiatry.Res.* **2013**, *210*, 761–768. [CrossRef]
9. Ambani, L.M.; Van Woert, M.H.; Murphy, S. Brain peroxidase and catalase in Parkinson Disease. *Arch. Neurol.* **1975**, *32*, 114–118. [CrossRef]
10. Niedzielska, E.; Smaga, I.; Gawlik, M.; Moniczewski, A.; Stankowicz, P.; Pera, J.; Filip, M. Oxidative stress in neurodegenerative diseases. *Mol. Neurobiol.* **2016**, *53*, 4094–4125. [CrossRef]
11. Terlecky, S.R.; Koepke, J.I.; Walton, P.A. Peroxisomes and aging. *Biochim. Biophy. Acta* **2006**, *1763*, 1749–1754. [CrossRef]
12. Begum, R.; Kim, C.S.; Fadriquela, A.; Bajgai, J.; Jing, X.; Kim, D.H.; Kim, S.K.; Lee, K.J. Molecular hydrogen protects against oxidative stress-induced RAW 264.7 macrophage cells through the activation of Nrf2 and inhibition of MAPK signaling pathway. *Mol. Cell Toxicol.* **2020**, *16*, 103–118. [CrossRef]
13. Ohsawa, I.; Ishikawa, M.; Takahashi, K.; Watanabe, M.; Nishimaki, K.; Yamagata, K.; Katsura, K.I.; Katayama, Y.; Asoh, S.; Ohta, S. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat. Med.* **2007**, *13*, 688–694. [CrossRef]
14. Ohta, S. Molecular hydrogen is a novel antioxidant to efficiently reduce oxidative stress with potential for the improvement of mitochondrial diseases. *Biochim. Biophys. Acta* **2012**, *1820*, 586–594. [CrossRef]
15. Ge, L.; Yang, M.; Yang, N.N.; Yin, X.X.; Song, W.G. Molecular hydrogen: A preventive and therapeutic medical gas for various diseases. *Oncotarget* **2017**, *8*, 102653–102673. [CrossRef]
16. Noda, M.; Fujita, K.; Hamner, M.A.; Yamafuji, M.; Akimoto, N.; Kido, M.A.; Tanaka, Y.; Nakabeppu, Y.; Ransom, B.R. Molecular hydrogen protects against central nervous system white matter ischemic injury. In Proceedings of the SfN 42nd Annual Meeting, New Orleans, LA, USA, 13–17 October 2012; Volume 660, p. 14.
17. Fujita, K.; Nakabeppu, Y.; Noda, M. Therapeutic effects of hydrogen in animal models of Parkinson's disease. *Parkinson Dis.* **2011**, *2011*, 307875. [CrossRef]
18. Ito, M.; Hirayama, M.; Yamai, K.; Goto, S.; Ichihara, M.; Ohno, K.; Ito, M. Drinking hydrogen water and intermittent hydrogen gas exposure, but not lactulose or continuous hydrogen gas exposure, prevent 6-hydorxydopamine-induced Parkinson's disease in rats. *Med. Gas. Res.* **2012**, *2*, 1–7. [CrossRef]
19. Nagatani, K.; Nawashiro, H.; Takeuchi, S.; Tomura, S.; Otani, N.; Osada, H.; Wada, K.; Katoh, H.; Tsuzuki, N.; Mori, K. Safety of intravenous administration of hydrogen-enriched fluid in patients with acute cerebral ischemia: Initial clinical studies. *Med. Gas. Res.* **2013**, *3*, 13. [CrossRef] [PubMed]
20. Ono, H.; Nishijima, Y.; Ohta, S.; Sakamoto, M.; Kinone, K.; Horikosi, T.; Tamaki, M.; Takeshita, H.; Futatuki, T.; Ohishi, W.; et al. Hydrogen gas inhalation treatment in acute cerebral infarction: A randomized controlled clinical study on safety and neuroprotection. *J. Stroke. Cerebrovasc. Dis.* **2017**, *26*, 2587–2594. [CrossRef] [PubMed]
21. LeBaron, T.W.; Laher, I.; Kura, B.; Slezak, J. Hydrogen gas: From clinical medicine to an emerging ergogenic molecule for sports athletes. *Can. J. Physiol. Pharmacol.* **2019**, *97*, 797–807. [CrossRef] [PubMed]
22. Nicolson, G.L.; de Mattos, G.F.; Settineri, R.; Costa, C.; Ellithorpe, R.; Rosenblatt, S.; Ohta, S. Clinical effects of hydrogen administration: From animal and human diseases to exercise medicine. *Int. J. Clin. Med.* **2016**, *7*, 32–76. [CrossRef]
23. Qin, L.; Liu, Y.; Wang, T.; Wei, S.J.; Block, M.L.; Wilson, B.; Liu, B.; Hong, J.S. NADPH oxidase mediates lipopolysaccharide-induced neurotoxicity and proinflammatory gene expression in activated microglia. *J. Biol. Chem.* **2004**, *279*, 1415–1421. [CrossRef] [PubMed]
24. Spulber, S.; Edoff, K.; Hong, L.; Morisawa, S.; Shirahata, S.; Ceccatelli, S. Molecular hydrogen reduces LPS-induced neuroinflammation and promotes recovery from sickness behaviour in mice. *PLoS ONE* **2012**, *7*, e42078. [CrossRef] [PubMed]
25. Mano, Y.; Kotani, T.; Ito, M.; Nagai, T.; Ichinohashi, Y.; Yamada, K.; Ohno, K.; Kikkawa, F.; Toyokuni, S. Maternal molecular hydrogen administration ameliorates rat fetal hippocampal damage caused by in utero ischemia–reperfusion. *Free Radic. Biol. Med.* **2014**, *69*, 324–330. [CrossRef]
26. Yang, L.; Li, D.; Chen, S. Hydrogen water reduces NSE, IL-6, and TNF-α levels in hypoxic-ischemic encephalopathy. *Open Med.* **2016**, *11*, 399–406. [CrossRef]
27. Yang, M.; Dong, Y.; He, Q.; Zhu, P.; Zhuang, Q.; Shen, J.; Zhang, X.; Zhao, M. Hydrogen: A Novel Option in Human Disease Treatment. *Oxid. Med. Cell Longev.* **2020**, *2020*, 8384742. [CrossRef]
28. Huang, C.S.; Kawamura, T.; Toyoda, Y.; Nakao, A. Recent advances in hydrogen research as a therapeutic medical gas. *Free Radic. Res.* **2010**, *44*, 971–982. [CrossRef] [PubMed]
29. Abraini, J.H.; Gardette-Chauffour, M.C.; Martinez, E.; Rostain, J.C.; Lemaire, C. Psychophysiological reactions in humans during an open sea dive to 500 m with a hydrogen-helium-oxygen mixture. *J. Appl. Physiol.* **1994**, *76*, 1113–1118. [CrossRef]
30. Fontanari, P.; Badier, M.; Guillot, C.; Tomei, C.; Burnet, H.; Gardette, B.; Jammes, Y. Changes in maximal performance of inspiratory and skeletal muscles during and after the 7.1-MPa Hydra 10 record human dive. *Eur. J. Appl. Physiol.* **2000**, *81*, 325–328. [CrossRef] [PubMed]
31. Ono, H.; Nishijima, Y.; Adachi, N.; Sakamoto, M.; Kudo, Y.; Kaneko, K.; Nakao, A.; Imaoka, T. A basic study on molecular hydrogen (H_2) inhalation in acute cerebral ischemia patients for safety check with physiological parameters and measurement of blood H_2 level. *Med. Gas Res.* **2012**, *2*, 1–7. [CrossRef]
32. Ohsawa, I.; Nishimaki, K.; Yamagata, K.; Ishikawa, M.; Ohta, S. Consumption of hydrogen water prevents atherosclerosis in apolipoprotein E knockout mice. *Biochem. Biophys. Res. Commun.* **2008**, *377*, 1195–1198. [CrossRef]

33. Nagata, K.; Nakashima-Kamimura, N.; Mikami, T.; Ohsawa, I.; Ohta, S. Consumption of molecular hydrogen prevents the stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice. *Neuropsychopharmacology* **2009**, *34*, 501–508. [CrossRef]
34. Sobue, S.; Yamai, K.; Ito, M.; Ohno, K.; Ito, M.; Iwamoto, T.; Ichihara, M. Simultaneous oral and inhalational intake of molecular hydrogen additively suppresses signaling pathways in rodents. *Mol. Cell. Biochem.* **2015**, *403*, 231–241. [CrossRef]
35. Liu, Y.; Liu, W.; Sun, X.; Li, R.; Sun, Q.; Cai, J.; Zhang, W. Hydrogen saline offers neuroprotection by reducing oxidative stress in a focal cerebral ischemia-reperfusion rat model. *Med. Gas. Res.* **2011**, *1*, 1–9. [CrossRef]
36. Grochowska, M.; Laskus, T.; Radkowski, M. Gut microbiota in neurological disorders. *Arch. Immunol. Ther. Exp.* **2019**, *67*, 375–383. [CrossRef]
37. Baird, L.; Dinkova-Kostova, A.T. The cytoprotective role of the Keap1–Nrf2 pathway. *Arch. Toxicol.* **2011**, *85*, 241–272. [CrossRef] [PubMed]
38. Katoh, Y.; Itoh, K.; Yoshida, E.; Miyagishi, M.; Fukamizu, A.; Yamamoto, M. Two domains of Nrf2 cooperatively bind CBP, a CREB binding protein, and synergistically activate transcription. *Genes Cells* **2001**, *6*, 857–868. [CrossRef] [PubMed]
39. Guo, X.; Han, C.; Ma, K.; Xia, Y.; Wan, F.; Yin, S.; Kou, L.; Sun, Y.; Wu, J.; Hu, J.; et al. Hydralazine protects nigrostriatal dopaminergic neurons from MPP+ and MPTP induced neurotoxicity: Roles of Nrf2-ARE signaling pathway. *Front. Neurol.* **2019**, *10*, 271. [CrossRef] [PubMed]
40. Oh, S.; Shimizu, H.; Satoh, T.; Okada, S.; Adachi, S.; Inoue, K.; Eguchi, H.; Yamamoto, M.; Imaki, T.; Hashimoto, K.; et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. *Nature* **2006**, *443*, 709–712. [CrossRef] [PubMed]
41. Lim, Y.W. Triple endobutton technique in acromioclavicular joint reduction and reconstruction. *Ann. Acad. Med. Singap.* **2008**, *37*, 294.
42. Buendia, I.; Michalska, P.; Navarro, E.; Gameiro, I.; Egea, J.; León, R.J. Therapeutics, Nrf2–ARE pathway: An emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. *Clin. Pharm. Therap.* **2016**, *157*, 84–104.
43. Sivandzade, F.; Prasad, S.; Bhalerao, A.; Cucullo, L.J. NRF2 and NF-κB interplay in cerebrovascular and neurodegenerative disorders: Molecular mechanisms and possible therapeutic approaches. *Redox Biol.* **2019**, *21*, 101059. [CrossRef]
44. Jakel, R.J.; Townsend, J.A.; Kraft, A.D.; Johnson, J.A. Nrf2-mediated protection against 6-hydroxydopamine. *Brain Res.* **2007**, *1144*, 192–201. [CrossRef]
45. Innamorato, N.G.; Jazwa, A.; Rojo, A.I.; García, C.; Fernández-Ruiz, J.; Grochot–Przeczek, A.; Stachurska, A.; Jozkowicz, A.; Dulak, J.; Cuadrado, A. Different susceptibility to the Parkinson's toxin MPTP in mice lacking the redox master regulator Nrf2 or its target gene heme oxygenase-1. *PLoS ONE* **2010**, *5*, e11838. [CrossRef] [PubMed]
46. Wang, F.; Yu, G.; Liu, S.Y.; Li, J.B.; Wang, J.F.; Bo, L.L.; Qian, L.R.; Sun, X.J.; Deng, X.M. Hydrogen-rich saline protects against renal ischemia/reperfusion injury in rats. *J. Surg. Res.* **2011**, *167*, e339–e344. [CrossRef] [PubMed]
47. Huang, L.; Lenahan, C.; Boling, W.; Tang, J.; Zhang, J.H. Molecular hydrogen application in stroke: Bench to bedside. *Curr. Pharm. Des.* **2021**, *27*, 1–9. [CrossRef]
48. Manaenko, A.; Lekic, T.; Ma, Q.; Zhang, J.; Tang, J. Hydrogen inhalation ameliorated mast cell mediated brain injury after ICH in mice. *Crit. Care Med.* **2013**, *41*, 1266. [CrossRef]
49. Yuan, L.; Shen, J. Hydrogen, a potential safeguard for graft-versus-host disease and graft ischemia-reperfusion injury? *Clinics* **2016**, *71*, 544–549. [CrossRef]
50. Liu, Q.; Shen, W.F.; Sun, H.Y.; Fan, D.F.; Nakao, A.; Cai, J.M.; Yan, G.; Zhou, W.P.; Shen, R.X.; Yang, J.M.; et al. Hydrogen-rich saline protects against liver injury in rats with obstructive jaundice. *Liver Int.* **2010**, *30*, 958–968. [CrossRef]
51. Choi, J.; An, E.S.; Ban, Y.H.; Seo, D.W.; Kim, T.S.; Lee, S.P.; Kim, Y.B. Hydrogen-enriched water eliminates fine particles from the lungs and blood by enhancing phagocytic activity. *J. Biomed. Res.* **2017**, *31*, 503–511.
52. Nishida, T.; Hayashi, T.; Inamoto, T.; Kato, R.; Ibuki, N.; Takahara, K.; Tanda, N. Dual gas treatment with hydrogen and carbon monoxide attenuates oxidative stress and protects from renal ischemia-reperfusion injury. *Transplant. Proc.* **2018**, *1*, 250–258. [CrossRef]
53. Nishimaki, K.; Asada, T.; Ohsawa, I.; Nakajima, E.; Ikejima, C.; Yokota, T.; Ohta, S. Effects of molecular hydrogen assessed by an animal model and a randomized clinical study on mild cognitive impairment. *Curr. Alzheimer Res.* **2018**, *15*, 482–492. [CrossRef]
54. Hayashi, T.; Yoshioka, T.; Hasegawa, K.; Miyamura, M.; Mori, T.; Ukimura, A.; Ishizaka, N. Inhalation of hydrogen gas attenuates left ventricular remodeling induced by intermittent hypoxia in mice. *Am. J. Physiol.* **2011**, *301*, H1062–H1069. [CrossRef]
55. Tamaki, N.; Orihuela-Campos, R.C.; Fukui, M.; Ito, H.O. Hydrogen-rich water intake accelerates oral palatal wound healing via activation of the Nrf2/antioxidant defense pathways in a rat model. *Oxid. Med. Cell Longev.* **2016**, *2016*, 5679040. [CrossRef]
56. Zhou, P.; Lin, B.; Wang, P.; Pan, T.; Wang, S.; Chen, W.; Liu, S. The healing effect of hydrogen-rich water on acute radiation-induced skin injury in rats. *J. Radiat. Res.* **2019**, *60*, 17–22. [CrossRef] [PubMed]
57. Ostojic, S.M. Does H_2 alter mitochondrial bioenergetics via GHS-R1α activation? *Theranostics* **2017**, *7*, 1330–1332. [CrossRef]
58. Kamimura, N.; Nishimaki, K.; Ohsawa, I.; Ohta, S. Molecular hydrogen improves obesity and diabetes by inducing hepatic FGF21 and stimulating energy metabolism in db/db mice. *Obesity* **2011**, *19*, 1396–1403. [CrossRef] [PubMed]
59. Yoritaka, A.; Ohtsuka, C.; Maeda, T.; Hirayama, M.; Abe, T.; Watanabe, H.; Hatano, T. Randomized, double-blind, multicenter trial of hydrogen water for Parkinson's disease. *Mov. Disord. Clin. Pract.* **2018**, *33*, 1505–1507. [CrossRef] [PubMed]
60. Yoritaka, A.; Abe, T.; Ohtsuka, C.; Maeda, T.; Hirayama, M.; Watanabe, H.; Hatano, T. A randomized double-blind multi-center trial of hydrogen water for Parkinson's disease: Protocol and baseline characteristics. *BMC Neurol.* **2016**, *16*, 66. [CrossRef]

61. Lin, C.P.; Chuang, W.C.; Lu, F.J.; Chen, C.Y. Anti-oxidant and anti-inflammatory effects of hydrogen-rich water alleviate ethanol-induced fatty liver in mice. *World J. Gastroenterol.* **2017**, *23*, 4920–4934. [CrossRef]
62. Kura, B.; Bagchi, A.K.; Singal, P.K.; Barancik, M.; LeBaron, T.W.; Valachova, K.; Šoltés, L.; Slezák, J. Molecular hydrogen: Potential in mitigating oxidative-stress-induced radiation injury. *Can. J. Physiol. Pharm.* **2018**, *97*, 287–292. [CrossRef]
63. Yuan, J.; Wang, D.; Liu, Y.; Chen, X.; Zhang, H.; Shen, F.; Liu, X.; Fu, J. Hydrogen-rich water attenuates oxidative stress in rats with traumatic brain injury via Nrf2 pathway. *J. Surg. Res.* **2018**, *228*, 238–246. [CrossRef]
64. Chen, H.G.; Xie, K.L.; Han, H.Z.; Wang, W.N.; Liu, D.Q.; Wang, G.L.; Yu, Y.H. Heme oxygenase-1 mediates the anti-inflammatory effect of molecular hydrogen in LPS-stimulated RAW 264.7 macrophages. *Int. J. Surg.* **2013**, *11*, 1060–1066. [CrossRef] [PubMed]
65. Niture, S.K.; Khatri, R.; Jaiswal, A.K. Regulation of Nrf2—An update. *Free Radic. Biol. Med.* **2014**, *66*, 36–44. [CrossRef]
66. Gao, Y.; Yang, H.; Fan, Y.; Li, L.; Fang, J.; Yang, W. Hydrogen-rich saline attenuates cardiac and hepatic injury in doxorubicin rat model by inhibiting inflammation and apoptosis. *Mediat. Inflamm.* **2016**, *2016*, 1320365. [CrossRef]
67. Tamura, T.; Hayashida, K.; Sano, M.; Onuki, S.; Suzuki, M. Efficacy of inhaled hydrogen on neurological outcome following brain ischemia during post-cardiac arrest care (HYBRID II trial): Study protocol for a randomized controlled trial. *Trials* **2017**, *18*, 1–9. [CrossRef] [PubMed]
68. Haam, S.; Lee, J.G.; Paik, H.C.; Park, M.S.; Lim, B.J. Hydrogen gas inhalation during ex vivo lung perfusion of donor lungs recovered after cardiac death. *J. Heart. Lung Transplant.* **2018**, *37*, 1271–1278. [CrossRef]
69. Abisso, T.G.; Adzavon, Y.M.; Zhao, P.; Zhang, X.; Liu, M.; Ma, X. Current progress in molecular hydrogen medication: Protective and therapeutic uses of hydrogen against different disease scenarios. *Intern. Med.* **2020**, *10*, 314.
70. Imai, K.; Kotani, T.; Tsuda, H.; Mano, Y.; Nakano, T.; Ushida, T.; Hirakawa, A. Neuroprotective potential of molecular hydrogen against perinatal brain injury via suppression of activated microglia. *Free Radic. Biol. Med.* **2016**, *91*, 154–163. [CrossRef] [PubMed]
71. He, J.; Xiong, S.; Zhang, J.; Wang, J.; Sun, A.; Mei, X.; Wang, Q. Protective effects of hydrogen-rich saline on ulcerative colitis rat model. *J. Surg. Res.* **2013**, *185*, 174–181. [CrossRef]
72. Chen, C.H.; Manaenko, A.; Zhan, Y.; Liu, W.W.; Ostrowki, R.P.; Tang, J.; Zhang, J.H. Hydrogen gas reduced acute hyperglycemia-enhanced hemorrhagic transformation in a focal ischemia rat model. *Neuroscience* **2010**, *169*, 402–414. [CrossRef] [PubMed]
73. Sato, Y.; Kajiyama, S.; Amano, A.; Kondo, Y.; Sasaki, T.; Handa, S.; Fujinawa, H. Hydrogen-rich pure water prevents superoxide formation in brain slices of vitamin C-depleted SMP30/GNL knockout mice. *Biochem. Biophys. Res. Commun.* **2008**, *375*, 346–350. [CrossRef]
74. Nakayama, M.; Nakano, H.; Hamada, H.; Itami, N.; Nakazawa, R.; Ito, S.A. Novel bioactive haemodialysis system using dissolved dihydrogen (H_2) produced by water electrolysis: A clinical trial. *Nephrol. Dial. Transplant.* **2010**, *25*, 3026–3033. [CrossRef]
75. Domoki, F.; Oláh, O.; Zimmermann, A.; Németh, I.; Tóth-Szűki, V.; Hugyecz, M.; Bari, F. Hydrogen is neuroprotective and preserves cerebrovascular reactivity in asphyxiated newborn pigs. *Pediatr. Res.* **2010**, *68*, 387–392. [CrossRef] [PubMed]
76. Fujita, K.; Seike, T.; Yutsudo, N.; Ohno, M.; Yamada, H.; Yamaguchi, H.; Katafuchi, T. Hydrogen in drinking water reduces dopaminergic neuronal loss in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model of Parkinson's disease. *PLoS ONE* **2009**, *4*, e7247. [CrossRef]
77. Fu, Y.; Ito, M.; Fujita, Y.; Ito, M.; Ichihara, M.; Masuda, A.; Ohsawa, I. Molecular hydrogen is protective against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease. *Neurosci. Lett.* **2009**, *453*, 81–85. [CrossRef] [PubMed]
78. Jucker, M.; Walker, L.C. Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann. Neurol.* **2011**, *70*, 532–540. [CrossRef] [PubMed]
79. Li, J.; Wang, C.; Zhang, J.H.; Cai, J.M.; Cao, Y.P.; Sun, X.J. Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress. *Brain Res.* **2010**, *1328*, 152–161. [CrossRef] [PubMed]
80. Wang, C.; Li, J.; Liu, Q.; Yang, R.; Zhang, J.H.; Cao, Y.P.; Sun, X.J. Hydrogen-rich saline reduces oxidative stress and inflammation by inhibit of JNK and NF-κB activation in a rat model of amyloid-beta-induced Alzheimer's disease. *Neurosci. Lett.* **2011**, *491*, 127–132. [CrossRef] [PubMed]
81. Noe, E.; Ferri, J.; Colomer, C.; Moliner, B.; Chirivella, J. APOE genotype and verbal memory recovery during and after emergence from post-traumatic amnesia. *Brain Inj.* **2010**, *24*, 886–892. [CrossRef] [PubMed]
82. Kubota, M.; Shimmura, S.; Kubota, S.; Miyashita, H.; Kato, N.; Noda, K.; Ozawa, Y.; Usui, T.; Ishida, S.; Umezawa, K.; et al. Hydrogen and N-acetyl-L-cysteine rescue oxidative stress-induced angiogenesis in a mouse corneal alkali-burn model. *Investig. Ophthal. Vis. Sci.* **2011**, *52*, 427–433. [CrossRef]
83. Chen, C.; Chen, Q.; Mao, Y.; Xu, S.; Xia, C.; Shi, X.; Sun, X. Hydrogen-rich saline protects against spinal cord injury in rats. *Neurochem. Res.* **2010**, *35*, 1111–1118. [CrossRef] [PubMed]
84. Eckermann, J.M.; Chen, W.; Jadhav, V.; Hsu, F.P.; Colohan, A.R.; Tang, J.; Zhang, J.H. Hydrogen is neuroprotective against surgically induced brain injury. *Med. Gas. Res.* **2011**, *1*, 7. [CrossRef]
85. Huang, Y.; Xie, K.; Li, J.; Xu, N.; Gong, G.; Wang, G.; Xiong, L. Beneficial effects of hydrogen gas against spinal cord ischemia–reperfusion injury in rabbits. *Brain Res.* **2011**, *1378*, 125–136. [CrossRef]
86. Matchett, G.A.; Fathali, N.; Hasegawa, Y.; Jadhav, V.; Ostrowski, R.P.; Martin, R.D.; Dorotta, I.R.; Sun, X.; Zhang, J.H. Hydrogen gas is ineffective in moderate and severe neonatal hypoxia–ischemia rat models. *Brain Res.* **2009**, *1259*, 90–97. [CrossRef] [PubMed]

87. Ono, H.; Nishijima, Y.; Adachi, N.; Tachibana, S.; Chitoku, S.; Mukaihara, S.; Nawashiro, H. Improved brain MRI indices in the acute brain stem infarct sites treated with hydroxyl radical scavengers, edaravone and hydrogen, as compared to edaravone alone. A non-controlled study. *Med. Gas. Res.* **2011**, *1*, 1–9. [CrossRef]
88. Oharazawa, H.; Igarashi, T.; Yokota, T.; Fujii, H.; Suzuki, H.; Machide, M.; Ohsawa, I. Protection of the retina by rapid diffusion of hydrogen: Administration of hydrogen-loaded eye drops in retinal ischemia–reperfusion injury. *Investig. Ophthalmol. Vis. Sci.* **2010**, *51*, 487–492. [CrossRef] [PubMed]
89. Taura, A.; Kikkawa, Y.S.; Nakagawa, T.; Ito, J. Hydrogen protects vestibular hair cells from free radicals. *Acta. Otolaryngol.* **2010**, *130*, 95–100. [CrossRef] [PubMed]
90. Lin, Y.; Kashio, A.; Sakamoto, T.; Suzukawa, K.; Kakigi, A.; Yamasoba, T. Hydrogen in drinking water attenuates noise-induced hearing loss in guinea pigs. *Neurosci. Lett.* **2011**, *487*, 12–16. [CrossRef]
91. Terasaki, Y.; Ohsawa, I.; Terasaki, M.; Takahashi, M.; Kunugi, S.; Dedong, K.; Ishikawa, A. Hydrogen therapy attenuates irradiation-induced lung damage by reducing oxidative stress. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2011**, *301*, L415–L426. [CrossRef]
92. Qian, L.; Cao, F.; Cui, J.; Wang, Y.; Huang, Y.; Chuai, Y.; Cai, J. The potential cardio protective effects of hydrogen in irradiated mice. *J. Radiat. Res.* **2010**, *51*, 741–747. [CrossRef]
93. Kawamura, T.; Wakabayashi, N.; Shigemura, N.; Huang, C.S.; Masutani, K.; Tanaka, Y.; Okumura, M. Inhaled hydrogen gas therapy for prevention of lung transplant-induced ischemia/reperfusion injury in rats. *Asthma. Res. Pract.* **2010**, *90*, 1344–1351.
94. Fang, Y.; Fu, X.J.; Gu, C.; Xu, P.; Wang, Y.; Yu, W.R.; Yao, M. Hydrogen-rich saline protects against acute lung injury induced by extensive burn in rat model. *J. Burn. Care Res.* **2011**, *32*, e82–e91. [CrossRef]
95. Fukuda, K.I.; Asoh, S.; Ishikawa, M.; Yamamoto, Y.; Ohsawa, I.; Ohta, S. Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. *Biochem. Biophys. Res. Commun.* **2007**, *361*, 670–674. [CrossRef]
96. Cardinal, J.S.; Zhan, J.; Wang, Y.; Sugimoto, R.; Tsung, A.; McCurry, K.R.; Nakao, A. Oral hydrogen water prevents chronic allograft nephropathy in rats. *Kidney Int.* **2010**, *77*, 101–109. [CrossRef] [PubMed]
97. Li, Y.; Hamasaki, T.; Nakamichi, N.; Kashiwagi, T.; Komatsu, T.; Ye, J.; Teruya, K.; Abe, M.; Yan, H.; Kinjo, T.; et al. Suppressive effects of electrolyzed reduced water on alloxan-induced apoptosis and type 1 diabetes mellitus. *Cytotechnology* **2011**, *63*, 119–131. [CrossRef] [PubMed]
98. Kajiyama, S.; Hasegawa, G.; Asano, M.; Hosoda, H.; Fukui, M.; Nakamura, N.; Adachi, T. Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. *Nutr. Res.* **2008**, *28*, 137–143. [CrossRef] [PubMed]
99. Ahearne, C.E.; Boylan, G.B.; Murray, D.M. Short and long term prognosis in perinatal asphyxia: An update. *World. J. Clin. Pediatr.* **2016**, *5*, 67–74. [CrossRef]
100. Kriz, J. Inflammation in ischemic brain injury: Timing is important. *Crit. Rev. Neurobiol.* **2006**, *18*, 145–157. [CrossRef]
101. Cai, J.; Kang, Z.; Liu, W.W.; Luo, X.; Qiang, S.; Zhang, J.H.; Li, R. Hydrogen therapy reduces apoptosis in neonatal hypoxia–ischemia rat model. *Neurosci. Lett.* **2008**, *441*, 167–172. [CrossRef]
102. Cai, J.; Kang, Z.; Liu, K.; Liu, W.; Li, R.; Zhang, J.H.; Sun, X. Neuroprotective effects of hydrogen saline in neonatal hypoxia–ischemia rat model. *Brain Res.* **2009**, *1256*, 129–137. [CrossRef] [PubMed]
103. Oláh, O.; Tóth-Szűki, V.; Temesvári, P.; Bari, F.; Domoki, F. Delayed neurovascular dysfunction is alleviated by hydrogen in asphyxiated newborn pigs. *Neonatology* **2013**, *104*, 79–86. [CrossRef] [PubMed]
104. Kharitonenkov, A.; Shiyanova, T.L.; Koester, A.; Ford, A.M.; Micanovic, R.; Galbreath, E.J.; Sandusky, G.E.; Hammond, L.J.; Moyers, J.S.; Owens, R.A.; et al. FGF-21 as a novel metabolic regulator. *J. Clin. Investig.* **2005**, *115*, 1627–1635. [CrossRef]
105. Kalkman, C.J.; Peelen, L.; Moons, K.G.; Veenhuizen, M.; Bruens, M.; Sinnema, G.; de Jong, T.P. Behavior and development in children and age at the time of first anesthetic exposure. *Anesthesiology* **2009**, *110*, 805–812. [CrossRef]
106. Yonamine, R.; Satoh, Y.; Kodama, M.; Araki, Y.; Kazama, T. Coadministration of hydrogen gas as part of the carrier gas mixture suppresses neuronal apoptosis and subsequent behavioral deficits caused by neonatal exposure to sevoflurane in mice. *Anesthesiology* **2013**, *118*, 105–113. [CrossRef]
107. Takaenoki, Y.; Satoh, Y.; Araki, Y.; Kodama, M.; Yonamine, R.; Yufune, S.; Kazama, T. Neonatal exposure to sevoflurane in mice causes deficits in maternal behavior later in adulthood. *Anesthesiology* **2014**, *120*, 403–415. [CrossRef]
108. JazvinšćakJembrek, M.; Hof, P.R.; Šimić, G. Ceramides in Alzheimer's disease: Key mediators of neuronal apoptosis induced by oxidative stress and Aβ accumulation. *Oxid. Med. CellLongev.* **2015**, *2015*, 346783.
109. Wang, X.; Wang, W.; Li, L.; Perry, G.; Lee, H.G.; Zhu, X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim. Biophys. Acta* **2014**, *1842*, 1240–1247. [CrossRef]
110. Lasagna-Reeves, C.A.; Castillo-Carranza, D.L.; Sengupta, U.; Clos, A.L.; Jackson, G.R.; Kayed, R. Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice. *Mol. Neurodegener.* **2011**, *6*, 39. [CrossRef]
111. Tan, M.S.; Yu, J.T.; Jiang, T.; Zhu, X.C.; Tan, L. The NLRP3 inflammasome in Alzheimer's disease. *Mol. Neurobiol.* **2013**, *48*, 875–882. [CrossRef] [PubMed]
112. Ren, J.D.; Wu, X.B.; Jiang, R.; Hao, D.P.; and Liu, Y. Molecular hydrogen inhibits lipopolysaccharide-triggered NLRP3 inflammasome activation in macrophages by targeting the mitochondrial reactive oxygen species. Biochim. Biophys. *Acta Mol. Cell Res.* **2016**, *1863*, 50–55.

113. Lin, C.L.; Huang, W.N.; Li, H.H.; Huang, C.N.; Hsieh, S.; Lai, C.; Lu, F.J. Hydrogen-rich water attenuates amyloid β-induced cytotoxicity through upregulation of Sirt1-FoxO3a by stimulation of AMP-activated protein kinase in SK-N-MC cells. *Chem. Biol. Interact.* **2015**, *240*, 12–21. [CrossRef]
114. Yao, H.; Zhao, D.; Khan, S.H.; Yang, L. Role of autophagy in prion protein-induced neurodegenerative diseases. *ActaBiochim. Biophy. Sin.* **2013**, *45*, 494–502. [CrossRef]
115. Henderson, L.E.; Abdelmegeed, M.A.; Yoo, S.H.; Rhee, S.G.; Zhu, X.; Smith, M.A.; Song, B.J. Enhanced phosphorylation of Bax and its translocation into mitochondria in the brains of individuals affiliated with Alzheimer's disease. *Open Neurol. J.* **2017**, *11*, 48–58. [CrossRef]
116. Han, B.; Zhou, H.; Jia, G.; Wang, Y.; Song, Z.; Wang, G.; Pan, S.; Bai, X.; Lv, J.; Sun, B. MAPK s and Hsc70 are critical to the protective effect of molecular hydrogen during the early phase of acute pancreatitis. *FEBS J.* **2016**, *283*, 738–756. [CrossRef] [PubMed]
117. Hou, C.; Peng, Y.; Qin, C.; Fan, F.; Liu, J.; Long, J. Hydrogen-rich water improves cognitive impairment gender-dependently in APP/PS1 mice without affecting Aβ clearance. *Free Radic. Res.* **2018**, *52*, 1311–1322. [CrossRef]
118. Fitzpatrick, J.L.; Mize, A.L.; Wade, C.B.; Harris, J.A.; Shapiro, R.A.; Dorsa, D.M. Estrogen-mediated neuroprotection against β-amyloid toxicity requires expression of estrogen receptor α or β and activation of the MAPK pathway. *J. Neurochem.* **2002**, *82*, 674–682. [CrossRef]
119. Hollands, C.; Tobin, M.K.; Hsu, M.; Musaraca, K.; Yu, T.S.; Mishra, R.; Lazarov, O. Depletion of adult neurogenesis exacerbates cognitive deficits in Alzheimer's disease by compromising hippocampal inhibition. *Mol. Neurodegener.* **2017**, *12*, 1–3. [CrossRef] [PubMed]
120. Gu, Y.; Huang, C.S.; Inoue, T.; Yamashita, T.; Ishida, T.; Kang, K.M.; Nakao, A. Drinking hydrogen water ameliorated cognitive impairment in senescence-accelerated mice. *J. Clin. Biochem. Nutr.* **2010**, *46*, 269–276. [CrossRef] [PubMed]
121. Alexander, S.; Kerr, M.E.; Kim, Y.; Kamboh, M.I.; Beers, S.R.; Conley, Y.P. Apolipoprotein E4 allele presence and functional outcome after severe traumatic brain injury. *J. Neurotrauma* **2007**, *24*, 790–797. [CrossRef] [PubMed]
122. Osborne, N.N.; Casson, R.J.; Wood, J.P.; Chidlow, G.; Graham, M.; Melena, J. Retinal ischemia: Mechanisms of damage and potential therapeutic strategies. *Prog. Retin. Eye Res.* **2004**, *23*, 91–147. [CrossRef]
123. Kikkawa, Y.S.; Nakagawa, T.; Horie, R.T.; Ito, J. Hydrogen protects auditory hair cells from free radicals. *Neuroreport* **2009**, *20*, 689–694. [CrossRef]
124. Kikkawa, Y.S.; Nakagawa, T.; Taniguchi, M.; Ito, J. Hydrogen protects auditory hair cells from cisplatin-induced free radicals. *Neurosci. Lett.* **2014**, *579*, 125–129. [CrossRef] [PubMed]
125. Zhou, Y.; Zheng, H.; Ruan, F.; Chen, X.; Zheng, G.; Kang, M.; Sun, X. Hydrogen-rich saline alleviates experimental noise-induced hearing loss in guinea pigs. *Neuroscience* **2012**, *209*, 47–53. [CrossRef] [PubMed]
126. Rubiano, A.M.; Carney, N.; Chesnut, R.; Puyana, J.C. Global neurotrauma research challenges and opportunities. *Nature* **2015**, *527*, S193–S197. [CrossRef]
127. Ji, X.; Liu, W.; Xie, K.; Liu, W.; Qu, Y.; Chao, X.; Fei, Z. Beneficial effects of hydrogen gas in a rat model of traumatic brain injury via reducing oxidative stress. *Brain Res.* **2010**, *1354*, 196–205. [CrossRef] [PubMed]
128. Dohi, K.; Kraemer, B.C.; Erickson, M.A.; McMillan, P.J.; Kovac, A.; Flachbartova, Z.; Banks, W.A. Molecular hydrogen in drinking water protects against neurodegenerative changes induced by traumatic brain injury. *PLoS ONE* **2014**, *9*, e108034. [CrossRef]
129. Liu, F.T.; Xu, S.M.; Xiang, Z.H.; Li, X.N.; Li, J.; Yuan, H.B.; Sun, X.J. Molecular hydrogen suppresses reactive astrogliosis related to oxidative injury during spinal cord injury in rats. CNS. *Neurosci. Ther.* **2014**, *20*, 778–786. [CrossRef] [PubMed]
130. Matsumoto, A.; Yamafuji, M.; Tachibana, T.; Nakabeppu, Y.; Noda, M.; Nakaya, H. Oral 'hydrogen water' induces neuroprotective ghrelin secretion in mice. *Sci. Rep.* **2013**, *3*, 1–5. [CrossRef]
131. Andrews, Z.B. The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci.* **2011**, *34*, 31–40. [CrossRef]
132. Kawamura, T.; Wakabayashi, N.; Shigemura, N.; Huang, C.S.; Masutani, K.; Tanaka, Y.; Okumura, M. Hydrogen gas reduces hyperoxic lung injury via the Nrf2 pathway in vivo. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2013**, *304*, L646–L656. [CrossRef] [PubMed]
133. Iuchi, K.; Imoto, A.; Kamimura, N.; Nishimaki, K.; Ichimiya, H.; Yokota, T.; Ohta, S. Molecular hydrogen regulates gene expression by modifying the free radical chain reaction-dependent generation of oxidized phospholipid mediators. *Sci. Rep.* **2016**, *6*, 1–12. [CrossRef]
134. Landucci, G.; Tugnoli, A.; Cozzani, V. Inherent safety key performance indicators for hydrogen storage systems. *J. Hazard Mater.* **2008**, *159*, 554–566. [CrossRef] [PubMed]
135. Ostojic, S.M. Molecular hydrogen: An inert gas turns clinically effective. *Ann. Med.* **2015**, *47*, 301–304. [CrossRef] [PubMed]
136. Li, H.M.; Shen, L.; Ge, J.W.; Zhang, R.F. The transfer of hydrogen from inert gas to therapeutic gas. *Med. Gas. Res.* **2017**, *7*, 265. [PubMed]