Molecular hydrogen therapy for neurological diseases: a review of current evidence

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Abstract

Reactive oxygen species and other free radicals cause oxidative stress which is the underlying pathogenesis of cellular injury in various neurological diseases. Molecular hydrogen therapy with its unique biological property of selectively scavenging pathological free radicals has demonstrated therapeutic potential in innumerable animal studies and some clinical trials. These studies have implicated several cellular pathways affected by hydrogen therapy in explaining its anti-inflammatory and antioxidative effects. This article reviews relevant animal and clinical studies that demonstrate neuroprotective effects of hydrogen therapy in stroke, neurodegenerative diseases, neurotrauma, and global brain injury.

Key words: animal; antioxidant; brain injury; clinical study; hydrogen therapy; molecular hydrogen; neurodegenation; neuroinflammation; oxidative stress; stroke

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Introduction

Molecular hydrogen scavenges reactive oxygen species and acts as a therapeutic antioxidant.[1] Since the initial demonstration of benefit of molecular hydrogen on the rat model of cerebral infarction in 2007, a plethora of animal research and several clinical studies have demonstrated significant beneficial results for various diseases.[1] Uniquely, molecular hydrogen selectively scavenges hydroxyl radicals and peroxy-nitric radicals that are responsible for oxidative stress and disease process, while sparing other reactive oxygen species such as hydrogen peroxide, superoxide and nitric oxide that are critical to normal cell physiology.[1] An overwhelming excess of reactive oxygen species and free radicals creates oxidative stress that is central to the pathogenesis of neurological diseases including ischemic stroke, subarachnoid hemorrhage (SAH), traumatic brain injury (TBI) and neurodegeneration. Thus, the selective antioxidant property and safety profile of molecular hydrogen create a tremendous potential for a wide range of clinical applications ranging from stroke treatment to antiaging therapy.

In this review, we aim to provide a succinct mechanistic overview of hydrogen therapy in neurological diseases based on related animal studies and an update of the evidence in human clinical studies.

Search Strategy

We used PubMed search to retrieve relevant published literature between 1978 to 2021. The terms used for the search were molecular hydrogen, hydrogen gas therapy, and neurological diseases. The search results obtained included both original research and review articles. All original research papers were classified as clinical, animal or *in vitro* studies. In this manuscript we review the studies focusing on neurological disorders in animal models and clinical settings.

Delivery Methods

With a safe biologic profile, molecular hydrogen can be administered clinically via several methods including hydrogen gas inhalation, intravascular hydrogenized saline infusions or orally drinking hydrogen water. In addition, increased intestinal hydrogen availability with drugs such as lactulose, acarbose and hydrogen rich tablets has been reported. Hydrogen gas is generally inert and not flammable at a concentration less than 4.7% in air, although it is highly flammable at higher concentrations.[1,2] Inhalational method of delivery provides a simple and practical strategy to administer hydrogen gas at different concentrations (1%, 1.3%, 2%, 4%) through a ventilator circuit/face mask, supplied by gas tank. The hydrogen oxygen nebulizer devices that can provide a high concentration of hydrogen gas (66%) are now available and approved for clinical use. It employs a unique water electrolysis method, splitting the water molecules into its stoichiometric 2:1 hydrogen to oxygen ratio.[2] As to hydrogen delivery through intravenous administration of hydrogen-rich saline, Nagatani et al.[3] described the use of hydrogen-enriched glucose-electrolyte solution produced using a non-destructive hydrogen adding apparatus wherein bags of glucose electrolyte solution were immersed, without opening or altering the bag in a water tank placed in the water. To produce hydrogen water, molecular hydrogen was dissolved in water under high pressure (0.4 MPa) to a supersaturated level using a hydrogen water producing apparatus (Blue Mercury Inc., Tokyo, Japan).[3] A comparative study evaluating the consumption of hydrogen-rich water orally, inhalational hydrogen gas, intraperitoneal/intravenous administration of hydrogen-rich saline in mouse models showed peak concentration of hydrogen in tissues

about 1 minute after intravenous administration, 5 minutes after oral administration and 30 minutes after inhalational hydrogen gas.[4] From the neurological perspective, no differences were noted in concentrations of hydrogen in the brain between hydrogen-rich water and hydrogen-rich saline administration, as hydrogen was noted to migrate to the brain regardless of any mode of administration.[4]

Hydrogen Therapy in Stroke

Ischemic stroke

As the second leading cause of death worldwide, ischemic cerebrovascular stroke is a major source of morbidity and mortality. Historically, the majority of treatments have focused on reperfusion most commonly via administration of recombinant tissue plasminogen activator, an enzyme that lyses fibrin cross links and ultimately resolves the clot, or by physically removing the clot via mechanical thrombectomy.[5] Although the advent of these "clot busting" therapies has revolutionized the management of ischemic stroke, they are not without risk, largely due to secondary injury of damaged parenchyma from reperfusion due to oxidative stress, especially if it occurs too rapidly.[6] Thus reducing reperfusion injury in stroke could potentially be a significant adjunct to the current treatment paradigm to improve clinical outcomes.

Ohsawa et al.[1,7-11] first reported that hydrogen gas acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals in a rat model of middle cerebral artery occlusion, followed by several other studies supporting those findings. Most studies of hydrogen gas therapy for ischemic cerebral stroke used animal models, particularly rat models of cerebral ischemia/reperfusion. Hydrogen sulfide has also been studied as a mode of hydrogen therapy in animal ischemic models with comparable beneficial neuroprotective results.[12,13]

Hyperglycemia is one of the major factors for hemorrhagic transformation after ischemic stroke. Chen et al.[14] reported that 2.9% hydrogen gas inhalation significantly attenuated the hemorrhagic transformation in a rat focal cerebral ischemia model by scavenging free radicals.

Clinically, several studies have embarked on studies of hydrogen gas therapy in patients with ischemic stroke. In a randomized controlled trial in 2017, Ono et al.[15] divided patients into two groups with the treatment group receiving hydrogen gas compared with a control that was administered the gas medium without hydrogen gas. The hydrogen gas treatment group demonstrated more rapid and complete recovery with earlier improvement in the National Institutes of Health Stroke Scale score and improved overall functional outcomes with higher modified Rankin scores, ability to perform activities of daily living, and greater functional independence. Furthermore, this trial highlighted the safety profile of hydrogen gas therapy in patients with ischemic stroke wherein no adverse effects reported.[15] The same group reported significantly smaller areas of infarct, as measured with magnetic resonance imaging indices in patients treated with hydrogen gas therapy following ischemic stroke.[16] The lack of any adverse effects of hydrogen therapy appears to hold true across multiple clinical studies.[3]

Further clinical trials to better understand the efficacy and optimize the treatment regimen for hydrogen gas therapy could help unravel its exciting potential as a useful adjunct to current reperfusion therapies in treating ischemic strokes.

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is a type of stroke characterized by bleeding within the brain tissue. Hydrogen therapy provides a neuroprotective effect in animal models of hemorrhagic stroke.[17,18] Manaenko et al.[17] observed the beneficial effects of an hour of 2.9% hydrogen inhalation in animal ICH models likely due to reduction of redox stress and blood-brain barrier disruption mediated through suppression of mast cell activation and degranulation. Hydrogen gas inhalation at 1.3% consistently exerted a neuroprotective effect against early brain injury after ICH through anti-inflammatory, neuroprotective, anti-apoptotic, and antioxidative activity.[19] However, clinical studies evaluating hydrogen therapy in ICH patients have not been reported.

SAH

SAH due to ruptured intracranial aneurysm is a devastating neurological condition with high mortality and severe morbidity.[20] The neurological prognosis depends both on the severity of vasospasm that causes delayed ischemic neurological deficit and the acute brain injury that occurs after SAH. Mechanistic details underlying acute brain injury and cerebral vasospasm after SAH are not completely understood and therefore no definitive therapy exists to effectively prevent or treat these phenomena. Many studies however point to an important role of oxidative stress in the pathophysiology of SAH and its sequelae.[21-26] Oxyhemoglobin formed by the oxidation of extravasated blood breakdown products is known to generate free radicals and oxidative stress, which leads to inflammation and neuronal injury/death.[27-29] Several downstream signaling pathways have been postulated for neuroinflammations, such as inflammasome signaling pathway and nuclear factor kappa B pathway, which are all triggered by excess reactive oxygen species. By inhibiting these pathways with its anti-oxidative, anti-inflammatory and anti-apoptotic properties, hydrogen has the potential to alleviate the early after-effects of SAH. Shao et al.[30] demonstrated in rat SAH models that hydrogenated saline administration decreased neuronal apoptosis by inhibiting Akt/glycogen synthase kinase 3beta pathway and also decreased vasospasm by inhibiting oxidative stress and vascular inflammation. Other studies have demonstrated similar inhibition of oxidative stress and decreased endothelial cell injury, partly by inhibiting reactive oxygen species/NOD-, LRR- and pyrin domain-containing protein 3 axis, leading to improved neurobehavioral outcomes and decreased vasospasm.[22,31] Zhan et al.[32] noted that inhaled hydrogen within one hour of SAH induction ameliorated oxidative stress, reduced apoptosis, preserved blood-brain barrier, alleviated brain edema and improved neurological deficits. In a subsequent study the group also demonstrated improvement in neurobehavioral outcomes in the rat model with inhaled hydrogen. They studied the survival rate and 24-hour neuroprotection as primary outcome measures. They found an early administration of

high concentration of inhaled hydrogen gas (66% at 3 L/min) reduced mortality and improved neurobehavioral function at 24 hours after SAH. However, no significant neurobehavioral difference was noted at 72 hours in the study.[33]

In addition to animal models, some human studies are currently ongoing for evaluating hydrogen therapy in SAH. Takechi et al.[34] initiated a double-blind randomized control trial that enrolled 450 patients with high grade SAH for evaluating the efficacy of hydrogen therapy in treating early brain injury, delayed cerebral ischemia and vasospasm. The study randomized patients into three arms based on the intervention they receive: combination intracisternal magnesium and intravenous hydrogen group, intracisternal magnesium group and a control group. Primary outcome measures studied include delayed cerebral ischemia and vasospasm. In addition, Rankin score at 3, 6, and 12 months are to be measured as secondary outcomes. The results of this trial are pending.

Hydrogen Therapy in Neurodegenerative Diseases

Parkinson's disease

Parkinson's disease (PD) is attributed to degeneration or loss of dopaminergic cells in the substantia nigra. Recent evidence demonstrates aggregation of extracellular alpha synuclein contributes to neuroinflammation and neuronal death. nuclear factor kappa B related signaling pathway is implicated in increased accumulation of alpha synuclein.[35] Oxidative stress and mitochondrial dysfunction are known to be a common pathway for several etiologies and activation of inflammatory cellular signal cascades.[36-38] The beneficial effects of hydrogen therapy for PD have been reported in both animal models and in clinical studies.[39,40] Yoritaka et al.[41] performed a clinical trial evaluating oxygen-rich water consumption for PD recently. In a placebo controlled, randomized double blind parallel group clinical pilot study, the authors assessed the efficacy of 1 L/d hydrogen water therapy in Japanese levodopa-medicated PD patients over 48 weeks. There was a significant improvement in the total unified PD rating scale in the hydrogen water group compared to the placebo group.

Alzheimer's disease

Alzheimer's disease (AD) is a common neurodegenerative dementia disorder associated with advanced age. Deposition of amyloid beta protein outside the neurons and accumulation of phosphorylated tau protein inside nerve cells leading to neuronal loss is known to be the hallmark of the pathogenesis.[42] Oxidative stress and neuroinflammation have been identified as causative mechanisms leading to the onset of AD.[43-49] Oral hydrogen water intake ameliorated cognitive impairment in senescent accelerated mice.[50] Similarly, hydrogen-rich saline administration intraperitoneally led to improved memory secondary to inhibition of oxidative stress, cytokine production and nuclear factor kappa B production.[51,52]

In AD mouse models, sustained release of bioactive hydrogen by palladium hydride nanoparticles could block synaptic and neuronal apoptosis, promote neuronal metabolism by eliminating oxidative stress, and activate anti-oxidative pathway, leading to amelioration of cognitive impairment.[53] A sustained, continuous *in situ* release of hydrogen in mouse brain tissue using the nanoparticles has been reported. Efficacy of hydrogen therapy with human studies has not been reported thus far.

Hydrogen Therapy in Neurotrauma

The efficacy of molecular hydrogen in treating brain injury has been investigated in mouse models of both TBI and surgical brain injury.[54-56] Inhalational hydrogen was reported to protect blood-brain barrier and decrease cerebral edema and inhibit the decrease in antioxidant enzymes such a superoxide dismutase and catalases in rat TBI model.[55] Several mechanisms such as inhibition of hypoxia inducible factor-1, Matrix metallopeptidase-9, and cyclophilin A, modulation of cytokines and chemokines are implicated in neuroprotective mechanisms of hydrogen therapy in TBI.[54] Another study by Eckermann et al.[56] reported decreased cerebral edema and improved neurobehavioral scores after frontal lobectomy in surgical trauma mouse models.

There are no large clinical studies evaluating hydrogen therapy in TBI. However, anecdotal individual use cases have reported clinical benefits. An athlete given a buccal administration of hydrogen producing dissolving tablet immediately and every 2 hours for a day after concussive injury presented with an improvement in concussion score from moderate to mild category.[57] In the future, larger clinical studies may provide more data on dose and efficacy of such therapies in the setting of TBI.

Hydrogen Therapy in Global Brain Injury

Hydrogen gas therapy has also been demonstrated to improve symptoms of septic encephalopathy in the mouse model of cecal ligation and puncture.[58] Liu et al.[58] performed a study using 2% inhaled hydrogen gas administration in mice, and demonstrated decreased brain edema, blood-brain barrier breakdown, cytokine production, and oxidative stress in the hippocampal CA1 region. In the rodent model of global brain ischemia/reperfusion, low-concentration hydrogen gas inhalation or hydrogen-rich saline intraperitoneal injection showed the neuroprotective effects and improved survival rate through anti-oxidant mechanism as well as mitochondrial protection.[7,59] Recently, Huang et al.[60,61] reported the water-electrolysis-generated 67% hydrogen improved the short- and long-term neurological deficits and decreased neuronal degeneration within the hippocampus in a rat model of asphyxia-induced cardiac arrest.

Conclusion

Numerous preclinical studies have pointed out the striking beneficial effects of hydrogen therapy across a wide range of diseases. Only a limited number of human studies have been reported till date, all of which have demonstrated the benefits of hydrogen therapy in the clinical setting. It is however remarkable to note that no adverse effects have been reported in the human studies related to administration of hydrogen therapy. With several ongoing studies and continued interest in hydrogen therapy, the future looks promising for its clinical use as an adjunctive treatment of various neurological diseases.

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Conflicts of interest
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