

HYDROGEN: THERAPEUTIC POTENTIAL IN WELLNESS AND MEDICINE

M. Lemaire¹, F. Barbier²

Abstract: Persistent oxidative stress plays an important role in a variety of pathologies, and the search for an effective and well tolerated antioxidant agent continues. Molecular hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. The non-specific mechanism of hydrogen as a therapeutic antioxidant gives it broad therapeutic potential across a wide range of medical applications, as has been shown by a substantial volume of preclinical data, as well as a growing body of clinical evidence. This review provides an overview of the therapeutic potential of hydrogen, in ageing and wellness applications as well as medical applications, including acute ischemia/reperfusion injury, inflammation and ulceration, metabolic disorders, neurodegenerative disorders, and cancer (anti-cancer effects, radiation toxicities, and side effects of cisplatin) with an emphasis on clinical data. Overall, this review shows that hydrogen is an effective antioxidant, anti-inflammatory and cytoprotective agent.

Key words: Hydrogen, ageing, wellness, inflammation, antioxidant.

Introduction

Hydrogen, a single proton and a lone electron, is the lightest and most abundant element in the universe. On Earth, hydrogen generally exists in compounds with other elements, and is not found by itself. The most common sources of hydrogen are hydrocarbons, water and carbohydrates from which molecular hydrogen can be produced (1).

With more than 50 million tons produced globally each year, hydrogen is one of the oldest known molecules that is used extensively by many industries. Most of its uses are based on its physical properties, such as its very low molecular weight (2.0159 g/mol H₂) and density (0.084 g/l at 20°C and 1 atm), and its chemical properties such as its reactivity, forming compounds or preventing oxidation of metals due to its reducing properties (1). Hydrogen has the potential to become an important future energy solution due its high calorific value and its environmentally friendly properties, generating only water vapor when used in fuel cells to produce electricity. The benefits of molecular hydrogen in therapeutic applications have been discovered relatively recently, and remain to be completely elucidated. Many consider

hydrogen to have healing properties, with its role as the fundamental antioxidant for every cell. Reactive oxygen species (ROS) are generated in the bodies of all aerobic organisms as by-products of energy metabolism via oxidative phosphorylation (2). Excess production of ROS or impaired endogenous antioxidant capacity result in a build-up of ROS, known as oxidative stress (2). It is widely accepted that persistent oxidative stress plays an important role in a variety of pathologies, including lifestyle-related diseases such as atherosclerosis and diabetes mellitus, hypertension, chronic inflammation, neurodegenerative diseases, cancer, decreased vascular function and the ageing process (2-7). However, the majority of prospective controlled clinical trials of antioxidant therapy to prevent oxidative stress-related diseases, mostly cardiovascular indications, have failed (8). Therefore, the search for an effective and well tolerated antioxidant agent continues.

Hydrogen is an odorless, tasteless gas that has demonstrated many biological effects against oxidative stress in almost all organs (9, 10). Molecular hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals (11). Hydrogen has a number of characteristics that suggest it might be an ideal antioxidant agent for use in humans. These include its ability to neutralize hydroxyl radicals (\bullet OH) in living cells (including penetration into organelles such as mitochondria) and to cross the blood-brain barrier, as well as its stability at room temperature and low solubility in water (1.9 mL H₂/100 mL H₂O at 20°C and 1 atm, Table 1) and a favorable tolerability profile (2, 10,

1. Air Liquide Sante International, Paris Saclay Research Center, Jouy-en-Josas, France, 2. Air Liquide R&D, Paris Saclay Research Center, Jouy-en-Josas, France.

Corresponding Author: Marc Lemaire, Air Liquide Sante International, Paris Saclay Research Center, 1, route de la porte des loges, Les Loges-en-Josas, 78354, Jouy-en-Josas, France. Tel: +33139076212; Fax:+33139076199; email: Marc.lemaire@airliquide.com

Table 1
Solubility of hydrogen in water

Units	mg H _{2(gas)} /100 ml H _{2O(liquid)}	ml H _{2(gas)} /100 ml H _{2O(liquid)}	ppmw (part per million weight)	mM (millimolar concentration) mmol H _{2(gas)} /100 ml H _{2O(liquid)}
H ₂ solubility in water* (20°C, 1 atm)	0.16	1.9	1.6	0.08
H ₂ enriched-water (drink, injection...) used in literature	1		10	0.5

*From Young C.L., 1981 (18).

Table 2
Summary of the therapeutic advantages of hydrogen as an antioxidant

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

•OH = hydroxyl radical; ROS = reactive oxygen species; •O₂- = superoxide; H₂O₂: hydrogen peroxide; ONOO-: peroxynitrite

12). The advantageous physical and chemical properties of hydrogen, in relation to its therapeutic benefits are summarized in Table 2. Therefore, hydrogen may be potentially useful in the many human diseases known to be associated with oxidative stress, and may have an important role in the prevention of ageing and in many wellness applications.

In addition to its role as an anti-oxidant, there is also evidence to suggest that molecular hydrogen has anti-inflammatory properties, via its reaction with the hydroxyl radical (•OH), which is generated during inflammation (13, 14). There is also evidence to suggest that hydrogen acts more directly on inflammation, via the inhibition of lipopolysaccharide/interferon γ-induced nitric oxide production, via modulation of signal transduction in macrophages (15). Hydrogen

may therefore also be therapeutically useful in the many inflammatory human diseases. Moreover, hydrogen has also been shown to prevent apoptosis, possibly via its ability to reduce or eliminate the hydroxyl radical (•OH) and peroxynitrite (ONOO-) (16).

Importantly, there are a wide variety of options for the administration of hydrogen, including inhalation as a medical gas, drinking of hydrogen-enriched water (dissolved hydrogen gas, created by exposing water to magnesium, by dissolving electrolyzed hydrogen into water, or by using high pressure to dissolve molecular hydrogen in water (16, 17)), taking a hydrogen bath, injection of hydrogen-enriched saline and use of hydrogen-enriched saline eye drops (12).

It is important to note that due to the low solubility of hydrogen in water (18), the resulting concentration

of hydrogen less than 2 % v/v is much lower than the concentration of hydrogen (4% v/v) needed to react with oxygen (1). As a result, hydrogen can be considered as safe and inert within the human body.

This review provides an overview of the therapeutic potential of hydrogen. Ageing and wellness applications are discussed first, followed by a variety of medical applications.

Ageing

Free radicals and reactive oxygen species (ROS) produced by aerobic metabolism play important roles in signal transduction, but also cause damage in biological systems (19). These free radicals and ROS are known to play a role in many human diseases and to be involved in premature ageing (Sun X, 2015).

The search for a simple method to delay or halt the ageing process has been going on for centuries based on efficient anti-oxidant products. Growing evidence of the ability of hydrogen, either as a gas or solution, to scavenge and selectively inactivate ROS suggest that it could exert protective effects (20). Bathing every day for 3 months in waters containing molecular hydrogen (N=18) has been shown to decrease the oxidation-reduction potential (ORP) and increased the elasticity of human skin (21, 22).

The ORP of the skin is increased by sun exposure and by ageing (23), suggesting that a reduction in the ORP might have anti-ageing effects.

Wellness

Hydrogen has been shown to be alkaline in water (24, 25). Hydrogen-rich alkaline water obtained by adding H₂ to electrolyzed water reduces the pH, but the hydrogen itself that can be expected to be of benefit (26). This has important implications for the wellness industry leading to the development of a beverage or food supplement that is able to take advantage of this hydrogen-associated alkalinity.

Exercise performance and sports injury

Exercise-induced production of free radicals is now a well-known phenomenon (27). The increased oxidative stress associated with exercise has the potential to diminish the overall beneficial effects that exercise has on wellbeing.

An open-label pilot study in 19 young, healthy men showed that daily intake of 2 L of hydrogen-enriched water (1.1 mM of dissolved hydrogen) for 7 days increased fasting and post-exercise blood pH, reflecting a reduction in exercise-associated acidosis, with no adverse effects (28). Athletes receiving 1 L of hydrogen water daily showed a significant decrease in the rates

of perceived exertion during exercise testing (29), and an attenuation of increases in blood lactate levels and prevention of the post-exercise decrease in peak torque, an indicator of muscle fatigue (30).

To investigate the effects of hydrogen in the management of sports injuries, 12 professional athletes presenting within the first 24 hours after a muscle and tendon strain were randomized in a double-blind study to receive standard care alone (control) or in combination with oral hydrogen tables (2 g/day) and topical hydrogen-enriched packs (6 times per day for 20 minutes). Follow-up after 7 days showed that the addition of hydrogen significantly reduced plasma viscosity (p=0.002) and limb circumference (p=0.04). These results indicate that the addition of oral and topical molecular hydrogen to traditional first-line treatment is effective in the management of musculotendinous injuries (31).

Endothelial function

The results of a study in healthy volunteers suggest that hydrogen might contribute to wellness via modulation of vascular vasomotor function secondary to suppression of subclinical vascular inflammation (32). Thirty minutes after drinking 530 mL of hydrogen-enriched water (each 500 mL containing 3.5 mg of H₂), healthy volunteers showed significantly improved flow-mediated dilation in the brachial artery compared with subjects who drank placebo water (p=0.0221). Potential mechanisms proposed for this effect were neutralization of ROS to preserve NO bioavailability, and suppression of inflammatory pre-atherosclerotic events.

Medical applications

Major syndromes

Acute ischemia/reperfusion injury

Stroke and myocardial infarction

For both stroke and myocardial infarction the successful treatment strategies to restore blood flow to ischemic tissue are associated with reperfusion injury. One mechanism thought to contribute to this negative outcome is the generation of ROS (33).

In an animal model, inhalation of 2% hydrogen prior to reperfusion has been shown to attenuate ischemia/reperfusion injury (IRI) occurring during coronary artery reperfusion, with a significant reduction in infarct size, (41.6% vs 21.2%: p<0.05) (34). Hydrogen-rich saline (0.6 mM) reduced the apoptosis IRI, (TUNEL-positive cells: 15% vs 24%: p<0.05), decreased infarct size (9.8% vs 32.1%: p<0.01) and improved heart function parameters 24 hours after reperfusion (35). Hydrogen-enriched saline

(0.6 mM) has also been shown to decrease infarct size ($p < 0.05$) as well as both oxidative stress and inflammation (36). In mice, inhalation of hydrogen (2%), alone and in combination with nitric oxide (NO), reduced infarct size after IRI. The hydrogen/NO combination was also associated with preservation of cardiac function after IRI (37). These findings suggest that patients may benefit from hydrogen inhalation as an add-on to percutaneous coronary intervention procedures.

ROS are generated during cerebral IRI and contribute significantly to brain injury. Inhalation of hydrogen at 2% to 4% during reperfusion decreased infarct volume in rats after middle cerebral artery occlusion and reperfusion ($p < 0.001$); inhalation of hydrogen during ischemia had no effect on infarct size in this model (11), hence to have an effect, hydrogen must be used following reperfusion, as is the case for all organ protective molecules.

In experimental hepatic IRI, inhalation of hydrogen (1% to 4%) and intraperitoneal injection of hydrogen-enriched saline (2.5, 5 or 10 mL/kg) have both been associated with reductions in the severity of liver injury, improved liver function and decreases in markers of lipid peroxidation and inflammation (38, 39). Similar findings have been reported after treatment with hydrogen-rich saline (>0.6 mM) in rats subjected to renal IRI (40).

In a clinical setting, the addition of intravenous hydrogen-rich saline (>250 $\mu\text{mol/L}$) to treatment with the hydroxyl radical scavenger/neuroprotective agent edaravone in acute brainstem infarction patients was associated with incremental improvements in magnetic resonance imaging (MRI) findings compared with the natural course: relative diffusion-weighted images (rDWIs), regional apparent diffusion coefficients (rADCs), and pseudo-normalization time of rDWI and rADC were all improved with the combined infusion of hydrogen and edaravone (41).

Cardiac arrest and hemorrhagic shock

Intraperitoneal injection of hydrogen (10 or 20 mL/kg) reduced neuronal injury and inhibited neuronal apoptosis in a rabbit model of cardiac arrest; these effects appeared to occur via reductions in oxidative stress indicators and enhanced antioxidant enzyme activity (42). Similar beneficial effects have been observed with inhalation of hydrogen (2% H₂ and 98% O₂) during cardiopulmonary resuscitation in a rat model of cardiac arrest, with treated animals having improved survival and fewer neurological deficits compared with animals who underwent therapeutic hypothermia (43).

The anti-inflammatory, antioxidant and beneficial effects of hydrogen have also been documented in a number of other acute oxidative stress settings, including a rat model of uncontrolled hemorrhagic shock, where hydrogen-rich saline (>0.6 mM) had better activity when administered via the intravenous versus intraperitoneal route (44).

Organ transplantation

Preclinical data show that the antioxidant effects of hydrogen therapy are evident in organ transplantation models. In a rat model of renal transplant, treatment with hydrogen-enriched water versus regular water reduced chronic allograft nephropathy and improved overall post-transplant survival; these effects appeared to be secondary to reductions in oxidative stress-induced tissue damage (45). Hydrogen-enriched water (0.5 or 0.6 mM) has also been shown to protect rat cardiac allografts from oxidative injury and inflammation-associated deterioration, with significant reductions in markers of oxidative injury and of inflammation ($p < 0.05$), thereby increasing allograft survival (46). Moreover, hydrogen-enriched water (0.55–0.65 mM) inhibited intimal hyperplasia and reduced oxidative damage in arterialized vein grafts in rats (47). Inhaled hydrogen (2%) appears to have beneficial effects in models of lung and intestinal transplantation, including improved spontaneous muscle contractile activity, reduced expression of inflammatory mediators and oxidative injury, prevention of IRI and improved graft survival (48, 49).

Inflammation and ulceration

The anti-inflammatory effect of hydrogen is related to the inhibition of the production of ROS and the release of pro-inflammatory cytokines.

In a rat model of ulcerative colitis (UC), intraperitoneal injection of hydrogen-enriched saline (0.6 mM) was shown to reduce weight loss and diarrhea, as well as alleviate colonic mucosal damage (50). Furthermore, hydrogen-enriched saline was also associated with inhibition of the increased expression of vascular endothelial growth factor seen in this UC model.

In another study, four patients with acute erythematous skin disease were found to experience rapid and significant improvements in symptoms after intravenous treatment with 500 mL of hydrogen-enriched water, with no subsequent recurrence (51).

Hydrogen enriched water (600 mL/day: 0.8–1.3 ppm) improved pressure ulcers in 12/22 (55%) of hospitalized elderly patients. The responders had a significant reduction in hospital stay (113.3 days vs 155.4 days; $p < 0.05$) and in the number of pressure ulcers (28.1% reduction) compared with the subgroup of patients for whom hydrogen treatment was not effective. Both groups of hydrogen-treated patients showed a significant reduction in wound size from baseline, which was greater in the effective group. The results of parallel *in vitro* studies led study investigators to suggest that the beneficial effects of hydrogen therapy were secondary to type-I collagen construction in dermal fibroblasts and/or promoted mitochondrial reducing ability and ROS repression in epidermal keratinocytes (52).

Twenty patients with rheumatoid arthritis (RA), drank

530 mL of hydrogen-rich water (4–5 ppm) every day for 4 weeks in addition to regular RA medication. This treatment period was followed by a 4-week washout then another 4 weeks of treatment (53). There was a mean decrease of 14.3% from baseline in 8-hydroxyguanine (8-OHdG is a standard biomarker for oxidative stress) during the first 4 weeks of treatment ($p < 0.01$) and after the second period of hydrogen-enriched water therapy the reduction in 8OHdG levels was 15.1% ($p < 0.01$ vs baseline). Disease activity scores significantly decreased in 18/20 patients during the first 4-weeks ($p < 0.01$) and remained lower than baseline levels at the end of the 4-week washout phase. At study end, 16 patients had improved disease activity scores and nine patients achieved remission. Four patients had not received any previous RA treatment and all achieved remission during the 12-week study. Apart from increased urinary frequency due to an increased fluid intake, no adverse effects of hydrogen were observed, suggesting that hydrogen water might be a useful addition to conventional therapy in patients with RA (53, 54).

Metabolic disorders

Oxidative stress plays a role in the development of type 2 diabetes mellitus, suggested by accumulation of molecular hydrogen in the liver with glycogen after oral administration of hydrogen water in rats (55), making this another possible target for hydrogen therapy. The consumption of hydrogen-enriched water reduced oxidative stress in the liver, improved fatty liver in mice with diabetes and in those with diet-induced obesity reduced plasma glucose and triglyceride levels, attenuated body weight gain, and stimulation of energy metabolism (55).

Patients with type 2 diabetes or impaired glucose tolerance were included in an 8-week randomized, double-blind, crossover study of hydrogen-enriched water (1.2 ± 0.1 mg/L) (56). Hydrogen was associated with significant reductions in levels of modified LDL cholesterol, small dense LDL and urinary 8-isoprostanes, plus smaller reductions in serum levels of oxidized LDL and free fatty acids and increased plasma levels of adiponectin and extracellular-superoxide dismutase (56).

Hydrogen-enriched water or saline (>0.6 mM) has been shown to contribute to atherosclerosis prevention in apolipoprotein-E knockout mice (57, 58) and improved plaque stability (59). Additionally, ad libitum access to hydrogen-enriched water (>0.8 mM) ameliorated pulmonary arterial hypertension in a rat model (60), and intraperitoneal administration of hydrogen-enriched saline (>0.6 mM) reduced oxidative stress and attenuated left ventricular hypertrophy in spontaneously hypertensive rats (61).

Three clinical trials have assessed the effects of hydrogen treatment in the metabolic syndrome setting. After 10 weeks of hydrogen water (0.2–

0.25 mM), significant reductions from baseline were seen in serum levels of total and low-density lipoprotein (LDL) cholesterol, apolipoproteins B and E, and malondialdehyde (MDA; an indicator of lipid peroxidation). Improvements were also seen in oxidation of LDL and high-density lipoprotein (HDL), and in LDL-mediated inflammation (62). In a similar group of potential metabolic syndrome patients, consumption of 1.5–2L of hydrogen-enriched water (0.55–0.65 mM) per day for 8 weeks increased HDL cholesterol levels and decreased the total cholesterol/HDL cholesterol ratio compared with baseline (63).

Neurodegenerative diseases

Evidence of increased levels of ROS have been found in post-mortem samples of brain tissue samples from patients with neurodegenerative diseases (3). There are a number of factors that make the brain particularly susceptible to oxidative stress, including its high metabolic rate and reduced capacity for cellular regeneration compared with other organs (3, 64).

Consumption of hydrogen-enriched water (>0.6 mM) ad libitum suppressed increases in oxidative stress markers and improved the proliferation of neural progenitor cells in a mouse chronic physical restraint model (65). Hydrogen-enriched saline reduced oxidative stress, inflammatory responses and amyloid-beta-induced astrocyte activation while improving learning and memory in a rat model of Alzheimer's disease (66).

In Parkinson's disease addition of hydrogen to drinking water (>0.4 mM or 0.08–1.5 ppm) prevented the development and progression of nigrostriatal degeneration and dopaminergic neuron loss (67, 68).

The efficacy of hydrogen-enriched water was assessed in a randomized, placebo-controlled, double-blind, parallel clinical trial conducted as a pilot study in levodopa-treated patients with Parkinson's disease (69). Participants drank 1 L per day of hydrogen-enriched water (prepared by dissolving 0.8 mM H₂; $n=9$) or placebo water ($n=8$) for 48 weeks. Total Unified Parkinson's Disease Rating Scale (UPDRS) scores in the hydrogen-enriched water group improved during the study, whereas UPDRS scores in the placebo group worsened ($p < 0.05$ at 48 weeks). Hydrogen-enriched water was well tolerated during the study and no adverse events were reported.

Spinal cord and brain injury

Intraperitoneal administration of hydrogen-enriched saline (0.6 mM) to rats at the time of spinal cord injury, and at 24 and 48 hours after injury was associated with a reduction in the number of apoptotic cells, decreased oxidative stress, increased release of brain-derived neurotrophic factor, and improved locomotor function (70). Similar beneficial effects were observed in a rat

model of traumatic brain injury (TBI) after treatment with 2% inhaled hydrogen in air (71). Hydrogen was administered from 5 minutes to 5 hours after TBI, and significantly attenuated TBI-induced increases in blood-brain barrier permeability, brain edema, lesion volume and neurological dysfunction. These effects were thought to occur via increases in endogenous antioxidant enzyme activities (71). Reduction in brain edema and protection from the neurodegenerative changes associated with TBI has also been documented when hydrogen is added to drinking water (>1.6 mM), starting 24 hours before TBI. In particular, expression of genes relating to oxidation, neuroinflammation and carbohydrate metabolism was effectively reversed by hydrogen water (72).

Cancer

Anti-cancer effects

The production of ROS by human cancer cells is higher than that for normal cell lines (73). In addition, elevated levels of ROS appear to play a role in the signaling cascades that trigger and maintain the oncogenic phenotype of cancer cells (74), and may contribute to DNA damage, and cell proliferation, migration and survival (75). Therefore, the possible anticancer effects of hydrogen, alone or in combination with traditional therapy, are the subject of growing research (76).

In an in vitro study, hydrogen-enriched water (1.0–1.3 ppm) supplemented with platinum nanocolloid showed rapid antioxidant effects and preferentially inhibited clonal growth of human tongue carcinoma cells compared with normal cells (77). Hydrogen-enriched water has also been shown to increase the inhibitory effects of the chemotherapy agent fluorouracil on colon cancer cells (76). In a mouse model of colon cancer, hydrogen-enriched water (\approx 0.8 mM) significantly increased survival compared with placebo water treatment, and survival was increased to an even greater extent when hydrogen-enriched water was combined with fluorouracil (76).

Radiation toxicities

Radiotherapy is associated with radiolysis of H₂O to •OH, which contributes to a range of adverse effects (33). The results of one preclinical study showed that hydrogen-enriched saline (>0.6 mM) protects cells against radiation-induced toxicity and ameliorates intestinal injury caused by radiation (78). Another showed that hydrogen-enriched saline (>0.6 mM) markedly reduced ROS levels after radiation and protected against radiation-induced immune dysfunction (79), while a third indicated that treatment with hydrogen-enriched saline (0.6 mM) before ionizing radiation could provide partial protection of both spermatogenesis and hematopoiesis (80). Hydrogen has been proposed as a possible

preventive strategy for radiation pneumonitis because of its ability to quickly scavenge free radicals produced by irradiation of the lungs (81).

The effects of drinking hydrogen-enriched water were investigated in a randomized, placebo-controlled study of patients receiving radiotherapy for liver tumors (82). Treatment with 1.5–2L hydrogen-enriched (0.55–0.65 mM) or placebo water was started on the first day of radiation treatment and continued for 6 weeks. Drinking hydrogen-enriched water prevented the marked increase in total serum hydroperoxide associated with radiotherapy, and attenuated the radiation-related reduction in serum antioxidant activity. Patients in the hydrogen-enriched water group reported significantly less loss of appetite and fewer taste disorders compared with those receiving placebo. Importantly, hydrogen-enriched water had no effect on the efficacy of radiotherapy (82).

Side effects of cisplatin

Based on the results of an in vivo study, hydrogen also has the potential to alleviate chemotherapy-associated toxicity. Two administration routes (oral hydrogen-enriched drinking water [0.8 mM] and inhaled hydrogen [1%]) were assessed in mice receiving cisplatin (83). Both forms of hydrogen improved survival, reduced body weight loss and ameliorated cisplatin-induced nephrotoxicity compared with control, although the effects of drinking hydrogen-enriched water appeared to be less than those of inhaled hydrogen with respect to prevention of severe nephrotoxicity. The anti-tumor efficacy of cisplatin was unaffected by concomitant administration of hydrogen by either route (83).

Other medical applications

Dermatomyositis and mitochondrial disease

The effects of drinking hydrogen-enriched water (0.5 ppm) were assessed in patients with muscle diseases (84). An open-label study was conducted in 14 patients who drank 1 L/day of hydrogen-enriched water for 12 weeks. Patients with mitochondrial myopathies (MM) and patients with progressive muscular dystrophy showed decreases in the lactate-to-pyruvate ratio ($p < 0.05$), and those with polymyositis/dermatomyositis had a decrease in serum matrix metalloproteinase-3 and triglyceride levels (84). Subsequently, a randomized, double-blind, placebo-controlled, crossover study in 22 patients with dermatomyositis (n=10) or MM (n=12) investigated the effects of drinking 0.5 L/day of hydrogen-enriched water for 8 weeks. Treatment was associated with significant improvement in serum lactate in MM patients, but there were no objective changes in clinical symptoms in this or the open-label study (84). Some patients did report subjective improvements in fatigue, diarrhea and

myalgia, but these were not consistent or statistically significant suggesting that the hydrogen dosage used may have been insufficient. It was suggested that >1 L/day of hydrogen-enriched water may be required to achieve beneficial effects (84).

Hemodialysis

The effects of using hydrogen-enriched water as a hemodialysis solution have been investigated in two clinical trials. In the first, regular hemodialysis patients received one month of treatment using a standard solution followed by another month of treatment using hydrogen-enriched water (99 parts per billion [ppb]) as the dialysis solution (85). Hemodialysis with both the standard and hydrogen-enriched water solutions was effective at reducing blood pressure. Compared with standard solution, hydrogen-enriched water was associated with preserved cellular viability of polymorphonuclear leukocytes, resulting in better ability to generate superoxide anions. Use of hydrogen-enriched water during hemodialysis was feasible and well tolerated, with no symptomatic adverse events observed during the study period (85). The second clinical trial included a larger number of patients (n=21) dialyzed with hydrogen-enriched solution (average H₂ levels ranged from 48 ppb to 210 ppb) over a longer period of time (6 months) (24). Once again, hemodialysis with hydrogen water had a good tolerability profile and was feasible, and significant reductions in blood pressure were achieved after each hemodialysis session; these were greater when hemodialysis was performed with hydrogen versus standard solution. Significant decreases were also observed in the oxidant markers plasma myeloperoxidase and monocyte chemoattractant protein-1 (24). These results suggest that use of hydrogen-enriched solutions during hemodialysis has the potential to ameliorate inflammatory reactions and improve blood pressure control.

Liver disease

Lipid peroxidation plays an important role in the pathology of viral hepatitis and has been suggested as a major cause of liver injury (86). The addition of hydrogen-enriched water (0.55–0.65 mM; three times daily) to standard treatment for 6 weeks in patients with chronic hepatitis B was associated with significant improvements in a number of oxidative stress parameters, including superoxide dismutase, glutathione S transferase, xanthine oxidase and malondialdehyde compared with both baseline (p<0.05) and the standard treatment only group (p<0.01) (87). There were trends towards improvements in liver function and reductions in hepatitis B virus DNA load in the hydrogen treatment versus routine treatment group, but these did not reach statistical significance (87).

Respiratory system

The role of oxidative stress in the development of acute lung injury is well established (33). In animal models, hydrogen-enriched saline and inhaled hydrogen (2%) reduced apoptosis, neutrophil infiltration, lipid membrane peroxidation, nuclear factor kappa B activation and proinflammatory cytokine levels (88–90).

Ocular effects

There are a number of ocular diseases that have been shown to benefit from hydrogen treatment in preclinical studies. Hydrogen-enriched saline has been shown to have antioxidant effects and to protect against blue light-induced retinal damage (91) and retinopathy associated with hyperoxia or diabetes (92, 93), and to prevent selenite-induced cataract (94).

Conclusion

Hydrogen is an effective antioxidant, anti-inflammatory and cytoprotective agent that selectively scavenges potent oxidants such as •OH and peroxynitrite in cells without affecting redox homeostasis. Key features of hydrogen as a therapeutic agent include selective reaction with highly reactive ROS, rapid diffusion into cells and onset of action, inert characteristics at body temperature in mammalian cells, an almost adverse event-free tolerability profile, the ability to administer therapy in a variety of ways to best suit the patient or indication being treated, and low cost. The non-specific nature of the effects of hydrogen mean that it has therapeutic potential across a wide range of medical applications, as has been shown by a good volume of preclinical data and a growing body of clinical evidence.

Accumulating data also show the potential for hydrogen as an anti-ageing solution and in wellness applications, particularly sports and injury. It is possible that drinking hydrogen-enriched water may become a novel and beneficial new rehydration strategy for athletes. Data from future clinical studies will help to better define the role of hydrogen in medical applications, exercise physiology and wellness strategies. Hydrogen has the potential to become a hugely important agent in many aspects of human health, particularly in reducing the effects of ageing.

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