ANTI-AGING

Hydrogen's size allows cell transformations responsible for longevity, performance enhancement and even weight loss without dieting.

Because of its size, molecular hydrogen can do a lot of things larger molecules of known antioxidants can't. Molecular hydrogen affects all cells of the body, crosses the blood-brain barrier and can move readily into the cell energy factories (mitochondria); it "even has the ability to translocate to the nucleus under certain conditions," reports Dr Brandon J Dixon in Medical Gas Research. Once in these ideal locations of the cell, molecular hydrogen's effects are documented as being an antioxidant, anti-inflammatory and influencing the genetics of cell life. Studies conducted since 2007 find molecular hydrogen's use in health could change the physiological fate of at least 183.6 million Americans—and what's more its effects can be obtained with a dietary supplement.

Studies show people with diabetes, arthritis, heart disease and high cholesterol who consume extra amounts of molecular hydrogen experience lower blood sugar, inflammation, cholesterol and higher antioxidant activity. Molecular hydrogen could also find its place in sports performance, age-related dementia and Parkinson's disease. How this one molecule affects so many different systems and organs is a question researchers have been examining ever since the seminal molecular hydrogen in health medicine article came out in Nature Medicine in 2007.

Therapeutic Gas

More than 400 scientific studies, including 30-plus human clinical evaluations, most conducted in the last seven years, find molecular hydrogen effective in seemingly every organ of the body and in 140 human disease models, says the Molecular Hydrogen Research Foundation.

Aging Diseases and Hydrogen

The human studies have focused, in particular, on diabetics. These participants went into their trials with high blood sugar, blood pressure, cholesterol levels, inflammation, obesity and insulin resistance, all hallmarks of aging diseases. Known as Syndrome X or metabolic disease, one in three adults in the US experience these symptoms.

In 2008 researchers looked at the effect of supplementing molecular hydrogen in diabetics and others with poor sugar control. The main cause of aging among diabetics especially is oxidative stress, caused by free radicals whose elevated production is linked with pre-disease states.
The study investigated the effects of H_2 intake on cholesterol and sugar levels in 30 patients with either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT). The patients consumed either pressurized hydrogen-rich pure water or 900 mL of placebo pure water for 8 weeks with a 12-week washout period. Patients in the hydrogen water group experienced "decreases in the levels of modified low- density lipoprotein (LDL) cholesterol... small dense LDL and urinary 8-isoprostanes."

Cholesterol and Weight Loss

Hydrogen intake decreased serum concentrations of oxidized LDLs, the kind of cholesterol linked with artery and heart disease. Levels of the fat-burning hormone adiponectin (that aids weight loss) and superoxide dismutase (SOD), one of the body's primary antioxidants, went up.

Diet Replacement

In 4 of 6 patients with IGT, hydrogen "normalized" oral glucose tolerance tests.

Long-term intake of hydrogen "controlled fat and body weights despite no change in the consumption of food and water" and decreased blood sugar, insulin and triglycerides, the effect of which was similar to diet restriction, according to an independently confirming study. Gene expression in the liver was enhanced and expressed as the protein-based fibroblast growth factor 21 "which should function to enhance fatty acid and glucose expenditure. These results suggest the potential benefit of H2 in treating obesity, diabetes and metabolic syndrome."

Hydrogen delivery

The difficulty of delivering hydrogen- enriched water is that it can only hold about 1.6 ppm of H2 unless pressurized. However H2 can also be produced via a dietary supplement and delivered to the tissues through the interaction of specific types of magnesium, malic acid and hydrogen bound in water. A molecular hydrogen dietary supplement can be taken daily. One supplement delivers three types of magnesium with micro-encapsulated malic and fumaric acids and 74 bio- available coral minerals. As the capsule ingredients react, millions of tiny H2 bubbles saturate the body's cells to raise mitochondrial (energy) and antioxidant activity, especially SOD and glutathione, as well as positively influence cell signalling and gene expression. These anti-aging effects may increase one's overall state of health, say anti-aging physicians such as Julian Whitaker, MD who's begun to recommend molecular hydrogen to patients as a daily supplement.

References

Abrous DN, Koehl M, Le Moal M. Adult neurogenesis: from precursors to network and physiology. Physiol Rev. 2005;85:523– 569. [PubMed]

Aoki K, Nakao A, Adachi T, Matsui Y, Miyakawa S. Pilot study: effects of drinking hydrogen-rich water on muscle fatigue caused by acute exercise in elite athletes. Med Gas Res. 2012 Jul 12;2:12. doi: 10.1186/2045-9912-2-12. ecollection 2012.

Dixon BJ, Tang J, Zhang JH. The evolution of molecular hydrogen: a noteworthy potential therapy with clinical significance. Med Gas Res. 2013; 3: 10. Published online 2013 May 16. doi: 10.1186/2045-9912-3-10PMcID: PMc3660246

Fujita K, Seike T, Yutsudo N, et al. 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. [PMc free article][PubMed]

Fu Y, Ito M, Fujita Y, et al. Molecular hydrogen is protective against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease. Neurosci Lett. 2009;453:81–55. [PubMed]

Ishibashi T, Sato B, Rikitake M, Seo T, Kurokawa R, Hara Y, Naritomi Y, Hara H, Nagao T. 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. Med Gas Res. 2012 Oct 2;2(1):27. doi: 10.1186/2045-9912-2-27.

Kajiyama S, Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, Kitawaki J, Imai S, Nakano K, Ohta M, Adachi T, Obayashi H, Yoshikawa T. Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. Nutr Res. 2008 Mar;28(3):137-43. doi: 10.1016/j.nutres.2008.01.008. 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 (Silver Spring) 2011 in press. [PubMed]

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. Prog Neuropsychopharmacol. 2009;34:501–508. [PubMed]

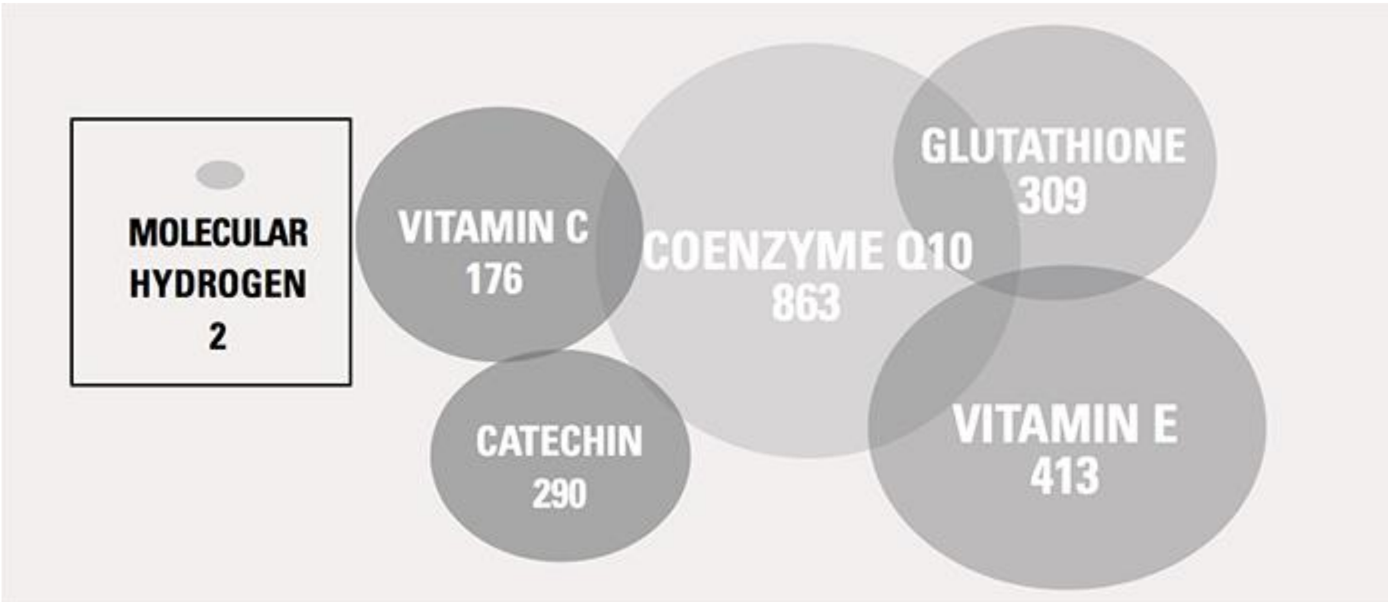
Nakao A, Toyoda Y, Sharma P, evans M, Guthrie N. effectiveness of hydrogen rich water on antioxidant status of subjects with potential metabolic syndrome-an open label pilot study. J clin Biochem Nutr. 2010 Mar;46(2):140-149. doi: 10.3164/jcbn.09-100. e-pub 2010 Feb 24.

Oharazawa H, Igarashi T, Yokota T, et al. Protection of the retina by rapid diffusion of hydrogen: administration of hydrogen- loaded eye drops in retinal ischemia-reperfusion injury. Invest Ophthalmol Vis Sci. 2010;51:487–492.

Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007, 13:688-694. PubMed Abstract | Publisher Full Text

6 Uses of Molecular Hydrogen

Hydrogen is hundreds of times smaller than other antioxidants like our old friends vitamin C and glutathione.



1. Antioxidant

Antioxidants fight oxidation inside and out, keep people younger and prevent premature tissue aging and death. As it turns out molecular hydrogen, because of its ease of access to interact with every area of the cell, is an effective antioxidant. A study examined the antioxidant potential of molecular hydrogen in an open label, 8-week study on 20 subjects with pre-diabetes symptoms. The consumption of molecular hydrogen for 8 weeks resulted in a 39% increase in antioxidant enzyme superoxide dismutase (SOD). Further, subjects demonstrated an 8% increase in high density lipoprotein (HDL)-cholesterol and a 13% decrease in total cholesterol/HDL-cholesterol from baseline to week 4.

2. Arthritis

Molecular hydrogen was studied for its ameliorating influence on rheumatoid arthritis (RA), a chronic inflammatory disease. Twenty patients received 4 to 5 parts per million molecular hydrogen every day for 4 weeks. All the 5 patients with early RA who did not show antibodies “achieved remission, and 4 of them became symptom-free at the end of the study. The symptoms of RA were significantly improved...”

3. Cognitive Decline

Additional experimental studies demonstrate hydrogen prevents brain rust that leads to dementia. “Continuous consumption of hydrogen reduced oxidative stress in the brain and prevented the stress-induced decline in learning and memory.”

4. Parkinson’sDdisease

In Parkinson’s disease, mitochondrial dysfunction and oxidative stress are causes of cell loss in the area of the brain called the substantia nigra. H2 was given in an experimental model of Parkinson’s disease and “prevented both the development and progression of nigrostriatal degeneration” and “likely retards the development and progression of Parkinson’s disease.”

5. Muscle Fatigue

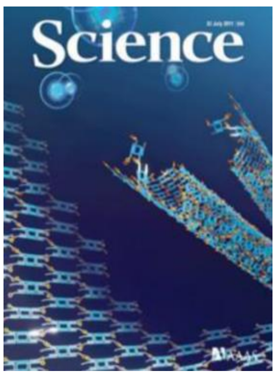
Muscle contraction during short intervals of intense exercise causes oxidative stress, which can develop overtraining symptoms including increased fatigue, muscle injury and inflammation. Ten male soccer players, average age 20, were subjected to exercise tests and blood sampling. Intake of molecular hydrogen prevented an elevation of blood lactate during heavy exercise. Peak torque significantly decreased in the control group in the early phase, suggesting muscle fatigue, but didn't among the molecular hydrogen water group. This means more endurance in the hydrogen group.

6. Glaucoma

H2-loaded eye drops were prepared by dissolving H2 in saline and directly administering to the ocular surface. The direct application of eye drops containing H2 ameliorated pressure and oxidation.

HYDROGEN: AN EMERGING MEDICAL GAS

INTRODUCTION



Molecular hydrogen (i.e. H2 gas) is gaining significant attention from academic researchers, medical doctors, and physicians around the world for its recently reported therapeutic potential [1]. One of the earliest publications on hydrogen as a medical gas was in 1975, by Dole and colleagues from Baylor University and Texas A&M [2]. They reported in the journal Science that hyperbaric (8 atm) hydrogen therapy was effective at reducing melanoma tumors in mice. However, the interest in hydrogen therapy only recently began after 2007, when it was demonstrated that administration of hydrogen gas via inhalation (at levels below the flammability limit of 4.6%) or ingestion of an aqueous-solution containing dissolved hydrogen, could also exert therapeutic biological effects [3]. These findings suggest hydrogen has immediate medical and clinical applications [4].

This MHF article does not discuss negative hydrogen ions, (hydride, H-), pH(e.g. alkaline water), microclustered water, or other topics that are subject to pseudoscientific claims.
For complete article and references, see www.molecularhydrogenfoundation.org

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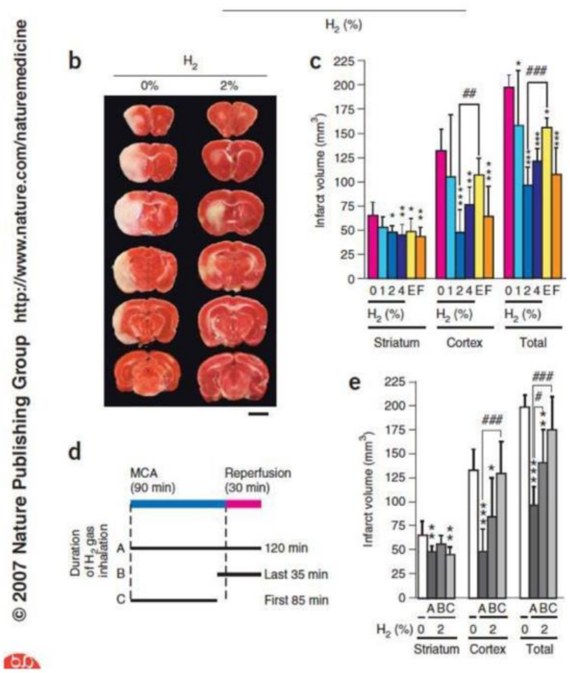


In 2007, Dr. Ohta's team reported in Nature Medicine that inhalation of 2-4% hydrogen gas significantly reduced the cerebral infarct volumes in a rat model of ischemia-reperfusion injury induced by middle cerebral artery occlusion. Hydrogen was more effective than edaravone, an approved clinical drug for cerebral infarction, but with no toxic effects (See figure on left). The authors further demonstrated that dissolved hydrogen in the media of cultured cells, at biologically relevant concentrations, selectively scavenges toxic hydroxyl radicals (*OH), but does not react with other physiologically important reactive oxygen species (e.g. superoxide, nitric oxide, hydrogen peroxide).

This biomedical research on hydrogen is still in its infancy with only around 500 articles and 1,600 researchers, but these publications and researchers suggest that hydrogen has therapeutic potential in over 170 different human and animal disease models, and in essentially every organ of the human body [5]. Hydrogen appears to provide these benefits via modulating signal transduction, protein phosphorylation, and gene expressions (See section Pharmacodynamics) [4].

The idea of therapeutic gaseous molecules is not a new concept. For example, carbon monoxide (CO), hydrogen sulfide (H2S), and of course nitric oxide (NO*), which was initially ridiculed by skeptics, but later was subject to a Nobel Prize, are all biologically active gases [6]. However, it may still be difficult to believe that H2 can exert any biological effect, because in contrast to these other gases, hydrogen is a non-radical, non-reactive, non-polar, highly diffusible neutral gas, thus it is unlikely to have specific binding sites, or interact with specificity on a specific receptor [7].

From an evolutionary perspective, it may not be strange that hydrogen exerts a biological effect [8]. In addition to its role in the origins of the universe, hydrogen was also involved in the genesis of life and played an active role in the evolution of eukaryotes [9]. Over the millions of years of evolution, plants and animals have developed a mutualistic relationship with hydrogen-producing bacteria resulting in basal levels of molecular hydrogen in eukaryotic systems. This constant exposure to molecular hydrogen may have conserved the original targets of hydrogen, as can be extrapolated by genetic remnants of hydrogenase enzymes in higher eukaryotes. Alternatively, but not exclusively, eukaryotes may have developed sensitivity to molecular hydrogen over the millions of years of evolution [7, 10].

METHODS OF ADMINISTRATION

Molecular hydrogen can be administered via inhalation [11], ingestion of solubilized (dissolved) hydrogen-rich solutions (e.g. water, flavored beverages, etc.) [12], hydrogen-rich hemodialysis solution [13], intravenous injection of hydrogen-rich saline [14], topical administration of hydrogen-rich media (e.g. bath, shower, and creams) [15], hyperbaric treatment [2], ingestion of hydrogen-producing material upon reaction with gastric acid [15], ingestion of non-digestible carbohydrates as prebiotic to hydrogen-producing intestinal bacteria [16], rectal insufflation [17], and other methods. [15].

PHARMACOKINETICS

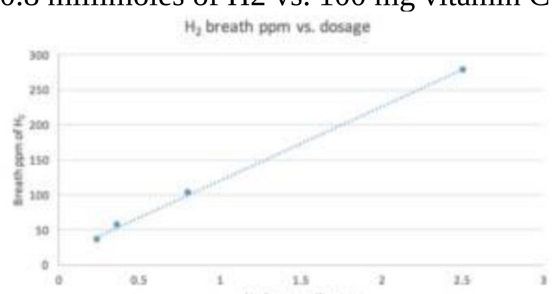
Hydrogen's unique physicochemical properties of hydrophobicity, neutrality, size, mass, etc. afford it with superior distribution properties allowing it to rapidly penetrate biomembranes (e.g. cell membranes, blood-brain, placental, and testis barrier) and reach subcellular compartments (e.g. mitochondria, nucleus, etc.) where it can exert its therapeutic effects [15].

Although various medical clinics in Japan use intravenous injection of hydrogen-rich saline, the most common methods are inhalation and drinking hydrogen-rich water. The pharmacokinetics of each method are still under investigation, but are dependent on dosage, route, and timing. An article published in Nature's Scientific Reports[18] compared inhalation, injection and drinking with different hydrogen concentrations and found helpful insights for clinical use. Based on this and various studies, we briefly summarize the pharmacokinetics of inhalation and drinking.

Inhalation of hydrogen.

For inhalation, a 2-4% hydrogen gas mixture is common because it is below the flammability level; however, some studies use 66.7% H_2 and 33.3% O_2, which is nontoxic and effective, but flammable. Inhalation of hydrogen reaches a peak plasma level (i.e. equilibrium based on Henry's Law) in about 30 min, and upon cessation of inhalation the return to baseline occurs in about 60 min. of drinking dissolved hydrogen.

The concentration/solubility of hydrogen in water at standard ambient temperature and pressure (SATP) is 0.8 mM or 1.6 ppm (1.6 mg/L). For reference, conventional water (e.g. tap, filtered, bottled, etc.) contains less than 0.0000002 ppm of H_2, which is well below the therapeutic level (See FAQ 7-8). The concentration of 1.6 ppm is easily achieved by many methods, such as simply bubbling hydrogen gas into water. Because of molecular hydrogen's low molar mass (i.e. 2.02 g/mol H_2 vs. 176.12 g/mol vitamin C), there are more hydrogen molecules in a 1.6-mg dose of H_2 than there are vitamin C molecules in a 100-mg dose of pure vitamin C (i.e. 1.6 mg H_2 has 0.8 millimoles of H_2 vs. 100 mg vitamin C has 0.57 millimoles of vitamin C).

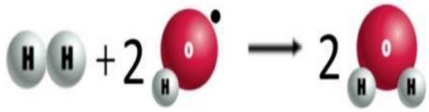


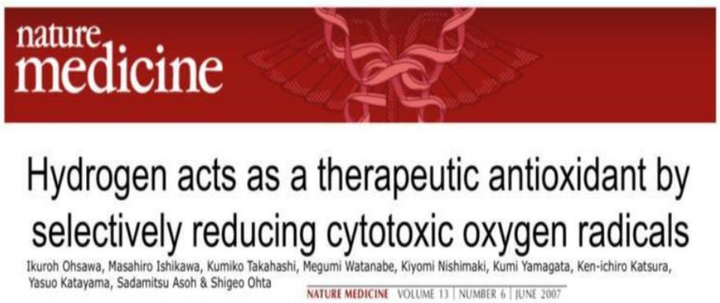
The half-life of hydrogen-rich water is shorter than other gaseous drinks (e.g. carbonated or oxygenated water), but therapeutic levels can remain for a sufficiently long enough time for easy consumption. Ingestion of hydrogen-rich water results in a peak rise in plasma and breath concentration in 5-15 min in a dose-dependent manner (see figure). The rise in breath hydrogen is an indication that hydrogen diffuses through the submucosa and enters systemic circulation where it is expelled out the lungs. This increase in blood and breath concentration returns to baseline in 45-90 min depending on the ingested dosage.

PHARMACODYNAMICS

Although a significant amount of research in cells, tissues, animals, humans and even plants have confirmed hydrogen's effect in biological systems, the exact underlying molecular mechanisms and primary targets remain elusive [19].

ANTIOXIDANT-LIKE EFFECT





nature medicine

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

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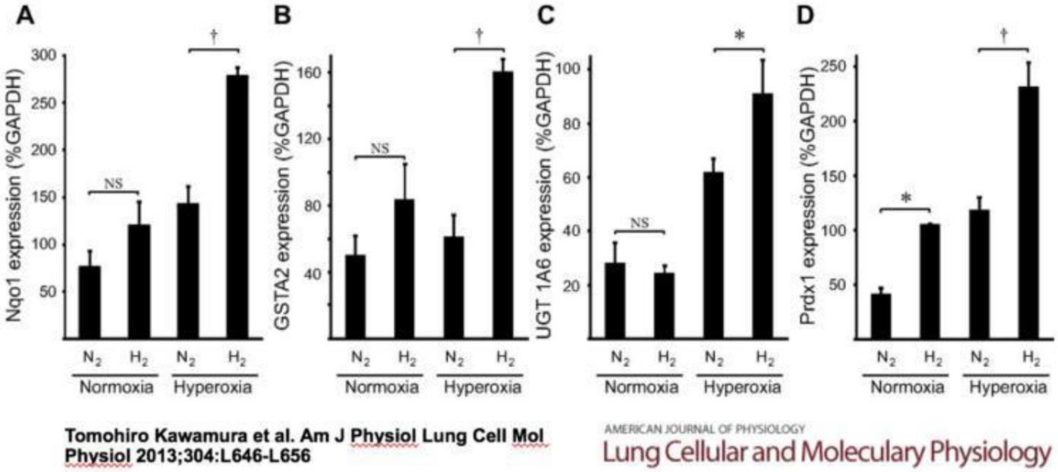
It was initially suggested that the beneficial effect of hydrogen was due to an antioxidant as hydrogen selectively neutralized cytotoxic hydroxyl radicals [3]. However, although this may happen [20], as has been shown in various systems [3, 21, 22], it cannot fully explain all the benefits of hydrogen [23]. For example, in a double-blinded placebo controlled trial in rheumatoid arthritis [24], hydrogen had a residual effect that continued improving the disease symptoms for four weeks after hydrogen administration was terminated [24]. Many cell studies also show that pre-treatment with hydrogen has marked beneficial effects even when the assault (e.g. toxin, radiation, injury, etc.) is administered long after all the hydrogen has dissipated out of the system [25-27]. Additionally, the rate constants of hydrogen against the hydroxyl radical are relatively slow (4.2 x 107 M-1sec-1) [20], and the concentration of hydrogen at the cellular level is also quite low (micromolar levels), thus making it unlikely that H2 could effectively compete with the numerous other nucleophilic targets of the cell [28]. Lastly, if the mechanism were primarily scavenging of hydroxyl radicals, then we should see a greater effect from inhalation compared to drinking, but this is not always the case [29, 30]. In short, we consider it inaccurate or at least incomplete to claim that the benefits of hydrogen are due to its acting directly as a powerful antioxidant. Indeed, hydrogen is selective because it is a very weak antioxidant and thus does not neutralize important ROS or disturb important biological signaling molecules. Nevertheless, a metabolic tracer study [31] using deuterium gas demonstrated that under physiological conditions, deuterium gas is oxidized, and the oxidation rate of hydrogen increases with an increasing amount of oxidative stress [32], but the physicochemical mechanism for this may still not be direct radical scavenging [31]. However, not all studies show that hydrogen is oxidized via mammalian tissues [33], and it has also been reported that deuterium gas did not exert a therapeutic effect in the model studied whereas 1H did (unpublished data).

NRF2 PATHWAY

Unlike conventional antioxidants [34], hydrogen has the ability to reduce excessive oxidative stress [23], but only under conditions where the cell is experiencing abnormally high levels of oxidative stress that would be harmful and not hormetic.



One mechanism that hydrogen uses to protect against oxidative damage is by the activation of the Nrf2-Keap1 system and subsequent induction of the antioxidant response element (ARE) pathway, which leads to the production of various cytoprotective proteins like glutathione, catalase, superoxide dismutase, glutathione peroxidase, heme-1 oxygenase, etc. [5, 35, 36]. In some disease models, the benefits of hydrogen are negated by using Nrf2 gene knockouts [37, 38], Nrf2 genetic silencing using iRNA [39], or pharmacologically blocking the Nrf2 pathway [40, 41]. Importantly, hydrogen only activates the Nrf2 pathway when there is an assault (e.g. toxin, injury, etc.) [40] as opposed to constituently acting as a promoter, which could be harmful [42, 43]. The method that hydrogen activates the Nrf2 pathway remains unclear [5].

CELL MODULATION

Besides the potential scavenging of hydroxyl radicals and/or activation of the Nrf2 pathway, hydrogen may ameliorate oxidative stress via a cell modulating effect [5] and reduce the formation of free radicals [44], such as downregulating the NADPH oxidase system [45]. The various cell modulating effects of hydrogen are responsible for mediating the anti-inflammatory, anti-allergy, and anti-obesity effects of hydrogen.

Hydrogen has been shown to downregulate pro-inflammatory cytokines (e.g. IL- 1, IL-6, IL-8, etc.) [46], attenuate the activation of TNF-a [24], NF- κB [47], NFAT [30, 48], NLRP3 [49, 50], HMGB1 [51], and other inflammatory mediators [5]. Additionally, hydrogen has beneficial effects on obesity and metabolism by increasing the expression of FGF21 [52], PGC-1a [53], PPARa [53], and more. [54]. Additional 2nd messenger molecules or transcription factors affected by hydrogen include ghrelin [55], JNK-1 [45], ERK1/2 [56], PKC [57], GSK [58], TXNIP [49], STAT3 [59], ASK1 [60], MEK [61], SIRT1 [62], and many more. Over 200 biomolecules are altered by hydrogen administration including over 1000 gene expressions.

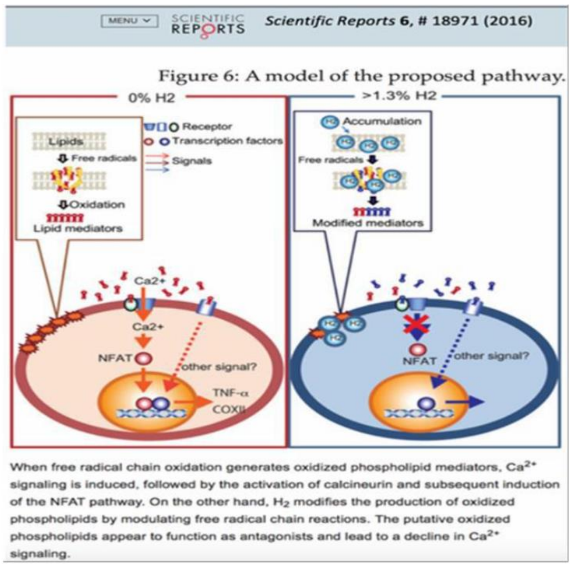


Figure 6: A model of the proposed pathway.

When free radical chain oxidation generates oxidized phospholipid mediators, Ca^{2+} signaling is induced, followed by the activation of calcineurin and subsequent induction of the NFAT pathway. On the other hand, H_2 modifies the production of oxidized phospholipids by modulating free radical chain reactions. The putative oxidized phospholipids appear to function as antagonists and lead to a decline in Ca^{2+} signaling.

However, the primary targets and master regulators responsible for these changes are still elusive [46]. There are many feedback systems and loops to consider, which makes it difficult to determine if we are detecting the cause or the effect of hydrogen administration.

The exact mechanism of how hydrogen modulates signal transduction, gene expression, and protein phosphorylation is still being investigated [5]. A recent publication [63] in Scientific Reports provides good evidence to suggest that one of the mechanisms through which hydrogen accomplishes the various cell-modulating effects is by modifying lipid peroxidation in the cell membrane. In cultured cells, at biologically relevant concentrations, hydrogen suppressed the free radical chain reaction-dependent peroxidation and recovered Ca2+-induced gene expressions, as determined by comprehensive microarray analysis (see figure 6) [63].

SCIENTIFIC RECOGNITION OF HYDROGEN

Although the primary targets or exact biochemical mechanisms of hydrogen are still not fully understood, the therapeutic effect in cells, tissues, animals, humans and even plants [64] is becoming widely accepted due to the now over 500 peer-reviewed articles and the 1,600 researchers on the medical effects of hydrogen. The quality of the publications is also improving with an average impact factor (IF) of the journals publishing hydrogen is about 3. The table below shows a few of the studies published in the higher IF journals, which range from six to 27.