Molecular hydrogen in the treatment of acute and chronic neurological conditions: mechanisms of protection and routes of administration

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Oxidative stress caused by reactive oxygen species (ROS) is a major mediator of tissue and cellular injuries in various neuronal conditions, including neurological emergencies and neurodegenerative diseases. Molecular hydrogen is well characterized as a scavenger of hydroxyl radicals and peroxynitrite. Recently, the neuroprotective effects of treatment with molecular hydrogen have been reported in both basic and clinical settings. Here, we review the effects of hydrogen therapy in acute neuronal conditions and neurodegenerative diseases. Hydrogen therapy administered in drinking water may be useful for the prevention of neurodegenerative diseases and for reducing the symptoms of acute neuronal conditions.

Key Words: hydrogen, central nervous system, neurodegenerative disease, oxidative stress, neuroinflammation

Oxidative stress caused by reactive oxygen species (ROS) is a major mediator of tissue and cellular injuries in various neuronal conditions, including neurological emergencies and neurodegenerative diseases.1–7 Control of oxidative stress is a major therapeutic strategy for various neuronal conditions.6,8,9 There are many methods for controlling oxidative stress with the use of free radical scavengers being the most common approach.6,8 Evidence from animal experiments supports the notion that free radical scavengers and antioxidants dramatically reduce cerebral damage.9 Edaravone (MCI-186), a novel free radical scavenger, was developed to prevent lipid peroxidation in pathological neurological conditions.6,9 Edaravone is currently the only antioxidant drug approved for treating cerebral infarction that improves the functional outcome of ischemic stroke.9 Brain hypothermia therapy (targeted temperature management) can also effectively control oxidative stress. Brain hypothermia therapy is effective in patients with various acute neuronal diseases.6,10,11

In 2007, Ohsawa et al.12 reported that molecular hydrogen (H2) can act as an antioxidant to prevent and treat middle cerebral artery occlusion–reperfusion injury in rats. This effect has been supported by additional reports. Recently, the beneficial effect of H2 has been reported in many other organs, including the brain.13–17 The first major therapeutic effect of H2 was that of an antioxidant, combining with hydroxyl ions to produce water.22 Recently, other biological mechanisms of H2 (anti-inflammatory, anti-apoptosis, anti-cytokine, DNA expression, and energy metabolism) have been proposed (Fig. 1 and 2).18 Therefore, the biology of H2 is not simple. In this review, we discuss the role of H2 in various neuronal conditions.

Neurological Diseases

Ischemic brain injury. It has been reported that H2 prevents ischemic brain damage in animal experiments.12,19–21 Ohsawa et al.12 reported that inhalation of 2% H2 gas strongly suppressed infarct volume after middle cerebral artery ischemia–reperfusion in rats. In an electron spin resonance (ESR) study, they showed that H2 had hydroxyl radical scavenging activity. Hydroxynonenal (HNE) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) immunoreactivity was suppressed in the damaged brain after treatment with 2% H2. H2 inhalation reduced ischemic damage and hemorrhagic volume after transient middle cerebral artery occlusion (MCAO) ischemia.19 Free radical generation after ischemia induces matrix metalloproteinase (MMP) expression.19,20 MMP-9 promotes hemorrhagic infarction by disrupting cerebral vessels.20 H2 inhalation has been found to reduce MMP-9 expression in an MCAO rat model. H2 also has a neuroprotective effect against global ischemia. Ji et al.21 reported that H2-rich saline injection [5 ml/kg intra-peritoneal (i.p.) administration] after global ischemia reduced neuronal cell death in hippocampal Cornet d’Ammon 1 (CA1) lesions in rats. Cerebral hypoxia–ischemia and neonatal asphyxia are major causes of brain damage in neonates. H2 gas inhalation and H2-rich saline injection provide early neuroprotection from neonatal neurological damage.22 Nagatani et al.23 reported that an H2-enriched intravenous solution is safe for patients with acute cerebral infarction, including patients treated with tissue plasminogen activator (t-PA) therapy.

Metabolic syndrome is a strong risk factor of stroke. It has been reported that H2 therapy can improve metabolic syndrome in basic and clinical settings.14,24–27 H2 therapy may reduce stroke in patients with metabolic syndrome involving diabetes mellitus.

Hemorrhagic stroke. Hemorrhagic stroke involving intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) is a critical neurological condition, and the mortality rate of hemorrhagic stroke is still high.28–30 Manaenko et al.29 reported a neuroprotective effect of H2 gas inhalation using an experimental ICH animal model. H2 gas inhalation suppresses redox stress and blood brain barrier (BBB) disruption by reducing mast cell activation and degranulation. Brain edema and neurological deficits were also suppressed. In SAH, there are several studies demonstrating

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Fig. 1. Beneficial effects of molecular hydrogen in pathophysiology of various acute neuronal conditions. ATP, adenosine triphosphate; miR-200, microRNA-200; ROS, reactive oxygen species.

Fig. 2. Effect of consumption of hydrogen-rich water as functional water in pathophysiology of neurodegenerative diseases. ATP, adenosine triphosphate; miR-200, microRNA-200; ROS, reactive oxygen species.

Table 1. Clinical trials of molecular hydrogen in central nervous system (CNS) diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hydrogen administration</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Intravenous infusion</td>
<td>(32)</td>
</tr>
<tr>
<td>Post cardiac arrest encephalopathy</td>
<td>2% H₂ gas inhalation</td>
<td>(none)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>water</td>
<td>(49, 50)</td>
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The neuroprotective effect of H₂ treatment. Clinical trials have started in patients with SAH (Table 1). Traumatic brain injury (TBI). The efficacy of H₂ for treating TBI has been investigated in several studies. Ji et al. reported that in a rat TBI model, H₂ gas inhalation has been found to protect BBB permeability and regulate posttraumatic brain edema, reduce excitotoxicity, cytokine production, oxidative stress, and caspase 3 and 9 production and reported that H₂-rich saline decreased glial activation, cytokine production, oxidative stress, and caspase 3 and 9 production as well as inhibited nerve cell death. It is known that stress causes nerve cell impairments. The consumption of H₂-rich water inhibits oxidative stress and thereby inhibits the onset of stress-induced brain damage.

Hypoxic brain injury caused by ischemia–reperfusion. In addition, H₂ gas inhalation has been found to inhibit apoptosis following spinal cord injury caused by ischemia–reperfusion. In recent years, re-search has shown that there is a high incidence of comorbid central nervous system symptoms in sepsis cases. Using a mice cecal ligation and puncture (CLP) model, Liu et al. reported that H₂ gas inhalation improves septic encephalopathy. They reported that 2% H₂ gas inhalation inhibited post-CLP apoptosis, brain edema, BBB permeability, cytokine production, oxidative stress and MMP-9, and cyclophilin A. However, H₂ gas inhalation has been found to inhibit the onset of stress-induced brain damage.

Neurodegenerative Diseases

Parkinson’s disease (PD). PD is a disorder that presents with extrapyramidal symptoms caused by the degeneration and loss of dopamine-producing cells in substantia nigra. Oxidative stress is known to be involved in the clinical condition of PD. Moreover, the involvement of mitochondrial dysfunction in PD has been reported. The effects of H₂ on PD have been reported in animal models of PD as well as in clinical studies. In 2009, Fujita et al. and Fu et al. reported that consuming H₂-rich water inhibits oxidative stress on the nigrostriatal pathway and prevents the loss of dopamine cells in a PD animal model. With the consumption of H₂-rich-water-drinking, oxidative stress in the nigrostriatal pathway was inhibited and loss of dopamine cells was decreased. These results suggest that consuming H₂-rich water could affect the onset of PD. In recent years, the results of a clinical trial on the effects of consuming H₂-rich water for PD have been reported. A randomized double-blind study showed that consuming H₂-rich water (1,000 ml/day) for 48 weeks significantly improved the total Unified Parkinson’s Disease Rating Scale (UPDRS) score of PD patients treated with levodopa. A double-blind multi-center trial of H₂ water is currently underway (Table 1).

Alzheimer’s disease (AD). AD, an age-related neurodegenerative disease, is the most common cause of dementia. Pathologically, it is characterized by the deposition of Aβ protein outside nerve cells and the accumulation of phosphorylated tau protein inside nerve cells. There is also a marked loss of nervous cells in the cerebral cortex. In recent years, oxidative stress and neuroinflammation have been reported to be involved in AD. To date, reports have centered on the involvement of oxidative...
stress in brain parenchyma.\(^{(1,51,53)}\) The accumulation of Aβ protein is strongly associated with the failure of Aβ clearance that is closely related to the pathogenesis of AD.\(^{(5)}\) It is known that low-density lipoprotein receptor-related protein 1 (LRP1) is involved in Aβ protein elimination. LRP dysfunction caused by oxidative stress and neuroinflammation may prevent the onset or progression of AD. A number of reports have investigated the effects of H\(_2\) for the prevention of AD onset.\(^{(51,53)}\)

In a rat AD model, it has been reported that the administration of H\(_2\)-rich saline (5 ml/kg, i.p., daily) inhibited oxidative stress, cytokine production, and nuclear factor-kB (NF-kB) production in the hippocampus and cerebral cortex, and improved impaired memory.\(^{(5,53)}\) It has also been reported that consuming H\(_2\)-rich water inhibits age-related brain alterations and spatial memory decline.\(^{(54)}\)

**Method and Route of Administration in H\(_2\) Therapy**

As a small (2 Da), uncharged molecule H\(_2\) would be expected to readily distribute throughout the body, including being able to easily penetrate cell membranes. However, we are unable to determine the distribution of H\(_2\) among organs and its concentrations in each organ and serum based on the administration methods and dosage. This problem was investigated in 2014.\(^{(55)}\) A comparative review was conducted on the consumption of H\(_2\)-rich water, i.p. or intravenous administration of H\(_2\)-rich saline, and inhalation of H\(_2\) gas. The results showed that the highest concentrations are reached 1 min after intravenous administration and 5 min after oral administration. The highest concentration was reached 30 min after the inhalation of H\(_2\) gas and was maintained for some time. Although H\(_2\) concentrations in the brain tend to be high after either intravenous administration or inhalation, no significant differences have been observed in comparison with the concentrations after the consumption of H\(_2\)-rich water and i.p. administration of H\(_2\)-rich saline. Thus, although there have been variations based on the administration method, all methods have been found to result in the presence of H\(_2\) in the serum and brain tissue. Liu et al.\(^{(39)}\) measured H\(_2\) levels in the arteries, veins, and brain tissues after the inhalation of 2% H\(_2\) gas. They found that arterial H\(_2\) peaked at 30 min after administration, whereas venous and brain tissue H\(_2\) peaked at 45 min after administration. They reported that H\(_2\) levels were similar in arteries and brain tissues. This demonstrated that H\(_2\) migrates to the brain tissue regardless of the method of administration. These results suggest that the consumption of H\(_2\)-rich water prevents neurodegenerative disease and that H\(_2\)-rich drinking water could be used to treat acute brain disorders (Fig. 1 and 2).

**Conclusions**

We have examined the effects of H\(_2\) treatment on acute central nervous system diseases and on chronic neurodegenerative diseases. We have also examined the various mechanism by which H\(_2\) exerts its neuroprotective effects. H\(_2\) acts as a scavenger for OH\(^{-}\) and ONOO\(^{-}\), affects neuroinflammation, preserves mitochondrial energy production, and possesses neuroprotective properties. Unlike more conventional drugs, H\(_2\) treatment, particularly the consumption of H\(_2\)-rich water, has no known serious side effects and is effective for preventing the onset of neurodegenerative disease and aggravation of acute neuronal conditions.

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**Abbreviations**

- AD: Alzheimer’s disease
- APP: amyloid precursor protein
- ATP: adenosine triphosphate
- BBB: blood brain barrier
- CA1: Cornet d’Armon I
- CLP: cecal ligation and puncture
- CO: carbon monoxide
- ICH: intracerebral hemorrhage
- LRP: lipoprotein receptor-related protein
- MCAO: middle cerebral artery occlusion
- miR-200: microRNA-200
- MMP: matrix metalloproteinase
- PD: Parkinson’s disease
- ROS: reactive oxygen species
- SAH: subarachnoid hemorrhage
- TBI: traumatic brain injury

**Conflict of Interest**

No potential conflicts of interest were disclosed.

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**References**

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