Research Abstracts – Hydrogen Rich Water

Molecular hydrogen alleviates nephrotoxicity induced by an anti-cancer drug cisplatin without compromising anti-tumor activity in mice

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Abstract
Purpose Cisplatin is a widely used anti-cancer drug in the treatment of a wide range of tumors; however, its application is limited by nephrotoxicity, which is affected by oxidative stress. We have reported that molecular hydrogen (H_2) acts as an efficient antioxidant (Ohsawa et al. in Nat Med 13:688–694, 2007). Here we show that hydrogen efficiently mitigates the side effects of cisplatin by reducing oxidative stress.

Methods Mice were administered cisplatin followed by inhaling hydrogen gas (1% H_2 in air). Furthermore, instead of inhaling hydrogen gas, we examined whether drinking water containing hydrogen (hydrogen water; 0.8 mM H_2 in water) is applicable by examining oxidative stress, mortality, and body-weight loss. Nephrotoxicity was assessed by morphological changes, serum creatinine and blood urea nitrogen (BUN) levels.

Results Inhalation of hydrogen gas improved mortality and body-weight loss caused by cisplatin, and alleviated nephrotoxicity. Hydrogen was detected in blood when hydrogen water was placed in the stomach of a rat. Consuming hydrogen water ad libitum also reduced oxidative stress, mortality, and body-weight loss induced by cisplatin in mice. Hydrogen water improved metamorphosis accompanying decreased apoptosis in the kidney, and nephrotoxicity as assessed by serum creatinine and BUN levels. Despite its protective effects against cisplatin-induced toxicity, hydrogen did not impair anti-tumor activity of cisplatin against cancer cell lines in vitro and tumor-bearing mice in vivo.

Conclusion Hydrogen has potential for improving the quality of life of patients during chemotherapy by efficiently mitigating the side effects of cisplatin.

Effects of drinking hydrogen-rich water on the quality of life of patients treated with radiotherapy for liver tumors

Kang et al. Medical Gas Research 2011, 1:11

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Abstract
Background: Cancer patients receiving radiotherapy often experience fatigue and impaired quality of life (QOL). Many side effects of radiotherapy are believed to be associated with increased oxidative stress and inflammation due to the generation of reactive oxygen species during radiotherapy. Hydrogen can be administered as a therapeutic medical gas, has antioxidant properties, and reduces inflammation in tissues. This study examined whether hydrogen treatment, in the form of hydrogen-supplemented water, improved QOL in patients receiving radiotherapy.

Methods: A randomized, placebo-controlled study was performed to evaluate the effects of drinking hydrogenrich water on 49 patients receiving radiotherapy for malignant liver tumors. Hydrogen-rich water was produced by placing a metallic magnesium stick into drinking water (final hydrogen concentration; 0.55~0.65 mM). The Korean version of the European Organization for Research and Treatment of Cancer's QLQ-C30 instrument was used to evaluate global health status and QOL. The concentration of derivatives of reactive oxidative metabolites and biological antioxidant power in the peripheral blood were assessed.

Results: The consumption of hydrogen-rich water for 6 weeks reduced reactive oxygen metabolites in the blood and maintained blood oxidation potential. QOL scores during radiotherapy were significantly improved in patients treated with hydrogen-rich water compared to patients receiving placebo water. There was no difference in tumor response to radiotherapy between the two groups.

Conclusions: Daily consumption of hydrogen-rich water is a potentially novel, therapeutic strategy for improving QOL after radiation exposure. Consumption of hydrogen-rich water reduces the biological reaction to radiationinduced oxidative stress without compromising anti-tumor effects.

Neutral pH Hydrogen-Enriched Electrolyzed Water Achieves Tumor-Preferential Clonal Growth Inhibition Over Normal Cells and Tumor Invasion Inhibition Concurrently With Intracellular Oxidant Repression

Oncology Research, Vol. 17, pp. 247–255

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(Submitted June 13, 2008; revision received August 27, 2008; accepted August 29, 2008)

Abstract
The properties and effects of neutral pH hydrogen-enriched electrolyzed water (NHE water) on tumor cells were examined. NHE water diminished hydroxyl radicals as demonstrated by ESR in a cell-free system. Human tongue carcinoma cells HSC-4 were inhibited for either colony formation efficiencies or colony sizes by NHE water without significant inhibition to normal human tongue epithelial-like cells DOK. Furthermore, NHE water caused growth inhibition, cell degeneration, and inhibition of invasion through the reconstituted basement membrane to human fibrosarcoma cells HT-1080. Intracellular oxidants such as hydroperoxides

and hydrogen peroxides were scavenged in HSC-4 or HT-1080 cells by NHE water. In the human oral cavity, a dissolved hydrogen concentrations (DH) of NHE water was drastically declined from 1.1 to 0.5 ppm, but settled to 0.3–0.4 ppm until 180 s, upon static holding without gargling. Thus, NHE water was shown to achieve tumor-preferential growth inhibition and tumor invasion together with scavenging of intracellular oxidants, and is expected as a preventive material against tumor progression and invasion.

Experimental verification of protective effect of hydrogen-rich water against cisplatin-induced nephrotoxicity in rats using dynamic contrast-enhanced CT

The British Journal of Radiology, 83 (2010), 509–514

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ABSTRACT.
Our aim was to assess the protective effect of hydrogen-rich water against cisplatin-induced nephrotoxicity in rats using dynamic contrast-enhanced CT (DCE-CT). DCE-CT studies were performed in 30 rats (8 weeks old) on days 0, 2, 4 and 7 using multidetector row CT. The rats were divided into three groups: a control group (n 56) with free access to standard water and without cisplatin injection, a non-treatment group (n 512) with free access to standard water and injected with cisplatin (3.6 mg kg–1 body weight) intraperitoneally on day 0 and a treatment group (n 512) with free access to hydrogen-rich water starting from 7 days before cisplatin injection. The contrast clearance per unit renal volume (K1) was estimated from the DCE-CT data using the Patlak model. The contrast clearance of the entire kidney (K) was obtained by multiplying K1 by the renal volume. The serum creatinine level was also measured on day 7. The K1 and K values normalised by those on day 0 in the treatment group were significantly greater than those in the non-treatment group on days 2, 4 and 7. There were no significant differences in the normalised K value between the treatment and control groups on days 2 and 7. The serum creatinine level in the treatment group was significantly lower than that in the non-treatment group and was not significantly different from that in the control group. This study demonstrated that hydrogen-rich water ameliorates renal dysfunction due to cisplatin-induced nephrotoxicity in rats.

"Electrolyzed-Reduced Water Scavenges Active Oxygen Species and Protects DNA from Oxidative Damage"

Biochem Biophys Res Commun. 1997 May 8;234(1):269-74.

Sanetaka Shirahata, Shirgeru Kabayama, Mariko Nakano, Takumi Miura, Kenichi Kusumoto, Miho Gotoh, Hidemitsu Hayashi, Kazumichi Otsubo, Shinkatsu Morisawa, and Yoshinori Katakura
Published in: *Biochemical and Biophysical Research Communications*, Vol. 234, No.1, May 8, 1997

Abstract
Active oxygen species or free radicals are considered to cause extensive oxidative damage to biological macromolecules, which brings about a variety of diseases as well as aging. The ideal scavenger for active oxygen should be 'active hydrogen'. 'hydrogen' can be produced in reduced water near the cathode during electrolysis of water. Reduced water exhibits high pH, low dissolved oxygen (DO), extremely high dissolved molecular hydrogen (DH), and extremely

negative redox potential (RP) values. Strongly electrolyzed-reduced water, as well as ascorbic acid, (+)-catechin and tannic acid, completely scavenged O.-2 produced by the hypoxanthine-xanthine oxidase (HX-XOD) system in sodium phosphate buffer (pH 7.0). The superoxide dismutase (SOD)-like activity of reduced water is stable at 4 degrees C for over a month and was not lost even after neutralization, repeated freezing and melting, deflation with sonication, vigorous mixing, boiling, repeated filtration, or closed autoclaving, but was lost by opened autoclaving or by closed autoclaving in the presence of tungsten trioxide which efficiently adsorbs active atomic hydrogen. Water bubbled with hydrogen gas exhibited low DO, extremely high DH and extremely low RP values, as does reduced water, but it has no SOD-like activity. These results suggest that the SOD-like activity of reduced water is not due to the dissolved molecular hydrogen but due to the dissolved atomic hydrogen (active hydrogen). Although SOD accumulated H2O2 when added to the HX-XOD system, reduced water decreased the amount of H2O2 produced by XOD. Reduced water, as well as catalase and ascorbic acid, could directly scavenge H2O2. Reduce water suppresses single-strand breakage of DNA b active oxygen species produced by the Cu(II)-catalyzed oxidation of ascorbic acid in a dose-dependent manner, suggesting that reduced water can scavenge not only O2.- and H2O2, but also 1O2 and .OH.

Electrolyzed-reduced water protects against oxidative damage to DNA, RNA, and protein

Applied Biochemistry and Biotechnology Volume 135, Number 2 / November, 2006

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Abstract
The generation of reactive oxygen species is thought to cause extensive oxidative damage to various bio molecules such as DNA, RNA, and protein. In this study, the preventive, suppressive, and protective effects of in vitro supplementation with electrolyzed-reduced water on H_2O_2-induced DNA damage in human lymphocytes were examined using a comet assay. Pretreatment, cotreatment, and posttreatment with electrolyzed-reduced water enhanced human lymphocyte resistance to the DNA strand breaks induced by H_2O_2 in vitro. Moreover, electrolyzed-reduced water was much more effective than diethylpyrocarbonate-treated water in preventing total RNA degradation at 4 and 25°C. In addition, electrolyzed-reduced water completely prevented the oxidative cleavage of horseradish peroxidase, as determined using sodium dodecyl sulfate-polyacrylamide gels. Enhancement of the antioxidant activity of ascorbic acid dissolved in electrolyzed-reduced water was about threefold that of ascorbic acid dissolved in nonelectrolyzed deionized water, as measured by a xanthine-xanthine oxidase superoxide scavenging assay system, suggesting an inhibitory effect of electrolyzed-reduced water on the oxidation of ascorbic acid.

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

***Science Direct; Nutrition Research 28* (2008) 137-143; Elsevier**

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Available online at www.sciencedirect.com : *Nutrition Research* www.elsevier.com/locate/nutres

Abstract
Oxidative stress is recognized widely as being associated with various disorders including diabetes, hypertension, and atherosclerosis. It is well established that hydrogen has a reducing action. We therefore investigated the effects of hydrogen-rich water intake on lipid and glucose metabolism in patients with either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT). We performed a randomized, double-blind, placebo-controlled, crossover study in 30 patients with T2DM controlled by diet and exercise therapy and 6 patients with IGT. The patients consumed either 900 mL/d of hydrogen-rich pure water or 900 mL of placebo pure water for 8 weeks, with a 12-week washout period. Several biomarkers of oxidative stress, insulin resistance, and glucose metabolism, 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 (i.e., modifications that increase the net negative charge of LDL), small dense LDL, and urinary 8-isoprostanes by 15.5% ($P < .01$), 5.7% ($P < .05$), and 6.6% ($P < .05$), 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.

"Consumption of Molecular Hydrogen Prevents the Stress-Induced Impairments in Hippocampus-Dependent Learning Tasks during Chronic Physical Restraint in Mice"

Neuropsychopharmacology. 2009 Jan;34(2):501-8. Epub 2008 Jun 18.

Kazufumi Nagata, Naomi Nakashima-Kamimura, Toshio Mikami, Ikuroh Ohsawa, Shigeo Ohta
Neuropsychopharmacology advance online publication 18 June 2008; doi:10.1038/npp.2008.95

Abstract
We have reported that hydrogen (H_2) acts as an efficient antioxidant by gaseous rapid diffusion. When water saturated with hydrogen (hydrogen water) was placed into the stomach of a rat, hydrogen was detected at several μM level in blood. Because hydrogen gas is unsuitable for continuous consumption, we investigated using mice whether drinking hydrogen water *ad libitum*, instead of inhaling hydrogen gas, prevents cognitive impairment by reducing oxidative stress. Chronic physical restraint stress to mice enhanced levels of oxidative stress markers, malondialdehyde and 4-hydroxy-2-nonenal, in the brain, and impaired learning and memory, as judged by three different methods: passive avoidance learning, object recognition task, and the Morris water maze. Consumption of hydrogen water *ad libitum* throughout the whole period suppressed the increase in the oxidative stress markers and prevented cognitive impairment, as judged by all three methods, whereas hydrogen water did not improve cognitive ability when no stress was provided. Neural proliferation in the dentate gyrus of the hippocampus was suppressed by restraint stress, as observed by 5-bromo-2'-deoxyuridine incorporation and Ki-67 immunostaining, proliferation markers. The consumption of hydrogen water ameliorated the reduced proliferation although the mechanistic link between the hydrogen-dependent changes in neurogenesis and cognitive impairments remains unclear. Thus, continuous consumption of hydrogen water reduces oxidative stress in the brain, and prevents the stress-induced decline in

learning and memory caused by chronic physical restraint. Hydrogen water may be applicable for preventive use in cognitive or other neuronal disorders.

"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 Sep 30;4(9):e7247.

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It has been shown that molecular hydrogen (H_2) acts as a therapeutic antioxidant and suppresses brain injury by buffering the effects of oxidative stress. Chronic oxidative stress causes neurodegenerative diseases such as Parkinson's disease (PD). Here, we show that drinking H_2-containing water significantly reduced the loss of dopaminergic neurons in PD model mice using both acute and chronic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyri dine (MPTP). The concentration-dependency of H_2 showed that H_2 as low as 0.08 ppm had almost the same effect as saturated H_2 water (1.5 ppm). MPTP-induced accumulation of cellular 8-oxoguanine (8-oxoG), a marker of DNA damage, and 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation were significantly decreased in the nigro-striatal dopaminergic pathway in mice drinking H_2-containing water, whereas production of superoxide ($O_2\bullet^-$) detected by intravascular injection of dihydroethidium (DHE) was not reduced significantly. Our results indicated that low concentration of H_2 in drinking water can reduce oxidative stress in the brain. Thus, drinking H_2-containing water may be useful in daily life to prevent or minimize the risk of life style-related oxidative stress and neurodegeneration.

Consumption of hydrogen water prevents atherosclerosis in apolipoprotein E knockout mice Ikuroh Ohsawa[a, b], Kiyomi Nishimaki[a], Kumi Yamagata[a], Masahiro Ishikawa[a] and Shigeo Ohta[a,]

I. Ohsawa et al. / Biochemical and Biophysical Research Communications xxx (2008) xxx–xxx

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Abstract
Oxidative stress is implicated in atherogenesis; however most clinical trials with dietary antioxidants failed to show marked success in preventing atherosclerotic diseases. We have found that hydrogen (dihydrogen; H_2) acts as an effective antioxidant to reduce oxidative stress

[I. Ohsawa, M. Ishikawa, K. Takahashi, M. Watanabe, K. Nishimaki, K. Yamagata, K. Katsura, Y. Katayama, S, Asoh, S. Ohta, Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals, Nat. Med. 13 (2007) 688–694]. Here, we investigated whether drinking H_2-dissolved water at a saturated level (H_2–water) *ad libitum* prevents arteriosclerosis using an apolipoprotein E knockout mouse (apoE$^{-/-}$), a model of the spontaneous development of atherosclerosis. ApoE$^{-/-}$ mice drank H_2–water *ad libitum* from 2 to 6 month old throughout the whole period. Atherosclerotic lesions were significantly reduced by *ad libitum* drinking of H_2–water (p = 0.0069) as judged by Oil-Red-O staining series of sections of aorta. The oxidative stress level of aorta was decreased. Accumulation of macrophages in atherosclerotic lesions was confirmed. Thus, consumption of H_2-dissolved water has the potential to prevent arteriosclerosis.

Molecular hydrogen is protective against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease.

Neurosci Lett. 2009 Apr 3;453(2):81-5. Epub 2009 Feb 12.

Fu Y, Ito M, Fujita Y, Ito M, Ichihara M, Masuda A, Suzuki Y, Maesawa S, Kajita Y, Hirayama M, Ohsawa I, Ohta S, Ohno K.

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Molecular hydrogen serves as an antioxidant that reduces hydroxyl radicals, but not the other reactive oxygen and nitrogen species. In the past year, molecular hydrogen has been reported to prevent or ameliorate eight diseases in rodents and one in human associated with oxidative stress. In Parkinson's disease, mitochondrial dysfunction and the associated oxidative stress are major causes of dopaminergic cell loss in the substantia nigra. We examined effects of approximately 50%-saturated molecular hydrogen in drinking water before or after the stereotactic surgery on 6-hydroxydopamine-induced nigrostrital degeneration in a rat model of Parkinson's disease. Methamphetamine-induced behavioral analysis showed that molecular hydrogen prevented both the development and progression of the nigrostrital degeneration. Tyrosine hydroxylase staining of the substantia nigra and striatum also demonstrated that pre- and post-treatment with hydrogen prevented the dopaminergic cell loss. Our studies suggest that hydrogen water is likely able to retard the development and progression of Parkinson's disease.

Rapid Diffusion of Hydrogen Protects the Retina: Administration to the Eye of Hydrogen-Containing Saline in Retinal Ischemia-Reperfusion Injury

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Abstract

PURPOSE. Retinal ischemia-reperfusion (I/R) injury by transient elevation of intraocular pressure (IOP) is known to induce neuronal damage through the generation of reactive oxygen species. Previous studies indicate that molecular hydrogen (H_2) is an efficient antioxidant gas that selectively reduces the hydroxyl radical (OH) and suppresses oxidative stress-induced injury in several organs. This study was conducted to explore the neuroprotective effect of H_2-loaded eye drops on retinal I/R injury.

RESULTS. When H_2-loaded eye drops were continuously administered, H_2 concentration in the vitreous body immediately increased and I/R-induced OH level decreased. The drops reduced the number of retinal apoptotic and oxidative stress marker-positive cells, and prevented retinal thinning with an accompanying activation of Müller glia, astrocytes, and microglia. The drops improved the recovery of retinal thickness by >70%.

CONCLUSIONS. H_2 has no known toxic effects on the human body. Thus, our study suggests that H_2-loaded eye drops will be a highly useful neuroprotective and anti-oxidative therapeutic treatment for acute retinal I/R injury.

Additional comment on above article by Dr. Shirahata:

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It has long been established that reactive oxygen species (ROS) cause many typesof damage to biomolecules and cellular structures, that, in turn result in the development of a variety of pathologic states such as diabetes, cancer and aging. Reduced water is defined as anti-oxidative water produced by reduction of water. Electrolyzed reduced water (ERW) has been demonstrated to be hydrogen-rich water and can scavenge ROS in vitro (Shirahata et al., 1997). The reduction of proton in water to active hydrogen (atomic hydrogen, hydrogen radical) that can scavenge ROS is very easily caused by a weak current, compared to oxidation of hydroxyl ion to oxygen molecule. Activation of water by magnetic field, collision, minerals etc. will also produce reduced water containing active hydrogen and/or hydrogen molecule. Several natural waters such as Hita Tenryosui water drawn from deep underground in Hita city in Japan, Nordenau water in Germany and Tlacote water in Mexico are known to alleviate various diseases. We have developed a sensitive method by which we can detect active hydrogen existing in reduced water, and have demonstrated that not only ERW but also natural reduced waters described above contain active hydrogen and scavenge ROS in cultured cells. ROS is known to cause reduction of glucose uptake by inhibiting the insulin-signaling pathway in cultured cells. Reduced water scavenged intracellular ROS and stimulated glucose uptake in the presence or absence of insulin in both rat L6 skeletal muscle cells and mouse 3T3/L1 adipocytes. This insulin-like activity of reduced water was inhibited by wortmannin that is specific inhibitor of PI-3 kinase, a key molecule in insulin signaling pathways. Reduced water protected insulin-responsive cells from sugar toxicity and improved the damaged sugar tolerance of type 2 diabetes model mice, suggesting that reduced water may improve insulin-independent diabetes mellitus. Cancer cells are generally exposed to high oxidative stress. Reduced water cause impaired tumor phenotypes of human cancer cells, such as reduced growth rate, morphological changes, reduced colony formation ability in soft agar, passage number-dependent telomere shortening, reduced binding abilities of telomere binding proteins and suppressed metastasis.

Reduced water suppressed the growth of cancer cells transplanted into mice, demonstrating their anti-cancer effects in vivo. Reduced water will be applicable to not only medicine but also food industries, agriculture, and manufacturing industries.

Shirahata, S. et al.: Electrolyzed reduced water scavenges active oxygen species and protects DNA from oxidative damage. Biochem. Biophys. Res. Commun., 234, 269174, 1997.

Pilot study: Effects of drinking hydrogen-rich water on muscle fatigue caused by acute exercise in elite athletes

Med Gas Res. 2012 Apr 20;2(1):12. [Epub ahead of print]

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Abstract
Background: Muscle contraction during short intervals of intense exercise causes oxidative stress, which can play a role in the development of overtraining symptoms, including increased fatigue, resulting in muscle microinjury or inflammation. Recently it has been said that hydrogen can function as antioxidant, so we investigated the effect of hydrogen-rich water (HW) on oxidative stress and muscle fatigue in response to acute exercise.

Methods: Ten male soccer players aged 20.9 ± 1.3 years old were subjected to exercise tests and blood sampling. Each subject was examined twice in a crossover double-blind manner; they were given either HW or placebo water (PW) for one week intervals. Subjects were requested to use a cycle ergometer at a 75 % maximal oxygen uptake (VO2) for 30 min, followed by measurement of peak torque and muscle activity throughout 100 repetitions of maximal isokinetic knee extension. Oxidative stress markers and creatine kinase in the peripheral blood were sequentially measured.

Results: Although acute exercise resulted in an increase in blood lactate levels in the subjects given PW, oral intake of HW prevented an elevation of blood lactate during heavy exercise. Peak torque of PW significantly decreased during maximal isokinetic knee extension, suggesting muscle fatigue, but peak torque of HW didn't decrease at early phase. There was no significant change in blood oxidative injury markers (d-ROMs and BAP) or creatine kinease after exercise.

Conclusion: Adequate hydration with hydrogen-rich water pre-exercise reduced blood lactate levels and improved exercise-induced decline of muscle function. Although further studies to elucidate the exact mechanisms and the benefits are needed to be confirmed in larger series of studies, these preliminary results may suggest that HW may be suitable hydration for athletes.

Open-label trial and randomized, double-blind, placebo-controlled, crossover trial of hydrogenated water for mitochondrial and inflammatory myopathies

Medical Gas Research 2011, 1:24 doi:10.1186/2045-9912-1-24

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Abstract
Background: Molecular hydrogen has prominent effects on more than 30 animal models especially of oxidative stress-mediated diseases and inflammatory diseases. In addition, hydrogen effects on humans have been reported in diabetes mellitus type 2, hemodialysis,

metabolic syndrome, radiotherapy for liver cancer, and brain stem infarction. Hydrogen effects are ascribed to specific radical-scavenging activities that eliminate hydroxyl radical and peroxynitrite, and also to signal-modulating activities, but the detailed molecular mechanisms still remain elusive. Hydrogen is a safe molecule that is largely produced by intestinal bacteria in rodents and humans, and no adverse effects have been documented.

Methods: We performed open-label trial of drinking 1.0 liter per day of hydrogen-enriched water for 12 weeks in five patients with progressive muscular dystrophy (PMD), four patients with polymyositis/dermatomyositis (PM/DM), and five patients with mitochondrial myopathies (MM), and measured 18 serum parameters as well as urinary 8- isoprostane every 4 weeks. We next conducted randomized, double-blind, placebo-controlled, crossover trial of 0.5 liter per day of hydrogen-enriched water or placebo water for 8 weeks in 10 patients with DM and 12 patients with MM, and measured 18 serum parameters every 4 weeks.

Results: In the open-label trial, no objective improvement or worsening of clinical symptoms was observed. We, however, observed significant effects in lactate-to-pyruvate ratios in PMD and MM, fasting blood glucose in PMD, serum matrix metalloproteinase-3 (MMP3) in PM/DM, and serum triglycerides in PM/DM. In the double-blind trial, no objective clinical effects were observed, but a significant improvement was detected in lactate in MM. Lactateto- pyruvate ratios in MM and MMP3 in DM also exhibited favorable responses but without statistical significance. No adverse effect was observed in either trial except for hypoglycemic episodes in an insulin-treated MELAS patient, which subsided by reducing the insulin dose.

Conclusions: Hydrogen-enriched water improves mitochondrial dysfunction in MM and inflammatory processes in PM/DM. Less prominent effects with the double-blind trial compared to the open-label trial were likely due to a lower amount of administered hydrogen and a shorter observation period, which implies a threshold effect or a dose-response effect of hydrogen.

Consumption of HydrogenWater Reduces Paraquat-Induced Acute Lung Injury in Rats

J Biomed Biotechnol. 2011;2011:305086. Epub 2011 Jan 24.

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Abstract
Exposure to paraquat leads to acute lung injury and oxidative stress is widely accepted as a contributor to paraquat-induced acute lung injury. Recent studies have reported that consumption of water with dissolved molecular hydrogen to a saturated level (hydrogen water) prevents oxidative stress-induced diseases. Here, we investigated whether consumption of saturated hydrogen saline protects rats against paraquat-induced acute lung injury. Adult male Sprague-Dawley (SD) rats were randomly divided into four groups: Control group; hydrogen water-only group (HW group); paraquat-only group (PQ group); paraquat and hydrogen water group (PQ + HW group). The rats in control group and HW group drank pure water or hydrogen water; the rats in PQ group and PQ + HW group were intraperitonealy injected with paraquat (35mg/kg) and then provided pure water or hydrogen water. Both biochemical and histological lung alterations weremeasured. The results showed that hydrogen water ameliorated

these alterations, demonstrating that hydrogen water alleviated paraquat-induced acute lung injury possibly by inhibition of oxidative damage.

Molecular Hydrogen Reduces LPS-Induced Neuroinflammation and Promotes Recovery from Sickness Behaviour in Mice

PLoS ONE;Jul2012, Vol. 7 Issue 7, p1

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Abstract
Molecular hydrogen has been shown to have neuroprotective effects in mouse models of acute neurodegeneration. The effect was suggested to be mediated by its free-radical scavenger properties. However, it has been shown recently that molecular hydrogen alters gene expression and protein phosphorylation. The aim of this study was to test whether chronic ad libitum consumption of molecular hydrogen-enriched electrochemically reduced water (H-ERW) improves the outcome of lipopolysaccharide (LPS)-induced neuroinflammation. Seven days after the initiation of H-ERW treatment, C57Bl/6 mice received a single injection of LPS (0.33 mg/kg i.p.) or an equivalent volume of vehicle. The LPS-induced sickness behavior was assessed 2 h after the injection, and recovery was assessed by monitoring the spontaneous locomotor activity in the homecage for 72 h after the administration of LPS. The mice were killed in the acute or recovery phase, and the expression of pro- and antiinflammatory cytokines in the hippocampus was assessed by real-time PCR. We found that molecular hydrogen reduces the LPS-induced sickness behaviour and promotes recovery. These effects are associated with a shift towards anti-inflammatory gene expression profile at baseline (downregulation of TNF- a and upregulation of IL-10). In addition, molecular hydrogen increases the amplitude, but shortens the duration and promotes the extinction of neuroinflammation. Consistently, molecular hydrogen modulates the activation and gene expression in a similar fashion in immortalized murine microglia (BV-2 cell line), suggesting that the effects observed in vivo may involve the modulation of microglial activation. Taken together, our data point to the regulation of cytokine expression being an additional critical mechanism underlying the beneficial effects of molecular hydrogen.