Hydrogen in Cerebrovascular Disease

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Abstract

Objective: Cerebrovascular diseases remain a leading cause of mortality and disability worldwide. Despite significant advances in acute interventions such as thrombolysis, endovascular therapy, and neurocritical care, effective neuroprotective strategies remain limited. Molecular hydrogen has recently attracted increasing attention due to its antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties. This review aims to summarize the mechanisms, experimental evidence, therapeutic effects, and future perspectives of hydrogen in cerebrovascular diseases.

Methods: A comprehensive review of studies investigating hydrogen therapy in cerebrovascular diseases was conducted, including hydrogen gas inhalation, hydrogen-rich saline, and hydrogen-rich water. We focused on delivery methods, biological mechanisms, effects on vascular risk factors, and therapeutic outcomes in experimental models such as carotid artery occlusion, ischemic brain injury, subarachnoid hemorrhage, and related conditions.

Results: Current evidence suggests that hydrogen exerts neuroprotective effects by selectively scavenging reactive oxygen species, suppressing neuroinflammation, regulating microglial polarization, inhibiting apoptosis-related signaling pathways, protecting the blood-brain barrier, and improving cerebral blood flow. In addition, hydrogen may improve major cerebrovascular risk factors, including hyperglycemia, hypertension, and hyperlipidemia. Experimental studies have demonstrated that hydrogen reduces oxidative stress, brain edema, neuronal apoptosis, infarct volume, and neurological deficits in various disease models.

Discussion: Hydrogen appears to be a promising adjunctive therapy for cerebrovascular diseases. However, current evidence is limited by inconsistent administration protocols, unclear optimal dosage and timing, and a lack of large-scale clinical trials with long-term follow-up. Future research should focus on standardized treatment strategies and rigorous clinical validation.

Keywords: hydrogen; cerebrovascular disease; neuroprotection; oxidative stress; anti-inflammatory; apoptosis

Introduction

Hydrogen was first discovered in the 17th century by Henry Cavendish. For nearly two centuries, it had no recognized medical application. In 1975, Dole et al.[1] first reported the potential therapeutic effects of hydrogen,

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suggesting its role in the treatment of squamous cell carcinoma. Since then, hydrogen has gradually gained attention in biomedical research.

A major milestone occurred in 2007 when Ohsawa et al.[2] demonstrated that hydrogen can selectively reduce cytotoxic oxygen radicals and exert neuroprotective effects through antioxidant mechanisms. Since this discovery, hydrogen has become an emerging topic in cerebrovascular research. Numerous studies have explored its biological mechanisms and therapeutic potential.

Hydrogen is now recognized to exert neuroprotective effects through antioxidant, anti-inflammatory, and cell signaling pathways, while also being easy to administer and exhibiting a favorable safety profile.

This review summarizes the mechanisms of hydrogen, its experimental and preclinical evidence in cerebrovascular diseases, and its future clinical prospects.

Hydrogen administration routes

Hydrogen is currently administered through three mainstream routes: inhalation of hydrogen gas, injection of hydrogen-rich saline (HRS), and consumption of hydrogen-rich water (HRW). When HRS was injected, hydrogen concentrations in both arterial and venous blood reached a maximum (1.8 mmol/L) within 15 min, and when the injection was interrupted, the concentration decreased rapidly. When HRW was consumed, 59% of the hydrogen in the body was lost through respiration, 0.1% was lost through the body surface, and only 40% remained to act in the body. After subjects consumed 500 mL of HRW within 60 s, the concentration of hydrogen in breath reached a maximum of 36 mmol/L within 10 min and then decreased to a standardized level of 7.0 mmol/L at 60 min[3]. In contrast, when hydrogen was inhaled at concentrations of 3% to 4%, hydrogen concentrations in arterial and venous blood rapidly rose to plateau levels (10–20 μmol/L) within less than 20 min after the onset of inhalation. Arterial hydrogen concentrations fell to as low as one-tenth of the plateau level within 6 min after hydrogen inhalation was interrupted, whereas venous blood took 18 min to reach this level[4]. Taken together, these data suggest that inhaled hydrogen is the most efficient of the three mainstream routes. At the same time, inhaled hydrogen has the advantage of convenience. Although drinking HRW is safer, inhaled hydrogen remains one of the first routes worth considering in cerebrovascular disease[5].

Direct effects of hydrogen

Antioxidant effect

When cerebrovascular diseases such as acute cerebral infarction occur, oxidative stress caused by large amounts of reactive oxygen species (ROS) is an important contributor to tissue damage. Among ROS, the hydroxyl radical (·OH) is the most important oxidant and can react with a variety of biomolecules to damage tissues. Ohsawa et al.[2] demonstrated that hydrogen can selectively reduce cytotoxic ROS, and because of this selectivity, it has very few side effects and does not interfere with other beneficial redox reactions, such as certain body defense mechanisms[6]. Regarding the safety of hydrogen, Ono et al.[4] used gas chromatography and found that physiological parameters remained stable for 30 min after hydrogen use, supporting the safety of hydrogen. Furthermore, hydrogen has high membrane permeability and excellent diffusion capacity, enabling it to readily reach organelles[2].

Anti-inflammatory effect

The neuroinflammatory response in stroke is a complex process. When acute cerebrovascular disease occurs, injured nerve cells trigger localized inflammatory responses that, if unchecked, can affect the patient's long-term neurological function. Microglia play a pivotal role in this process. In practice, microglia are commonly classified into two phenotypes: M1 (pro-inflammatory), which secrete pro-inflammatory cytokines (e.g., IL-1β and tumor necrosis factor-α [TNF-α]); and M2 (anti-inflammatory), which can secrete anti-inflammatory factors. Macrophages can also differentiate into M1- and M2-like phenotypes[7], and when an inflammatory response occurs, macrophages and microglia increase significantly. Ning et al.[7] found that when hydrogen was applied to mice with stroke, M1-type cells began to decrease from the first day onward, whereas M2 cells remained basically unchanged, suggesting that

this effect may be related to the anti-inflammatory effect of hydrogen on neuroinflammation. Yang et al.[8] also supported this point. They applied hydrogen to diabetic rats with stroke and detected changes in several inflammatory factors within 10 days, finding that serum IL-6, TNF-α, and several other inflammatory indices were reduced. This may be attributed to inhibition of the TLR4/NF-κB pathway, which decreases NF-κB p65 phosphorylation and thereby produces anti-inflammatory efficacy.

Anti-apoptotic effect

Neuroapoptosis plays an important role in the course of cerebrovascular diseases. It is not only deeply involved in the pathogenesis of ischemic brain injury but also has a significant impact on disease outcomes and neurological recovery. Once neuroapoptosis is intensified, it may aggravate neurological impairment and threaten the patient's prognosis. Caspases (cysteine proteases) are involved in the regulation and execution of apoptosis, and injection of hydrogen-enriched saline after traumatic brain injury can reduce caspase expression, thereby alleviating neurological impairment by inhibiting apoptosis[9]. This was corroborated by Chen et al.[10], who found that hydrogen can reduce caspase expression and thus control apoptosis. Apoptosis can be detected by TUNEL assay (TdT-mediated dUTP labeling), and the number of TUNEL-positive cells increased after cerebrovascular disease but decreased with the addition of hydrogen[11]. Zhuang et al.[12] conducted a study on hydrogen and subarachnoid hemorrhage (SAH) in rats, measuring NLRP3 inflammasomes and apoptosis-associated speck-like proteins (ASC) after hydrogen application compared with controls, and found that NLRP3 inflammasomes and ASC were significantly reduced after hydrogen application. Compared with the control group, NLRP3 and ASC were significantly elevated in all brain subregions of rats with SAH after 24 h ($P < 0.05$). However, after hydrogen inhalation for 120 min, NLRP3 and ASC decreased in all brain subregions ($P < 0.05$). These findings indicate that hydrogen has anti-inflammatory and anti-apoptotic effects.

Preventive effects of hydrogen

Hypertension, hyperglycemia, and hyperlipidemia—the so-called "three highs"—are all high-risk factors for cerebrovascular disease, and current research suggests that hydrogen improves all three of these high-risk factors to varying degrees. Previous studies have shown that oxidative stress caused by excess ROS advances the onset and development of diabetes[13]. The antioxidant effect of hydrogen may be one of the most important reasons for its improvement of diabetes. Amitani et al.[14] found that significant control of blood glucose could be achieved by oral administration of hydrogen. As for other mechanisms of lowering blood glucose, Amitani et al.[14] concluded that hydrogen can lower blood glucose by increasing the uptake of glucose from the blood by skeletal muscles. Shirahata et al.[15] proposed an alternative mechanism for hydrogen's effect on blood glucose, namely that hydrogen promotes glucose uptake in myotubular cells by facilitating signaling pathway.

In recent years, the incidence of hypertension has been increasing annually, with a trend toward younger patients, and the effect of hydrogen on hypertension is a relatively cutting-edge research area. Wang et al.[16] concluded that injection of hydrogen-enriched saline can alleviate pulmonary hypertension in rats. In a more recent study, Sugai et al.[17] investigated the therapeutic effect of hydrogen on hypertensive rats. The researchers used hydrogen gas (1 h daily) in hypertensive rats with 5/6 nephrectomy as the hydrogen-treated group, while the control group did not receive hydrogen gas. After four weeks, the degree of renal damage was similar in both groups, while postoperative body-weight recovery was better in the hydrogen-treated group than in the control group; blood pressure was also significantly lower in the hydrogen-treated group than in the control group over the four weeks. This experiment showed that hydrogen is safe and has a lowering effect on blood pressure.

The hardening and narrowing of the cerebral blood vessels caused by hyperlipidemia may lead to insufficient blood supply, triggering strokes. In 2011, Zong et al.[18] applied saturated hydrogen saline to rats fed via a high-fat diet. After four weeks, they found that, compared with controls, TC and LDL-C within the blood of the rats were significantly decreased, and ApoB and ApoE were also showed marked reductions. While HDL

quantity remained unchanged, the researchers found that hydrogen improved HDL quality, i.e., it restored a portion of the HDL impaired by hyperlipidemia (i.e., increased the amount of cholesterol excreted to the liver). In 2013, Song et al.[19] extended these findings to humans by administering hydrogen to subjects, and the conclusions were consistent with the previous studies: significant reductions in TC, LDL-C, Apo B, and Apo E, as well as partial restoration of HDL's function. Regarding the mechanism, the researchers proposed that hydrogen reduces LDL oxidation and LDL-induced inflammation, which is an important part of hyperlipidemia-induced atherosclerosis[19].

Practical applications of hydrogen in cerebrovascular diseases

Numerous researchers have used hydrogen in experiments for its effects on cerebrovascular disease, and several researchers have gradually confirmed its therapeutic effects of hydrogen in a wide range of diseases.

Carotid occlusion

Nagatani et al.[20] used a bilateral common carotid artery occlusion (BCCAO) model in mice to evaluate the therapeutic effects of 1.3% hydrogen. The experiment consisted of a sham-operated group, a BCCAO model group, and a BCCAO model + hydrogen group. Oxidative stress was assessed by immunohistochemistry (i.e., measurement of the 8-OHdG level), and brain water content was assessed by the wet-dry method (i.e., after 24 h of occlusion, mice were euthanized, and brain tissues were collected, heated, and directly weighed). After the experiment began, the bilateral carotid arteries were first occluded for 45 min, after which the clamps were removed to allow reperfusion for 180 min, and the incisions were closed after 180 min.

In the experimental group, hydrogen was used throughout occlusion and reperfusion (225 min); in contrast, oxygen was used throughout in the control group. At the end of the experiment, no neuronal damage was observed in the sham-operated group. Both the experimental and control groups had obvious damage, but there were more residual neurons in the experimental group than in the control group. Immunohistochemistry staining was negative in the sham-operated group, while positive staining was observed in both the experimental and control groups. However, the experimental group had a lower level of positive 8-OHdG, indicating a lower level of oxidative stress than that of the control group. Using the cerebral water content of the sham-operated group as a reference, cerebral water content increased significantly in the control group, whereas that of the hydrogen-treated group was not significantly different from the sham-operated group. It can be concluded from the results of this experiment that hydrogen can reduce oxidative stress in the mouse brain and has a therapeutic effect on carotid artery occlusion in mice.

Ischemic brain injury

Li et al.[21] investigated whether hydrogen could alleviate hypoxic-ischemic brain damage (HIBD) by protecting brain pericytes in neonatal rats. After establishing the HIBD model, they compared different hydrogen treatment conditions and found that the higher concentration produced a better protective effect, which was therefore used in subsequent experiments. Hydrogen treatment significantly increased cerebral vessel diameter, preserved pericyte abundance, improved ipsilateral cortical blood flow, and reduced blood-brain barrier permeability compared with the untreated HIBD group. In addition, hydrogen markedly reduced neuronal death and cerebral infarct size, alleviated neurological deficits, and improved learning and memory performance. These findings suggest that hydrogen exerts neuroprotective effects in hypoxic-ischemic brain injury, at least in part by attenuating pericyte injury and thereby improving cerebrovascular function, possibly through its antioxidative and anti-inflammatory properties. Consistently, Oláh et al.[22] reported that hydrogen alleviated delayed neurovascular dysfunction in asphyxiated newborn pigs, further supporting its protective effect in neonatal hypoxic-ischemic injury.

Subarachnoid hemorrhage

Kumagai et al.[23] applied hydrogen to rats with SAH to investigate whether hydrogen could ameliorate the early brain injury (EBI) as well as delayed brain injury (DBI) that it causes. S100-binding protein B (S110B) and phosphorylated c-Jun N-terminal kinase (P-JNK), to be studied in this experiment, are important proteins

and kinases that contribute to brain injury; S100B enhances ROS expression, which increases oxidative stress; P-JNK increases apoptosis. In other studies[24–26], researchers have concluded in other disease models that hydrogen reduces the expression of S100B and P-JNK, suggesting a therapeutic effect on these diseases. In this experiment, the investigators assessed EBI by S100B and P-JNK expression and neurological deficits on the 3rd day, DBI by neurological deficits on the 7th day, and also assessed whether hydrogen could reduce DBI by improving cerebral vasospasm (CV). The experimental group inhaled 1.3% hydrogen for several hours each day. On the 3rd day, the neurological scores of the experimental group were significantly higher than those of the control group, and the expression of S100B and P-JNK was significantly reduced in the experimental group, but there was no significant reduction of CV in the experimental group and the control group. On day 7, neurological function scores of the experimental group were still significantly higher than those of the control group, and both groups showed some improvement. The results showed that hydrogen could reduce EBI after SAH, which might be related to the reduction of S100B and P-JNK expression, but it did not improve CV, which needs to be further analyzed in subsequent studies.

Potential and outlook for future applications of hydrogen

As the understanding of the biological role and mechanisms of hydrogen has deepened, researchers have begun to explore the possibility of novel hydrogen therapies to provide new and more effective treatments for patients with cerebrovascular disease. Herein, we explore the potential for future applications of hydrogen in cerebrovascular disease.

Lactulose in cerebrovascular disease

Lactulose can produce sufficient hydrogen through bacterial fermentation in the digestive tract[27], and if lactulose is used for gastric gavage, the hydrogen concentration will increase significantly, which may be a new way of applying hydrogen in the clinic. Zhai et al.[11] conducted a further study on this issue, and the results showed that hydrogen concentrations in a rat model of cerebral ischemia-reperfusion injury increased significantly after lactulose gastric gavage; neurological scores were lower than those in the untreated model group, and the cerebral infarct area was reduced. In contrast, lactulose-treated rats had significantly lower hydrogen concentrations after antibiotic administration, suggesting that bacteria are key to hydrogen production. Lactulose enema was more effective after comparison with edaravone-treated rats, which may be related to lactulose's ability to induce nuclear factor erythroid 2-related factor 2 (Nrf2) expression in the brain. Previous studies have concluded that hydrogen induces an increase in Nrf2 expression, which controls the increase in antioxidant enzymes and thus exerts an anti-oxidative stress effect[28], and lactulose may also exert an anti-oxidative stress effect through this pathway. It is possible that the linkage between lactulose and hydrogen is a novel therapeutic pathway for cerebrovascular diseases in the future.

AMS-H-01 high-dose hydrogen inhalation device

Previously, when researchers studied the therapeutic effects of hydrogen inhalation, they usually used bottled hydrogen gas mixtures for the study. Considering safety, the flammable gas contained in the gas mixture should not be more than one-third of the lower explosive limit (4%), so the limited amount of hydrogen that can be used is within 2.9%. Therefore, previous studies have investigated the effect of low-concentration hydrogen inhalation on cerebrovascular diseases, and the results show that low-concentration hydrogen does have a good therapeutic effect, but the effect of high-dose hydrogen has not been fully investigated. The AMS-H-01, a hydrogen-oxygen nebulizer, may be a key part of research on high-dose hydrogen. The device has a special method of splitting water molecules into a mixture of two-thirds hydrogen and one-third oxygen, which allows high concentrations of hydrogen to be used in practical applications while maintaining safety, as the device is designed to avoid fires due to gas buildup[29]. This device is a good step forward in the research of high-dose hydrogen, and if the therapeutic effect of high-dose hydrogen is proved in the future by this device or other new devices that fulfill the requirements, it will certainly be another major breakthrough in the field of hydrogen medicine.

Hydrogen-powered microswimmers

Microswimmers are a novel therapeutic drug delivery tool with the advantages of miniaturization, rich functionality, and wide applicability[30]. Hydrogen-powered microswimmers (HPMs) are now a state-of-the-art delivery tool that can be applied in vivo for the treatment of cerebrovascular diseases. They mainly use Mg particles as carriers, and soluble poly(lactic-co-glycolic acid) is coated on the surface of Mg particles to form a hydrogen producer and deliverer. When entering the body, Mg particles can react with water to produce large amounts of hydrogen. Because of their small openings, the release of hydrogen can be easily controlled. Researchers used Mg particles alone and HPMs in artificial cerebrospinal fluid (ACSF) to compare the differences[30]. They found that Mg particles broke down rapidly in ACSF and hydrogen was produced rapidly. In contrast, HPMs decomposed significantly more slowly than Mg particles and HPMs could move rapidly in ACSF, indicating that hydrogen production by HPMs was continuous and maneuverable due to their special structure. The researchers then applied both groups simultaneously in RAW 264.7 macrophages treated with lipopolysaccharide (LPS). After treatment with LPS, inflammatory factors in RAW 264.7 macrophages increased rapidly. Inflammatory factors decreased after both additions, but the decrease was significantly greater in HPM-treated cells because their unique mobility enhanced hydrogen transport. To further investigate the therapeutic effect of HPMs on cerebrovascular diseases, the researchers added both Mg particles and HPMs into a mouse cerebral ischemia-reperfusion (MCAO) model and found that neurological scores decreased significantly after treatment in both groups. The best results were obtained in the HPM group, in which HPMs reduced the cerebral infarct area of mice to the greatest extent after several days, suggesting that HPMs have a good therapeutic effect on stroke. The researchers also measured the safety of HPMs, and blood results showed normal liver and kidney function indices, no damage in pathological sections of major organs, and an almost negligible hemolysis rate, proving the safety of HPMs. HPMs have both safety and functionality, and it is very likely that HPMs can be applied to the treatment of cerebrovascular diseases in the future if further research and development are carried out.

Conclusion

Extensive research has explored the application of hydrogen in cerebrovascular diseases. Hydrogen can play a therapeutic role in cerebrovascular diseases through its antioxidant, anti-apoptotic, and signaling-pathway modulation mechanisms, and its safety has been confirmed by many studies. After applying hydrogen to several cerebrovascular disease models, researchers have confirmed the therapeutic effect of hydrogen on cerebrovascular diseases through the results of several studies and practical applications. Hydrogen has been shown to be effective in stroke, SAH, ischemic brain injury, and many other diseases. However, there are still some unresolved issues and challenges, such as the appropriate dosage of hydrogen and the optimal mode of administration[31], and whether there are interactions between the mechanisms of action of hydrogen, which need to be further addressed. There are also several brand-new studies in this area that are currently underway, and it is believed that hydrogen will be applied in the clinic in the near future.

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Authors' contributions

Shiqin Ju: conceptualization, methodology, writing-original draft. Qintao Xie: data curation, literature review, writing-review & editing. Yu Feng: supervision, project administration, writing-review & editing. All authors reviewed and approved the final manuscript.

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During the preparation of this work, the authors used AI-assisted tools to improve language clarity, academic structure, and manuscript formatting. The authors

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Competing interests

The authors declare no conflicts of interest.

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Data availability statement

No datasets were generated or analyzed for this work.

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