Molecular Hydrogen: Quench the Hydroxyl Radical
Clinical Human Research on Molecular Hydrogen
Forms of Hydrogen

Hydrogen 1

Hydrogen 2

Hydrogen Molecule (H₂)
Oxidation-Reduction
“OILRIG”
Size of different anti-oxidants by Molecular Weight
H2: Crosses the Blood Brain Barrier
Molecular Hydrogen-H2 Functions

1.) Anti-oxidant for dangerous hydroxyl radical without destroying free radicals needed for metabolism

2.) Activates Nrf2 anti-oxidant cascade including glutathione peroxidase, catalase, and superoxide dismutase (SOD)

3.) Decreases pro-inflammatory cytokines through cell signaling

4.) Promotes mitochondrial ATP energy function
Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

Ikuroh Ohsawa¹, Masahiro Ishikawa¹, Kumiko Takahashi¹, Megumi Watanabe²,³, Kiyomi Nishimaki³, Kumi Yamagata¹, Ken-ichiro Katsura², Yasuo Katayama², Sadamitsu Aso¹ & Shigeo Ohta¹

Acute oxidative stress induced by ischemia-reperfusion or inflammation causes serious damage to tissues, and persistent oxidative stress is accepted as one of the causes of many common diseases including cancer. We show here that hydrogen (H₂) has potential as an antioxidant in preventive and therapeutic applications. We induced acute oxidative stress in cultured cells by three independent methods. H₂ selectively reduced the hydroxyl radical, the most cytotoxic of reactive oxygen species (ROS), and effectively protected cells; however, H₂ did not react with other ROS, which possess physiological roles. We used an acute rat model in which oxidative stress damage was induced in the brain by focal ischemia and reperfusion. The inhalation of H₂ gas modestly suppressed brain injury by buffering the effects of oxidative stress. Thus H₂ can be used as an effective antioxidant therapy, owing to its ability to rapidly diffuse across membranes, it can reach and react with cytotoxic ROS and thus protect against oxidative damage.

Oxidative stress arises from the strong cellular oxidizing potential of excess reactive oxygen species (ROS), or free radicals³–⁴. Most of the superoxide anion radical (O₂⁻) produced is generated in mitochondria by electron leakage from the electron transport chain and the Krebs cycle⁵. O₂⁻ is also produced by metabolic oxidases, including NADPH oxidase and xanthine oxidase⁶. Superoxide dismutase converts O₂⁻ into hydrogen peroxide (H₂O₂), which is detoxified into H₂O by the enzyme catalase. Excess O₂⁻ reduces transition metal ions such as Fe³⁺ and Cu²⁺ (ref. 2), the reduced forms of which in turn can react with H₂O₂ to produce hydroxyl radicals (•OH) by the Fenton reaction. •OH is the strongest of the oxidant species and reacts indiscriminately with nucleic acids, lipids and proteins. There is no known detoxification system for •OH; therefore, scavenging •OH is a critical antioxidant process⁹.

Despite their cytotoxic effects, O₂⁻ and H₂O₂ play important physiological roles at low concentrations: they function as regulatory signaling molecules that are involved in numerous signal transduction cascades and also regulate biological processes such as apoptosis, cell proliferation and differentiation⁹. At higher concentrations, H₂O₂ is converted into hypochlorous acid by myeloperoxidase; hypochlorous acid defends against bacterial invasion①. Nitric oxide (NO•), another ROS, functions as a neurotransmitter and is essential for the dilation of blood vessels①. Thus, cytotoxic radicals such as •OH must be neutralized without compromising the essential biological activities of other, physiologically beneficial, ROS. Here we demonstrate that molecular hydrogen (diluted hydrogen, H₂) can alleviate •OH-induced cytotoxicity without affecting the other ROS, and propose that H₂ has potential as an antioxidant for preventive and therapeutic applications.

RESULTS
H₂ selectively reduces •OH in cultured cells
H₂ reduces the •OH that is produced by radiolysis or photolysis of water①; however, whether H₂ can effectively neutralize •OH in living cells has not been directly investigated. As the cellular damage produced by spontaneous generation of •OH is not sufficient to be detectable, we induced •OH production in PC12 cultured cells. To do this, we treated the cells with a mitochondrial respiratory complex III inhibitor, antimycin A (ref. 13); following such treatment, •OH in these cells is rapidly converted into H₂O₂. The addition of antimycin A increased levels of O₂⁻ and H₂O₂, as judged by the fluorescent signals emitted by the oxidized forms of MitoSOX (Fig. 1a) and 2',7'-dichlorofluorescein diacetate (H₂DCF) (Supplementary Fig. 1 online), respectively. We dissolved H₂ and O₂ into medium as described in the Methods, and confirmed the prolonged (24 h) maintenance of H₂ levels (Supplementary Fig. 2 online). H₂ dissolved in culture medium did not decrease MitoSOX and DCF signals in the cells (Fig. 1a,b and Supplementary Fig. 1). Additionally, H₂ did not decrease the steady-state level of NO• (Supplementary Fig. 1). In contrast, H₂ treatment significantly decreased levels of •OH, as assessed by the fluorescent signal emitted by the oxidized form of 2'-[6-(4-hydroxyphenylazo)-3,7-difluor-9-(1-naphthaleneazo)benzene] (HPF) (refs. 14,15 and Fig. 1c,d). When we exposed the cells to antimycin A (30 μM) in the absence of H₂, the HPF signals increased in both the nuclear region and the cytoplasm, probably because H₂O₂ diffused from mitochondria to produce •OH. Notably, H₂ decreased •OH levels even in the nuclear region (Fig. 1c).

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One molecule of H2 removes 2 hydroxyl radical molecules to form 2 water molecules

ACTS AS A CONVENTIONAL ANTI-OXIDANT

OH OH = Two H$_2$O

WATER MOLECULES!
Strength of Oxidative Activity for ROS
Molecular Hydrogen-H2 Functions

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4.) Promotes mitochondrial ATP energy function
Nrf2: Nuclear Factor 2

- Master regulator of the antioxidant system
- Mechanism: A Nrf2 activator releases protein into the cell nucleus where it binds to DNA and activates anti-oxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase and these enzymes can neutralize up to 1 million free radicals
Natural Nrf2 Activators

- Molecular hydrogen
- Curcumin
- Resveratrol
- Sulforaphane
- Flavanols: tea (EGCG), chocolate
- Vitamin D
- Coffee
- R-Lipoic Acid
Increase in Nrf2 in animals with TBI treated with molecular hydrogen water compared to TBI with no molecular hydrogen.

Pathological damage of brain tissue in hydrogen water group was significantly milder.

Molecular Hydrogen-H2 Functions

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Types of cell signaling

- Hydrogen-rich water decreases the inflammation in the liver after acetaminophen
- Hydrogen-rich water (HRW) decreases
  - TNF-alpha
  - IL-6 concentrations
Beneficial biological effects and the underlying mechanisms of molecular hydrogen - comprehensive review of 321 original articles -

Masatoshi Ichihara¹, Sayaka Sobue¹, Mikako Ito², Masafumi Ito³, Masaaki Hirayama⁴ and Kinji Ohno²*

Abstract
Therapeutic effects of molecular hydrogen for a wide range of disease models and human diseases have been investigated since 2007. A total of 321 original articles have been published from 2007 to June 2015. Most studies have been conducted in Japan, China, and the USA. About three-quarters of the articles show the effects in mice and rats. The number of clinical trials is increasing every year. In most diseases, the effect of hydrogen has been reported with hydrogen water or hydrogen gas, which was followed by confirmation of the effect with hydrogen-rich saline. Hydrogen water is mostly given ad libitum. Hydrogen gas of less than 4% is given by inhalation. The effects have been reported in essentially all organs covering 31 disease categories that can be subdivided into 166 disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants with a predominance of oxidative stress-mediated diseases and inflammatory diseases. Specific extinctions of hydroxyl radical and peroxynitrite were initially presented, but the radical-scavenging effect of hydrogen cannot be held solely accountable for its drastic effects. We and others have shown that the effects can be mediated by modulating activities and expressions of various molecules such as Lyn, ERK, p38, JNK, ASK1, Akt, GTP-Rac1, iNOS, Nox1, NF-κB p65, IkBα, STAT3, NFATc1, c-Fos, and ghrelin. Master regulator(s) that drive these modifications, however, remain to be elucidated and are currently being extensively investigated.

Keywords: Molecular hydrogen, Ischemia-reperfusion injury, Inflammatory diseases
Molecular Hydrogen-H2 Functions

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Protection of mitochondrial DNA

- H2 decreases the formation of free radicals by downregulating NADPH Oxidase
Neuroinflammation

- Microglial activation
- Astrocytic activation with elevated levels of GFAP (glial fibrillary acidic protein)
- Proinflammatory profile of cytokines in the brain, CSF and blood
- Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation
- Abnormal protein accumulation in some forms of dementia
- Oxidative stress with cellular damage and cellular death
Neuroinflammation: Disease states

- Neurodegeneration
  - Alzheimer’s
  - Parkinson’s
  - ALS
  - Autism

- Toxicity:
  - ex. Heavy metals

- Infections
  - Ex: Lyme disease

- Autoimmunity
  - Ex: Multiple Sclerosis

- Traumatic brain injury
- Stroke
- Ischemic Event
- Metabolic imbalance
  - Insulin resistance
- Aging
- Abnormal microbiome
  - Gut inflammation
- Depression
Alzheimer’s Research Study

**Research: Animal study with hydrogen rich saline**

3 groups: control, induced amyloid-beta neural inflammation, and induced amyloid inflammation plus hydrogen saline

**Results:** Hydrogen-saline prevented amyloid-beta induced neuroinflammation and oxidative stress

Cognitive Impairment: Improvement with Molecular hydrogen

- Placebo controlled study in senescence accelerated animals
- 30 days of molecular hydrogen water:
  - Prevented age-related declines in cognitive ability seen in controls
  - Increased brain serotonin levels
  - Elevated serum antioxidant activity.
  - Drinking hydrogen water for 18 weeks inhibited neurodegeneration in hippocampus, while marked loss of neurons was noted in control

Molecular Hydrogen: Parkinson’s Disease: Clinical Study

- Randomized placebo controlled trial
  - 48 weeks consuming either 1000 ml of molecular hydrogen water or placebo

- Statistically significant improvement in the molecular hydrogen group: Unified Parkinson’s Disease Rating Scale (UDPRS)

- Worsening disease rating in the placebo group

Hydrogen as a novel hypothesized emerging treatment for oxidative stress in autism

Dear Editor,

Hydrogen H(2) is a "novel antioxidant" can be potentially used for many medical conditions. Both human and animal studies indicated the protective effects of hydrogen inhalation. H(2) decreases the hydroxyl radical while it does not react with other types of reactive oxygen species (ROS) including superoxide, hydrogen peroxide (H2O2) and nitric oxide (NO). This is very important because H2O2 and NO have some roles as second messengers during cell growth and differentiation. Although H(2) can be explosive and inflammable, however, it will not flame in temperatures less than 527°C. It does not react with oxygen at room temperature. It has been used in humans for diving. A few advantages are reported for H(2) as an antioxidant: (1) It passes through biomembranes and can enter the cytosol, while some other antioxidants do not; (2) H(2) is able to pass the blood brain barrier; and (3) Molecular hydrogen lacks any cytotoxicity effects, even at high concentration. Molecular hydrogen can be easily consumed through inhalation, drinking hydrogen water, injection, eye-dropping of hydrogen saline, and taking a hydrogen bath.

The continuous consumption of hydrogen water decreases oxidative stress in the mouse brain and prevents the stress-induced decline in learning and memory. Moreover, molecular hydrogen in drinking water has preventive and therapeutic effects on the animal models of Parkinson disease. Hydrogen, through effect on IL-6 and TNF-alpha, plays a therapeutic role in intestinal ischemia/reperfusion injury. The inhalation of hydrogen gas decreases oxidative stress resulting in a reduction in hepatic injury due to ischemia/reperfusion. Moreover, hydrogen water prevents atherosclerosis in animals.

Autism Spectrum Disorders (ASDs) consisted of several disorders including Autistic Disorder, Asperger’s Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). The clinical manifestations of ASD are impaired language and verbal communication, limited or impaired social relationships, restricted interests, and repetitive behaviors. These disorders usually start in early childhood. Autism a neuro-developmental disorder involves multiple organs. ASDs are associated with mitochondrial dysfunction.

There should be an equilibrium between oxidative stress and antioxidant defense capacity. Oxidative stress plays a causative role for autism. While oxidative stress is increased in autism, methylation capacity is impaired. The deficit in antioxidant and methylation capacity in autism is a specific finding for autism. Glutathione (GSH) is responsible for the reduction of oxidative stress. The major intracellular redox (reduction/oxidation) buffer is GSH. The enzymes of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px) are involved in elimination of reactive oxygen species (ROS). The level of SOD and GSH-Px are increased in autism. This increase is explained in that the levels of oxidants are increased and these enzymes have already been triggered to counterbalance the level of oxidant and antioxidant levels. The increased level of ROS may oxidize some biomolecules such as membrane lipids.

According to the mentioned above evidence, there is an increased level of oxidative stress, and a decreased antioxidant capacity in autism. In addition, there is a lack of evidenced-based research into treatments to address this issue. Considering the apparent usefulness of hydrogen as a non-toxic antioxidant that can readily cross the BBB and cellular membrane, it is worthwhile to conduct studies to examine the possible therapeutic role of molecular hydrogen for the treatment of autism.

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Neuroprotection from Molecular Hydrogen:

Traumatic Brain Injury

Research has shown specific changes in neuropathology such as decrease in brain edema, blocked tau protein expression and maintenance of ATP energy production often seen with brain injury

Sports Medicine Uses

- **Subjects**: 18 healthy athletes between 20 and 30 years of age who were experienced in endurance training (> 2 yr)
- **Experimental design**: Randomized, double-blind, cross-over
- **Treatments Protocol**: Each participant was randomized to receive 1 L/day of hydrogen water or placebo
- **Summary of research findings**:
  - Serum bicarbonate levels were significantly higher following exercise in the NORP group compared with the control group (31.2 vs 26.5 mmol/L; \( P < .05 \)).
  - Heart rate during exercise was significantly lower in the NORP group compared with the control group (\( P < .05 \)).
  - Blood lactate levels were significantly lower in the NORP group compared with the control group (\( P < .05 \)).
Rheumatoid Arthritis: Human Research

- 20 patients with RA: 4 weeks with hydrogen water then 4 weeks washout period and then repeat (high dose H2)

- Urinary 8-OHdG was significantly reduced by 14.3% (p < 0.01) on average. Disease Activity Scale 28 also decreased from 3.83 to 3.02 (p < 0.01) after 4 weeks. During the second drinking period, the mean DAS28 was reduced from 2.83 to 2.26 (p < 0.01).

- All the 5 patients with early RA (duration < 12 months) who did not show antibodies against cyclic citrullinated peptides (ACPAs) achieved remission, and 4 of them became symptom-free at the end of the study.

- Conclusions: The results suggest that the hydroxyl radical scavenger H2 effectively reduces oxidative stress in patients with this condition. The symptoms of RA were significantly improved with high H2 water.

Consumption of water containing a high concentration of molecular hydrogen reduces oxidative stress and disease activity in patients with rheumatoid arthritis: an open-label pilot study

Tori Ishibashi MD, Bunpei Sato, Mariko Rikita, Tomoki Sue, Ryosuke Kurikawa, Yuichi Hara, Yui Nantom, Hiroshi Hara and Tetsuhiko Nagao

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Abstract

Background
Molecular Hydrogen: Type 2 DM and impaired glucose tolerance

Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance

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Assessed by an oral glucose tolerance test, were evaluated at baseline and at 8 weeks. Intake of hydrogen-rich water was associated with significant decreases in the levels of modified low-density lipoprotein (LDL) cholesterol (ie, modifications that increase the net negative charge of LDL), small dense LDL, and urinary 8-isoprostanes by 15.5% (P < 0.01), 5.7% (P < 0.05), and 6.6% (P < 0.05), respectively. Hydrogen-rich water intake was also associated with a trend of decreased serum concentrations of oxidized LDL and free fatty acids, and increased plasma levels of adiponectin and extracellular-superoxide dismutase. In 4 of 6 patients with IGT, intake of hydrogen-rich water normalized the oral glucose tolerance test. In conclusion, these results suggest that supplementation with hydrogen-rich water may have a beneficial role in prevention of T2DM and insulin resistance.
Anti-obesity

- Regulates
  - FGF21
  - Ghrelin

Is it safe?

- Naturally produced by bacteria in the intestine in low doses
- Molecular hydrogen water related toxic changes were not seen in terms of any items such as clinical symptoms, body weight, food consumption, urinalysis, hematology, blood chemistry, necropsy, each organ weight and histopathology.

Intake options

- Inhalation
- IV hydrogen saline
- Molecular Hydrogen Water
  - Ionizers that use electrolysis to separate water into alkaline and acid water.
  - Small amount of hydrogen water
  - Inconsistent.
- Molecular hydrogen combined with stabilized minerals
  - Diffused into water and minerals released
H₂ Absorb™

Supplement Facts
Serving Size: 1 Tablet
Servings Per Container: 60

Amount Per Serving % Daily Value
Magnesium (from RN Ionic Hydrogen Matrix) 55 mg 14%
RN Ionic Hydrogen matrix 499 mg *
(Maltose, malic acid, magnesium oxide, glycinate, and malate), fumaric acid.)

* Daily Value not established

OTHER INGREDIENTS: Sodium hydrogen phosphate, potassium citrate, calcium citrate.
FREE OF: Artificial flavors and colors.
Directions for use of H2Absorb™

1. Directions:
   - Drop 1 tablet into a small bottle of water (8 oz. preferred) and close the lid
   - Let the tablet dissolve for a few minutes
   - Drink the water within a short time period and keep the lid on between sips

2. Dose:
   - 2 tablets daily
   - Research uses equivalent of 2 to 4 tablets daily
Clinical Use

Summary

(Bold conditions with human research)
## H2: Summary

<table>
<thead>
<tr>
<th>Physical and Chemical Properties</th>
<th>Molecular Hydrogen Features</th>
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<tbody>
<tr>
<td>Low molecular weight</td>
<td>Rapid and easy diffusion across cellular membranes to reach key intracellular structures (e.g. mitochondria)</td>
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<tr>
<td>Small size, high diffusivity</td>
<td>Crosses the blood-brain barrier</td>
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<tr>
<td>Strong covalent bond between hydrogen atoms</td>
<td>Stability at room and body temperature</td>
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<td>H2 molecule is non-polar</td>
<td>Slightly soluble in water at atmospheric pressure</td>
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<tr>
<td>Reducing agent - neutralizes toxic free radicals such as •OH</td>
<td>Selective antioxidant effects</td>
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<tr>
<td>Selective reducing agent - does not affect important ROS</td>
<td>No effect on redox homeostasis</td>
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<tr>
<td>such as •O2- and H2O2</td>
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<tr>
<td>Reaction with the hydroxyl radical</td>
<td>Multiple mechanisms of action:</td>
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<tr>
<td></td>
<td>- antioxidant</td>
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<td></td>
<td>- anti-inflammatory</td>
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<td></td>
<td>- anti-apoptotic</td>
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<tr>
<td>Reaction with the hydroxyl radical; inhibition of</td>
<td>Can be given via a variety of routes including oral, injection and inhalation</td>
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<td>lipopolysaccharide/interferon γ-induced nitric oxide production</td>
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<tr>
<td>Possibly via reducing/eliminating •OH and ONOO-</td>
<td>Application across a wide range of wellness and medical applications</td>
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<tr>
<td>Gas at room temperature</td>
<td>Well tolerated</td>
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<td>Antioxidant, anti-inflammatory agent, anti-apoptotic agent</td>
<td>Biologically safe and inert with the body</td>
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<td>Endogenous gas - no cytotoxicity</td>
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<td>Dissolution concentration in water (less than 2 % v/v) is well</td>
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<td>below the lower flammability limit of molecular hydrogen (4% v/v)</td>
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<td>in air needed for reaction with oxygen</td>
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<tr>
<td>Authors/Year</td>
<td>Disease</td>
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<tr>
<td>Kajiyama et al., 2008</td>
<td>Diabetes mellitus type II</td>
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<td>Acki et al., 2012</td>
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<td>Vascular endothelial function.</td>
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<tr>
<td>Song et al., 2015</td>
<td>Hyperlipidemia</td>
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References for Molecular Hydrogen

- Molecular hydrogen foundation: [www.molecularhydrogenfoundation.org](http://www.molecularhydrogenfoundation.org)
Dr. Debby Hamilton, MD, MPH
Researched Nutritionals

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