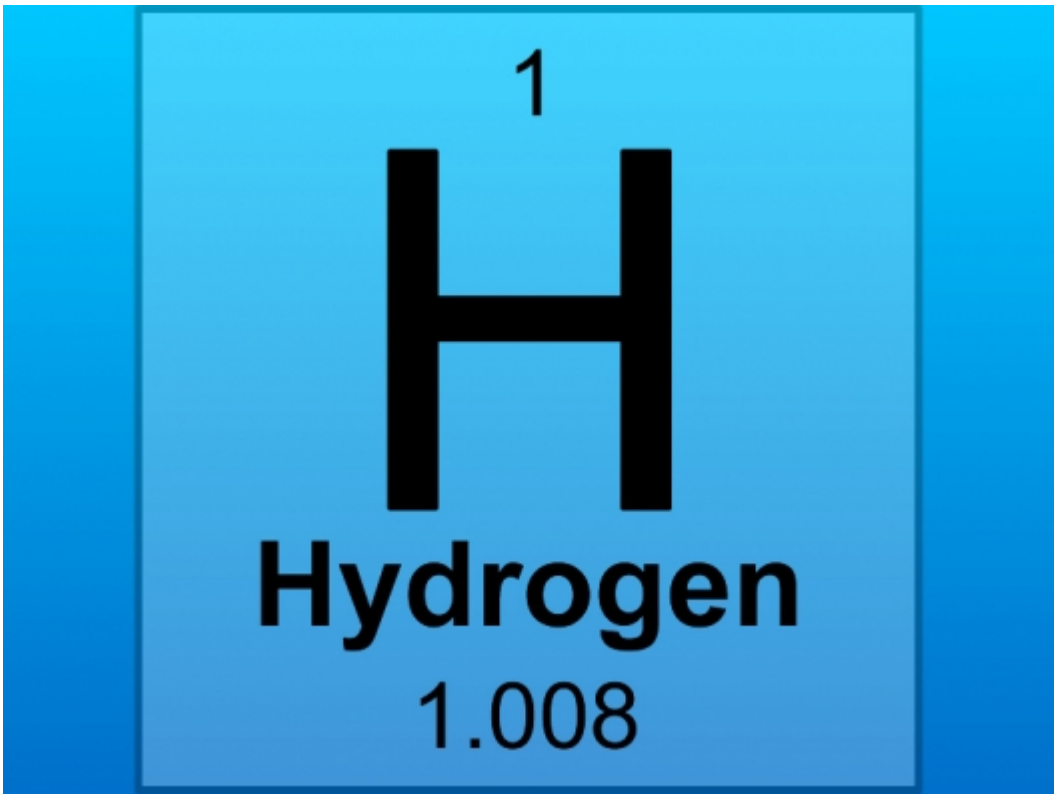
Hydrogen: Alternative Fuel to Alternative Medicine



Hydrogen: Alternative Fuel to Alternative Medicine

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HydrogenElementPeriodicTable.jpg

IMAGE BY CAM HOWARD / FAIM

Hydrogen gas (H_2) has been extolled for its use in "green energy" as an alternative fuel, but biomedical research over the past decade suggests it also has therapeutic biological benefits. For example, the preliminary 1,000+ animal and clinical studies have reported hydrogen to have antioxidant, anti-inflammatory, anti-allergy, anti-obesity, and anti-aging effects.[1, 2] This is rather surprising from a biochemistry perspective since hydrogen gas, a natural byproduct of fermentation by the intestinal microbiota, has long been considered to be "biologically inert."[3]

What exactly is molecular hydrogen?

Molecular hydrogen is simply two hydrogen atoms bonded together to form hydrogen gas. It has the chemical structure of H-H with a simple chemical formula of "H_2." Although in nature, hydrogen atoms are often found bonded to other atoms, such as oxygen, to form water (H_2O), or to carbon to form methane (CH_4), for therapeutic benefit, we specifically need the H_2 molecule (H_2 gas). Additionally, to avoid any confusion, it is also important that we distinguish between pH and H_2; they are completely different. The term pH has reference to the concentration of positively charged hydrogen ions (H+) in solution, which is totally different from H_2 gas. Indeed molecular hydrogen has no influence on pH, and has no reference to alkaline water. Furthermore, when H_2 gas is dissolved in water, it does not alter water chemistry/properties (e.g. does not form H_4O), but is simply H_2 gas that is dissolved into water.

How do we administer molecular hydrogen?

In the clinical studies, we normally administer molecular hydrogen via inhalation, drinking water that contains the dissolved H_2 gas (i.e. hydrogen water), bathing in hydrogen water, intravenous administration of hydrogen saline, and even hyperbaric hydrogen chambers.[4]

What are some of the key benefits to molecular hydrogen?

Hydrogen has now been demonstrated to have therapeutic effects in over 170 different human and animal disease models, and in essentially every organ of the human body.[5] The main reason for this is because H_2 helps attenuate excessive oxidative stress and inflammation, both of which are at the root of virtually every disease and pathology.[1, 2]

How does hydrogen gas provide antioxidant, anti-inflammatory, and anti-aging effects?

Molecular hydrogen was first reported in *Nature Medicine* to protect the brain during ischemia/reperfusion injury, and to selectively reduce cytotoxic oxygen radicals.[6] Many animal and clinical studies have subsequently demonstrated that hydrogen gas administered via inhalation or drinking hydrogen water can attenuate markers of oxidative stress and improve antioxidant status. For example, in a small open label study of 20 patients with potential metabolic syndrome, subjects ingested 1.5-2 L of hydrogen water (≈0.6 mM) per day for 8 weeks.[7] On average, besides improving cholesterol and glucose tolerance, the patients had a 43% decrease in the oxidative marker TBARS (thiobarbituric acid reactive substances) in the urine, and a 39% increase in the antioxidant enzyme superoxide dismutase.[7] Similar benefits were also demonstrated in 16 healthy subjects in a randomized, double-blinded placebo controlled study.[8] Drinking hydrogen water for 4 weeks decreased the oxidative marker malondialdehyde (MDA) by ≈26 %, $p<0.001$, increased superoxide dismutase, and the master antioxidant glutathione levels by 25.9% ($p=0.003$), and 10.1% ($p=0.007$), respectively.[8]

Besides demonstrating similar antioxidant effects, other animal and clinical studies also report decreased inflammation.[9] For example, H_2 can decrease and modify pro-inflammatory mediators/transcription factors (e.g. cytokines, C-reactive protein, TNF-a, NF-κB, NFAT, etc.).[1, 2, 5, 9, 10, 11]

The exact mechanism(s) by which H_2 attenuates oxidative stress are still under investigation. However, it has been demonstrated using miRNA interference, gene knockout studies, etc., that hydrogen can activate the Nrf2 pathway,[5, 12] which regulates the transcription of over 200 cytoprotective genes.[13] The activation of the Nrf2 pathway regulates phase ii enzymes involving detoxification (e.g., ABCG2, MRP3, MRP4, GST), antioxidation (e.g., NQO1, NQO2, HO-1), antiapoptotic (e.g., Bcl-2), and metabolic (e.g., G6PD, TKT, PPARγ) pathways.[14] This may help explain why H_2 can also exerts anti-diabetic and anti-obesity effects.[15, 16]

Autophagy benefits

Animal and cell studies similarly demonstrate hydrogen's beneficial effect on signal transduction and gene expression.[5] The benefits of autophagy and mitophagy (self-cannibalizing mechanisms to remove damaged/dysfunctional cells and mitochondria) have also been investigated. Hydrogen therapy in rodents activated autophagy pathways, increased autophagosomes, autolysosomes,[17, 18] and mitophagy mediated by the PINK1/Parkin signaling pathway.[19] However, too much autophagy can also be

pathological, which was the case in a study of myocardial ischemic/reperfusion injury in rats.[20] However, hydrogen was able to exert protective effects in this disease model by attenuating the endoplasmic reticulum stress and down-regulating the excessive autophagy.[20]

Neurological and other health benefits

Some exciting neurological research on hydrogen is also showing promise. The Japanese government has approved H_2 inhalation as an advanced medicine for the treatment of postcardiac arrest syndrome, which will also have neurological benefits.[21] A small randomized controlled clinical study of 50 patients with cerebral infarction[22] compared inhalation of hydrogen to the approved medical drug, edaravone. According to the MRI, and NIHSS scores for clinically quantifying stroke severity, these preliminary results suggest that hydrogen therapy was more effective than the approved medical drug.[22] Simply drinking hydrogen water also appears to have good effects in ≈1-year randomized-placebo controlled trials of Parkinson's,[23] and mild cognitive impairments (n= 73) (particularly those of APOE4 genotype).[24] A small double-blinded, placebo-controlled, cross over study also reported neurological benefits in healthy subjects. Drinking hydrogen water (600 mL/day) for 4 weeks resulted in decreased sympathetic nerve activation at rest, and improved mood and anxiety.[25] This correlated well to an early animal study we performed where hydrogen therapy was effective at increasing resilience to acute and chronic stress by regulating the hypothalamic-pituitary-adrenal axis and the inflammatory responses to stress.[26] We subsequently provided evidence in a study published in Frontier's Journal of Behavioral Neuroscience, that oral ingestion of hydrogen water can reverse the autistic-like behaviors (e.g. impaired social behavior, memory impairment, inflammation TNF-α and IL-6, etc.) induced by maternal exposure to the toxin VPA in mice.[27]

However, the research on hydrogen is still in its infancy, and H_2 therapy is not a panacea for every condition. For example, although many studies have found that hydrogen is beneficial to the brain in models of ischemia reperfusion,[28-31] one study found that H_2 inhalation was ineffective in a moderate to severe model of neonatal ischemia-reperfusion injury in rats.[32]Nevertheless, the preliminary data from animal and clinical studies continue to suggest that hydrogen may have significant implications in current medicine because it is safe, easy to administer, and has immediate clinical applications.[1, 2]

How can doctors and patients access molecular hydrogen?

There are a growing number of hydrogen products that are widely available on the market. Some products include hydrogen inhalation devices, ready-to-drink hydrogen beverages, hydrogen-producing machines, hydrogen-producing tablets, etc. The science-based Molecular Hydrogen Institute does not sell, recommend, or endorse hydrogen products or companies, but we do encourage consumers to verify that the products actually contain/produce hydrogen gas and have consistent performance, as many products do not reach the levels we use in research, or fulfill the claims made by the companies selling them.

For more information watch the video below and/or visit the Molecular Hydrogen Institutewebsite.

Bones

Protective effects of molecular hydrogen on steroid-induced osteonecrosis in rabbits viareducing oxidative st ress and apoptosis.

Li J[1], Ge Z[2], Fan L[3], Wang K[3].

Author information

Abstract

BACKGROUND:

The objective of this study was to investigate
the protective effects of molecular hydrogen, a novel and selective antioxidant,
on steroid-induced osteonecrosis (ON) in a rabbit model.

METHODS:

Sixty rabbits were randomly divided into two groups (model group
and hydrogen group). Osteonecrosis was induced according to an established protocol of steroid-induced ON. Rabbits in the hydrogen group were treated with intraperitoneal injections of molecularhydrogen at 10 ml/kg body weight for seven consecutive days. Plasma levels of total cholesterol, triglycerides, soluble thrombomodulin(sTM), glutathione(GSH) and malondialdehyde(MDA) were measured before and after steroid administration. The presence or absence of ON was examined
histopathologically. Oxidative injury and vascular injury were assessed in vivo by immunohistochemical staining of 8-hydoxy-2-deoxyguanosine(8-OHdG) and MDA, and ink artery infusion angiography. The terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assays were performed to measure apoptosis.

RESULTS:

The incidence of steroid-induced ON was significantly lower in hydrogen group (28.6%) than that in model group (68.0%). No statistically differences were observed on the levels of total cholesterol and triglycerides. Oxidative injury, vascular injury and apoptosis were attenuated in the hydrogen group compared with those in the model group in vivo.

CONCLUSIONS:

These results suggested that molecular hydrogen prevents steroid-induced osteonecrosis in rabbits by suppressing oxidative injury, vascular injury and apoptosis.

Hydrogen supplementation of preservation solution improves viability of osteochondral grafts.

Yamada T[1], Uchida K[2], Onuma K[2], Kuzuno J[1], Ujihira M[1], Inoue G[2], Sato B[3], Kurokawa R[3], Sakai R[1], Takaso M[2].

Author information

Abstract

Allogenic osteochondral tissue (OCT) is used for the treatment of large cartilage defects. Typically, OCTs collected during the disease-screening period are preserved at 4°C; however, the gradual reduction in cell viability during cold preservation adversely affects transplantation outcomes. Therefore, improved storage methods that maintain the cell viability of OCTs are needed to increase the availability of high-quality OCTs and improve treatment outcomes. Here, we evaluated whether long-term hydrogen delivery to preservation solution improved the viability of rat OCTs during cold preservation. Hydrogen-supplemented Dulbecco's Modified Eagles Medium (DMEM) and University of Wisconsin (UW) solution both significantly improved the cell viability of OCTs during preservation at 4°C for 21 days compared to nonsupplemented media. However, the long-term cold preservation of OCTs in DMEM containing hydrogen was associated with the most optimal maintenance of chondrocytes with respect to viability and morphology. Our findings demonstrate that OCTs preserved in DMEM supplemented with hydrogen are a promising material for the repair of large cartilage defects in the clinical setting.

Effectiveness of oral and topical hydrogen for sports-related soft tissue injuries.

Ostojic SM[1], Vukomanovic B, Calleja-Gonzalez J, Hoffman JR.

Author information

Abstract

BACKGROUND:

Because hydrogen therapy has been found beneficial for the treatment of inflammation, ischemia-reperfusion injury, and oxidative stress in humans, it seems useful to evaluate the effects of exogenously administered hydrogen as an element in the immediate management of sports-related soft tissue injuries. The main aim of this pilot study was to examine the effects of 2-week administration of hydrogen on the biochemical markers of inflammation and functional recovery in male professional athletes after acute soft tissue injury.

METHOD:

During the 2013 season (from March to May), 36 professional athletes were recruited as participants and examined by a certified sports medicine specialist in the first 24 hours after an injury was sustained. Subjects were allocated to 3 randomly assigned trials in a single-blind design. Those in the control group received a traditional treatment protocol for soft tissue injury. Subjects in the first experimental group followed the same procedures as the control group but with additional administration throughout the study of oral hydrogen-rich tablets (2 g per day). Subjects in the second experimental group also followed the procedures of the control group, with additional administration throughout the study of both oral hydrogen-rich tablets (2 g per day) and topical hydrogen-rich packs (6 times per day for 20 minutes). Participants were evaluated at the time of the injury report and at 7 and 14 days after baseline testing.

RESULTS:

Oral and topical hydrogen intervention was found to augment plasma viscosity decrease as compared with the control group ($P = 0.04$). Differences were found for range-of-motion recovery between the 3 groups; oral and topical hydrogen intervention resulted in a faster return to normal joint range of motion for both flexion and extension of the injured limb as compared with the control intervention ($P < 0.05$).

CONCLUSION:

These preliminary results support the hypothesis that the addition of hydrogen to traditional treatment protocols is potentially effective in the treatment of soft tissue injuries in male professional athletes. Trial identification: Clinicaltrials.gov number NCT01759498.

Hydrogen water consumption prevents osteopenia in ovariectomized rats.

Guo JD[1], Li L, Shi YM, Wang HD, Hou SX.

Author information

Abstract

BACKGROUND AND PURPOSE:

Accumulating evidence indicates an important role of oxidative stress in the progression of osteoporosis. Recently, it was demonstrated that hydrogen gas, as a novel antioxidant, could selectively reduce hydroxyl radicals and peroxynitrite anion to exert potent therapeutic antioxidant activity. The aim of the present work was to investigate the effect of hydrogen water (HW) consumption on ovariectomy-induced osteoporosis.

EXPERIMENTAL APPROACH:

Ovariectomized rats were fed with HW (1.3 ± 0.2 mg·L^{-1}) for 3 months. Then, blood was collected and femur and vertebrae were removed for evaluation of the effect of HW on bone.

KEY RESULTS:

HW consumption in ovariectomized rats had no significant effect on oestrogen production, but prevented the reduction of bone mass including bone mineral content and bone mineral density in femur and vertebrae, and preserved mechanical strength including ultimate load, stiffness, and energy, and bone structure including trabecular bone volume fraction, trabecular number, and trabecular thickness in femur, and preserved mechanical strength including ultimate load and stiffness, and bone structure including trabecular bone volume fraction and trabecular number in vertebrae. In addition, treatment with HW abated oxidative stress and suppressed IL-6 and TNF-α mRNA expressions in femur of ovariectomized rats; treatment with HW increased femur endothelial NOS activity and enhanced circulating NO level in ovariectomized rats.

CONCLUSIONS AND IMPLICATIONS:

HW consumption prevents osteopenia in ovariectomized rats possibly through the ablation of oxidativestress induced by oestrogen withdrawal.

Molecular hydrogen inhibits lipopolysaccharide/interferon γ-induced nitric oxide production through modulation of signal transduction in macrophages.

Itoh T[1], Hamada N, Terazawa R, Ito M, Ohno K, Ichihara M, Nozawa Y, Ito M.

Author information

Abstract

Molecular hydrogen has been reported to be effective for a variety of disorders and its effects have been ascribed to the reduction of oxidative stress. However, we have recently demonstrated that hydrogen inhibits type I allergy through modulating intracellular signal transduction. In the present study, we examined the hydrogen effects on lipopolysaccharide/interferon γ LPS/IFNγ-induced nitric oxide (NO) production in murine macrophage RAW264 cells. Treatment with hydrogen reduced LPS/IFNγ-induced NO release, which was associated with a diminished induction of inducible isoform of nitric oxide synthase (iNOS). Hydrogen treatment inhibited LPS/IFNγ-induced phosphorylation of apoptosis signal-regulating kinase 1 (ASK1) and its downstream signaling molecules, p38 MAP kinase and JNK, as well as IκBα, but did not affect activation of NADPH oxidase and production of reactive oxygen species (ROS). As ROS is an upstream activator of ASK1, inhibition of ASK1 by hydrogen without suppressing ROS implies that a potential target molecule of hydrogen should be located at the receptor or immediately downstream of it. These results suggested a role for molecular hydrogen as a signal modulator. Finally, oral intake of hydrogen-rich water alleviated anti-type II collagen antibody-induced arthritis in mice, a model for human rheumatoid arthritis. Taken together, our studies indicate that hydrogen inhibits LPS/IFNγ-induced NO production through modulation of signal transduction in macrophages and ameliorates inflammatory arthritis in mice, providing the molecular basis for hydrogen effects on inflammation and a functional interaction between two gaseous signaling molecules, NO and molecular hydrogen.

BRAIN

Hydrogen-rich water attenuates oxidative stress in rats with traumatic brain injury via Nrf2pathway.

Yuan J[1], Wang D[2], Liu Y[1], Chen X[1], Zhang H[1], Shen F[1], Liu X[1], Fu J[1].

Author information

Abstract

BACKGROUND:

Several studies have recently found that oxidative stress plays a pivotal role in the pathogenesis of traumatic brain injury(TBI) and may represent a target in TBI treatment. Hydrogen-rich water was recently shown to exert neuroprotective effects in various neurological diseases through its antioxidant properties. However, the mechanisms underlying its effects in TBI are not clearly understood. The purpose of our study was to evaluate the neuroprotective role of hydrogen-rich water in rats with TBI and to elucidate the possible mechanisms underlying its effects.

MATERIALS AND METHODS:

The TBI model was constructed according to the modified Feeney weight-drop method. In part 1 of the experiment, we measured oxidative stress levels by observing the changes in catalase (CAT), glutathione peroxidase (GPx), and malondialdehyde (MDA) expressions. We also evaluated nuclear factor erythroid 2-related factor 2 (Nrf2) levels to determine the role of the protein in the neuroprotective effects against TBI. In part 2, we verified the neuroprotective effects of hydrogen-rich water in TBI and observed its effects on Nrf2. All the experimental rats were divided into sham group, TBI group, and TBI + hydrogen-rich water-treated (TBI + HW) group. We randomly chose 20 rats from each group and recorded their 7-d survival rates. Modified neurological severity scores were recorded from an additional six rats per group, which were then sacrificed 24 h after testing. Spectrophotometry was used to measure GPx, CAT, and MDA levels, whereas western blotting, reverse transcription polymerase chain reaction, and immunohistochemistry were used to measure the expression of Nrf2 and downstream factors like heme oxygenase 1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1).

RESULTS:

GPx and CAT activity was significantly decreased, and MDA content was increased in the TBI group compared with the sham group at 6 h after TBI. MDA content peaked at 24 h after TBI. Nrf2 nucleoprotein levels were upregulated in the TBI group compared

with the sham group and peaked at 24 h after TBI; however, no significant changes in Nrf2 mRNA levels were noted after TBI. Hydrogen-rich wateradministration significantly increased 7-d survival rates, reduced neurologic deficits, and lowered intracellular oxidative stress levels. Moreover, hydrogen-rich water caused Nrf2 to enter the cell nucleus, which resulted in increases in the expression of downstream factors such as HO-1 and NQO1.

CONCLUSIONS:

Our results indicate that hydrogen-rich water has neuroprotective effects against TBI by reducing oxidative stress and activating the Nrf2 pathway.

Hydrogen exerts neuroprotective effects on OGD/R damaged neurons in rat hippocampal by protecting mitochondrial function via regulating mitophagy mediated by PINK1/Parkin signalingpathway.

Wu X[1], Li X[1], Liu Y[2], Yuan N[3], Li C[4], Kang Z[5], Zhang X[1], Xia Y[1], Hao Y[1], Tan Y[6].

Author information

Abstract

Cerebral ischemia/reperfusion injury (IRI) is a serious complication during the treatment of stroke patients with very few effective clinical treatment. Hydrogen (H2) can protect mitochondria function and have favorable therapeutic effects on cerebral IRI. Mitophagy plays an important role in eliminating damaged or dysfunctional mitochondria and maintaining mitochondria homeostasis. However, whether the protection of H2 on cerebral IRI is via regulating mitophagy is still unknown. In this study, OGD/R damaged hippocampal neurons were used to mimic cerebral IRI in vivo and we detected the effect of H2, Rap (autophagy activator) and 3-MA (autophagy inhibitor) on OGD/R neurons. The results of MTT indicated that H2 and RAP could increase cell viability after OGD/R treatment, while 3-MA further aggravated injury and inhibited the protection of H2 and RAP. Furthermore, the intracellular ROS and apoptosis ratio were determined, the results showed that ROS and apoptosis level significantly increased after OGD/R, H2 and RAP effectively restrained the increment of ROS level and apoptosis ratio but their protective effect can be weakened by 3-MA. Mitochondrial membrane potential (MMP) and mitophagy level were also determined, the data showed that H2 and RAP protected against the loss of MPP and increased the co-localization of mitochondria with GFP-LC3 while 3-MA exerted antagonistic effect. At last, the mitophagy-related factors

LC3, PINK1 and Parkin expression were detected and analyzed. We found that the expression of LC3 was increased after OGD/R which can be further enhanced by H2 and RAP treatment, but treatment with 3-MA was opposite. The result revealed H2 and RAP could activate mitophagy while 3-MA inhibit mitophagy. In addition, the study found H2 and RAP could significantly induce the expression of PINK1 and Parkin in OGD/R neurons which was inhibited by 3-MA. Taken together, our findings demonstrated H2 had a neuroprotective effect on OGD/R damaged neurons by protecting mitochondrial function and the potential protection mechanism may closely related to enhancement of mitophagy mediated by PINK1/Parkin signaling pathway.

Effects of Molecular Hydrogen Assessed by an Animal Model and a Randomized Clinical Studyon Mild Cognitive Impairment.

Nishimaki K[1], Asada T[2,3], Ohsawa I[1,4], Nakajima E[2], Ikejima C[2], Yokota T[1], Kamimura N[1], Ohta S[1,5].

Author information

Abstract

BACKGROUND:

Oxidative stress is one of the causative factors in the pathogenesis of neurodegenerative diseases including mild cognitiveimpairment (MCI) and dementia. We previously reported that molecular hydrogen (H2) acts as a therapeutic and preventive antioxidant.

OBJECTIVE:

We assess the effects of drinking H2-water (water infused with H2) on oxidative stress model mice and subjects with MCI.

METHODS:

Transgenic mice expressing a dominant-negative form of aldehyde dehydrogenase 2 were used as a dementia model. The mice with enhanced oxidative stress were allowed to drink H2-water. For a randomized double-blind placebo-controlled clinical study, 73 subjects with MCI drank ~300 mL of H2-water (H2-group) or placebo water (control group) per day, and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores were determined after 1 year.

RESULTS:

In mice, drinking H2-water decreased oxidative stress markers and suppressed the decline of memory impairment and neurodegeneration. Moreover, the mean lifespan in the H2-water group was longer than that of the control group. In MCI subjects, although there was no significant difference between the H2- and control groups in ADAS-cog score after 1 year, carriers of the apolipoprotein E4 (APOE4) genotype in the H2-group were improved significantly on total ADAS-cog score and word recall task score (one of the sub-scores in the ADAS-cog score).

CONCLUSION:

H2-water may have a potential for suppressing dementia in an oxidative stress model and in the APOE4 carriers with MCI.

Administration of molecular hydrogen during pregnancy improves behavioral abnormalities of offspring in a maternal immune activation model.

Imai K[1], Kotani T[2], Tsuda H[3], Nakano T[1], Ushida T[1], Iwase A[1], Nagai T[4], Toyokuni S[5], Suzumura A[6], Kikkawa F[1].

Author information

Abstract

The aim of the present study was to investigate long-term outcomes of the offspring in a lipopolysaccharide (LPS)-induced maternal immuneactivation (MIA) model and the effect of maternal molecular hydrogen (H_2) administration. We have previously demonstrated in the MIA mouse model that maternal administration of H_2 attenuates oxidative damage and neuroinflammation, including induced pro-inflammatory cytokines and microglial activation, in the fetal brain. Short-term memory, sociability and social novelty, and sensorimotor gating were evaluated using the Y-maze, three-chamber, and prepulse inhibition (PPI) tests, respectively, at postnatal 3 or 4 weeks. The number of neurons and oligodendrocytes was also analyzed at postnatal 5 weeks by immunohistochemical analysis. Offspring of the LPS-exposed dams showed deficits in short-term memory and social interaction, following neuronal and oligodendrocytic loss in the amygdala and cortex. Maternal H_2 administration markedly attenuated these LPS-induced abnormalities. Moreover, we evaluated the effect of H_2 on LPS-induced

astrocytic activation, both in vivo and in vitro. The number of activated astrocytes with hypertrophic morphology was increased in LPS-exposed offspring, but decreased in the offspring of H_2-administered dams. In primary cultured astrocytes, LPS-induced pro-inflammatory cytokines were attenuated by H_2 administration. Overall, these findings indicate that maternal H_2 administration exerts neuroprotective effects and ameliorates MIA-induced neurodevelopmental deficits of offspring later in life.

Preventive Effects of Drinking Hydrogen-Rich Water on Gingival Oxidative Stress and AlveolarBone Resorption in Rats Fed a High-Fat Diet.

Yoneda T[1], Tomofuji T[2,3], Kunitomo M[4], Ekuni D[5], Irie K[6], Azuma T[7], Machida T[8], Miyai H[9], Fujimori K[10], Morita M[11].

Author information

Abstract

Obesity induces gingival oxidative stress, which is involved in the progression of alveolar bone resorption. The antioxidant effect of hydrogen-rich water may attenuate gingival oxidative stress and prevent alveolar bone resorption in cases of obesity. We examined whether hydrogen-rich water could suppress gingival oxidative stress and alveolar bone resorption in obese rats fed a high-fat diet. Male Fischer 344 rats (*n* = 18) were divided into three groups of six rats each: a control group (fed a regular diet and drinking distilled water) and two experimental groups (fed a high-fat diet and drinking distilled water or hydrogen-rich water). The level of 8-hydroxydeoxyguanosine was determined to evaluate oxidative stress. The bone mineral density of the alveolar bone was analyzed by micro-computerized tomography. Obese rats, induced by a high-fat diet, showed a higher gingival level of 8-hydroxydeoxyguanosine and a lower level of alveolar bone density compared to the control group. Drinking hydrogen-rich water suppressed body weight gain, lowered gingival level of 8-hydroxydeoxyguanosine, and reduced alveolar bone resorption in rats on a high-fat diet. The results indicate that hydrogen-rich water could suppress gingival oxidativestress and alveolar bone resorption by limiting obesity.

Hydrogen-rich water for improvements of mood, anxiety, and autonomic nerve function in dailylife.

Mizuno K[1,2], Sasaki AT[1,3,4], Ebisu K[1,3], Tajima K[5,3], Kajimoto O[1,2], Nojima J[6], Kuratsune H[7], Hori H[1,3], Watanabe Y[1,8,4].

Author information

Abstract

Health and a vibrant life are sought by everyone. To improve quality of life (QOL), maintain a healthy state, and prevent various diseases, evaluations of the effects of potentially QOL-increasing factors are important. Chronic oxidative stress and inflammation cause deteriorations in central nervous system function, leading to low QOL. In healthy individuals, aging, job stress, and cognitive load over several hours also induce increases in oxidative stress, suggesting that preventing the accumulation of oxidative stress caused by daily stress and daily work contributes to maintaining QOL and ameliorating the effects of aging. Hydrogen has anti-oxidant activity and can prevent inflammation, and may thus contribute to improve QOL. The present study aimed to investigate the effects of drinking hydrogen-rich water (HRW) on the QOL of adult volunteers using psychophysiological tests, including questionnaires and tests of autonomic nerve function and cognitive function. In this double-blinded, placebo-controlled study with a two-way crossover design, 26 volunteers (13 females, 13 males; mean age, 34.4 ± 9.9 years) were randomized to either a group administered oral HRW (600 mL/d) or placebo water (PLW, 600 mL/d) for 4 weeks. Change ratios (post-treatment/pre-treatment) for K6 score and sympathetic nerve activity during the resting state were significantly lower after HRW administration than after PLW administration. These results suggest that HRW may reinforce QOL through effects that increase central nervous system functions involving mood, anxiety,
and autonomic nerve function.

Effects of hydrogen-rich water on depressive-like behavior in mice.

Zhang Y[1], Su WJ[1], Chen Y[2], Wu TY[1], Gong H[1], Shen XL[1], Wang YX[1], Sun XJ[3], Jiang CL[1].

Author information

Abstract

Emerging evidence suggests that neuroinflammation and oxidative stress may be major contributors to major depressive disorder (MDD). Patients or animal models of depression show significant increase of proinflammatory cytokine interleukin-1β (IL-1β) and oxidative stress biomarkers in the periphery or central nervous system (CNS). Recent studies show that hydrogen selectively reduces cytotoxic oxygen radicals,

and hydrogen-rich saline potentially suppresses the production of several proinflammatory mediators. Since current depression medications are accompanied by a wide spectrum of side effects, novel preventative or therapeutic measures with fewer side effects might have a promising future. We investigated the effects of drinking hydrogen-rich water on the depressive-like behavior in mice and its underlying mechanisms. Our study show that hydrogen-rich water treatment prevents chronic unpredictable mild stress (CUMS) induced depressive-like behavior. CUMS induced elevation in IL-1β protein levels in the hippocampus, and the cortex was significantly attenuated after 4 weeks of feeding the mice hydrogen-rich water. Over-expression of caspase-1 (the IL-1β converting enzyme) and excessive reactive oxygen species (ROS) production in the hippocampus and prefrontal cortex (PFC) was successfully suppressed by hydrogen-rich watertreatment. Our data suggest that the beneficial effects of hydrogen-rich water on depressive-like behavior may be mediated by suppression of the inflammasome activation resulting in attenuated protein IL-1β and ROS production.

Inhalation of water electrolysis-derived hydrogen ameliorates cerebral ischemia-reperfusioninjury in rats - A possible new hydrogen resource for clinical use.

Cui J[1], Chen X[2], Zhai X[1], Shi D[1], Zhang R[3], Zhi X[1], Li X[1], Gu Z[2], Cao L[2], Weng W[2], Zhang J[2], Wang L[4], Sun X[3], Ji F[2], Hou J[5], Su J[6].

Author information

Abstract

Hydrogen is a kind of noble gas with the character to selectively neutralize reactive oxygen species. Former researches proved that low-concentration of hydrogen can be used to ameliorating cerebral ischemia/reperfusion injury. Hydrogen electrolyzed from water has a hydrogen concentration of 66.7%, which is much higher than that used in previous studies. And water electrolysis is a potential new hydrogenresource for regular clinical use. This study was designed and carried out for the determination of safety and neuroprotective effects of waterelectrolysis-derived hydrogen. Sprague-Dawley rats were used as experimental animals, and middle cerebral artery occlusion was used to make cerebral ischemia/reperfusion model. Pathologically, tissues from rats in hydrogen inhalation group showed no significant difference compared with

the control group in HE staining pictures. The blood biochemical findings matched the HE staining result. TTC, Nissl, and TUNEL staining showed the significant improvement of infarction volume, neuron morphology, and neuron apoptosis in rat with hydrogentreatment. Biochemically, hydrogen inhalation decreased brain caspase-3, 3-nitrotyrosine and 8-hydroxy-2-deoxyguanosine-positive cells and inflammation factors concentration. Water electrolysis-derived hydrogen inhalation had neuroprotective effects on cerebralischemia/reperfusion injury in rats with the effect of suppressing oxidative stress and inflammation, and it is a possible new hydrogenresource to electrolyze water at the bedside clinically.

CANCER

Anti-inflammatory and antitumor action of hydrogen via reactive oxygen species.

Yang Y[1], Zhu Y[1], Xi X[1].

Author information

Abstract

Hydrogen (H_2) has advantages that lead it to be used as a novel antioxidant in preventive and therapeutic applications. H_2 can permeate into biomembranes, cytosol, mitochondria and nuclei, and can be dissolved in water or saline to produce H_2 water or H_2-rich saline. H_2 selectively reduces oxidants of the detrimental reactive oxygen species (ROS), including hydroxyl radicals (·OH) and peroxynitrite ($ONOO^-$), which serve a causative role in the promotion of tumor cell proliferation, invasion and metastasis, but do not disturb metabolic oxidation-reduction

reactions in cell signaling. Compared with traditional antioxidants, H_2 is a small molecule that can easily dissipate throughout the body and cells; thus, it may be a safe and effective antioxidant for inflammatory diseases and cancer, since ROS usually initiates tumor progression. Treatment with H_2 may involve correction of the oxidative/anti-oxidative imbalance and suppression of inflammatory mediators. Therefore the present review will discuss the anti-inflammatory and anti-tumorigenic action of H_2 via ROS.

Hydrogen gas inhibits lung cancer progression through t argeting SMC3.

Wang D[1], Wang L[1], Zhang Y[1], Zhao Y[1], Chen G[2].

Author information

Abstract

Lung cancer is one of the most common lethal malignancies in the globe. The patients' prognoses are dim due to its high metastatic potential and drug resistance. Therefore, in the present study, we aim to find a more potent therapeutic approach for lung cancer. We mainly explored the function of hydrogen gas (H_2) on cell viability, apoptosis, migration and invasion in lung cancer cell lines A549 and H1975 by CCK-8, flow cytometry, wound healing and transwell assays, respectively. We used RNA-seq, qPCR and western blotting to detect the different expression genes (DEGs) between H_2 group and control group to find the gene related to chromosome condensation. Besides, we confirmed the structural maintenance of chromosomes 3 (SMC3) and H_2 on the progression of lung cancer in vitro and vivo. Results showed that H_2inhibited cell viability, migration and invasion, and catalyzed cell apoptosis and H_2 induced A549 and H1975 cells G2/M arrest. Besides, H_2down-regulated the expression of NIBPL, SMC3, SMC5 and SMC6, and also reduced the expression of Cyclin D1, CDK4 and CDK6. H_2translocated the subcellular location of SMC3 during cell division and decreased its stability and increased its ubiquitination in both A549 and H1975 cells. In addition, inhibition of the proliferation, migration and invasion and promotion of the apoptosis of A549 and H1975 cells induced by H_2 were all abolished when overexpressed SMC3 in the presence of H_2. Animal experimental assay demonstrated that the tumor weight in H_2 group was significantly smaller than that in control group, but was bigger than cis-platinum group. The expression of Ki-67, VEGF and SMC3 were decreased when mice were treated with H_2 or cis-platinum, especially for cis-platinum. All data suggested that

H_2inhibited lung cancer progression through down-regulating SMC3, a regulator for chromosome condensation, which provided a new method for the treatment of lung cancer.

Hydrogen-water enhances 5-fluorouracil-induced inhibition of colon cancer.

Runtuwene J[1], Amitani H[2], Amitani M[2], Asakawa A[2], Cheng KC[2], Inui A[2].

Author information

Abstract

Oxidative stress is involved in cancer development. Hydrogen (H2) is a potent antioxidant and exhibits anti-inflammatory and potentially anticancer-like activities. This study aimed to investigate the role of H2 incombination with 5-fluorouracil (5-FU) in cancer treatment both in vitro and in vivo using the colon 26 cell line. The survival rate was determined using the Kaplan-Meier survival test, and cell viability was assessed using cell viability imaging kit and the MTT assay, and activation of the cell apoptosis pathway (Phosphorylated adenosine monophosphate activated protein kinase (p-AMPK), Apoptosis-inducing factor (AIF) and Caspase 3) were characterized by western blots. Hydrogen water administration improved the survival of mice with colon 26-induced cancer. Furthermore, hydrogen water enhanced cell apoptosis in cancer cells, resulting in a marked increase in the expression of p-AMPK, AIF and Caspase 3 in colon 26 cells. Hydrogen wateralso increased the inhibitory effect of 5-FU on colon 26 cells with spect to cell survival rate and anticancer functions. Additionally, high-content hydrogen water exhibited stronger antioxidative and anticancer activity than did the natural hydrogen water. In conclusion, high-content hydrogen water can inhibit colon cancer, particularly in combination with 5-fluorouracil.

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

Kang KM[1], Kang YN, Choi IB, Gu Y, Kawamura T, Toyoda Y, Nakao A.

Author information

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 hydrogen-rich water on 49 patientsreceiving 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 radiation-induced oxidative stress without compromising anti-tumor effects.

Antitumor effects of nano-bubble hydrogen-dissolved water are enhanced by coexistent platinum colloid and the combined hyperthermia with apoptosis-like cell death.

Asada R[1], Kageyama K, Tanaka H, Matsui H, Kimura M, Saitoh Y, Miwa N.

Author information
Abstract

In order to erase reactive oxygen species (ROS) related with the proliferation of tumor cells by reducing activity of hydrogen, we developed functional water containing nano-bubbles (diameters: <900 nm for 71%/population) hydrogen of 1.1-1.5 ppm (the theoretical maximum: 1.6 ppm) with a reducing ability (an oxidation-reduction potential -650 mV, normal water: +100-200 mV) using a microporous-filter hydrogen-jetting device. We showed that hydrogen water erased ROS indispensable for tumor cell growth by ESR/spin trap, the redox indicator CDCFH-DA assay, and was cytotoxic to Ehrlich ascites tumor cells as assessed by WST-8 assay, crystal violet dye stain and scanning electron microscopy, after 24-h or 48-h incubation sequent to warming at 37°C or 42°C. Hydrogen water supplemented with platinum colloid (0.3 ppm Pt in 4% polyvinylpyrrolidone) had more antitumor activity than hydrogen water alone, mineral water alone (15.6%), hydrogen waterplus mineral water, or platinum colloid alone as observed by decreased cell numbers, cell shrinkage and pycnosis (nuclear condensation)/karyorrhexis (nuclear fragmentation) indicative of apoptosis, together with cell deformation and disappearance of microvilli on the membrane surface. These antitumor effects were promoted by combination with hyperthermia at 42°C. Thus, the nano-bubble hydrogen water with platinum colloid is potent as an anti-tumor agent.

Certain minerals can produce alkaline reduced water with high pH and low oxidation-reduction potential (ORP) when dissolved in water. Alkaline reduced water (ARW) showed significant anticancer effect. When B16 melanoma cells were inoculated subcutaneously and intra-peritoneally, C56BL/6 mice fed with ARW showed tumor growth delay and the survival span was significantly lengthened. ARW also showed the inhibition of metastasis by reducing the numbers of B16 melanoma colonies when injected through tail vein. The amount of reactive oxygen species (ROS) was very reduced when fed with ARW except for spleen, which is a major organ for immunity. Even for normal mice, ARW intake invoked systemic cytokines, such as, Th1 (IFN-γ, IL-12) and Th2 (IL-4, IL-5), suggesting strong immuno-modulation effect. Both ROS scavenging effect and immuno-

Electrolyzed Reduced Water Which Can Scavenge Active Oxygen Species Supresses Cell Growth and Regulates Gene Expression of Animal Cells

modulation effect might be responsible for anticancer effect of alkaline reduced water.

Active oxygen species are considered to cause extensive oxidative damage to biological macromolecules, which bring about a variety of diseases as well as aging. Reduced water produced near cathode during electrolysis of water exhibits high pH, low dissolved oxygen, extremely high dissolvedmolecular hydrogen, and extremely negative redox potential values. Recently we found that strongly electrolyzed reduced water scavenges active oxygen species and protects DNA from oxidative damage (Shirahata, S. *et al., Biochem. Biophys. Res. Commun.*, **234**, 269–274 (1997)). Electrolyzed reduced water suppressed the growth of human normal fibroblast TIG-1, human lung adenocarcinoma A549, and human uterine cervix cancer HeLa, indicating that reduced water affects the signaling pathway of cell cycle. The expression of the interleukin-6 gene was enhanced by reduced water as well as ascorbic acid, (+)-catechin and tannic acid when added to the culture of human osteosarcoma MG-63 cells, suggesting that reduced water acts as a reductant to cells.

Hyperbaric hydrogen therapy: a possible treatment for cancer.

Dole M, Wilson FR, Fife WP.

Abstract

Hairless albino mice with squamous cell carcinoma were exposed to a mixture of 2.5 percent oxygen and 97.5 percent hydrogen at a total pressure of 8 atmospheres for periods up to 2 weeks in order to see if a free radical decay catalyzer, such as hydrogen, would cause a regression of the skin tumors. Marked aggression of the tumors was found, leading to the possibility that hyperbaric hydrogen therapy might also prove to be of significance in the treatment of other types of cancer.

EYE & EAR

Prevention of ischemia-induced hearing loss by intravenous administration of hydrogen-richsaline in gerbil.

Ogawa H[1], Okada M[2], Shudou M[3], Gyo K[4], Hato N[5].

Author information

Abstract

OBJECTIVE:

Hydrogen-rich water, which is a potent antioxidant agent, was investigated for its protective effects against ischemic damage of the cochlea in gerbils.

METHODS:

The animals were subjected to transient cochlear ischemia by occluding the bilateral vertebral arteries for l5min. Five milliliters of hydrogen-rich saline was then intravenously administered immediately after the insult. Saline without hydrogen was used as a control. Effects of hydrogen were evaluated using the auditory brainstem response (ABR) and histological studies of the inner ear.

RESULTS:

In non-ischemia animals, ABR thresholds and histological findings of the cochlea did not change by administration of saline or hydrogen-rich saline. In contrast, transient cochlear ischemia caused a 24.2±3.8dB increase in the ABR threshold at 8kHz, and a decrease of 14.1%±1.8% in the number of inner hair cells (IHCs) at the basal turn on day 7. Ischemic damage was more severe at 16 and 32kHz. When the animals were treated with hydrogen-rich saline, cochlear damage was significantly reduced: the increase in ABR threshold was 11.7±2.6dB at 8kHz and the IHC loss was 7.5%±2.1% at the basal turn on day 7. The effects of hydrogen-rich saline were more prominent at higher frequencies.

CONCLUSIONS:

Intravenous administration of hydrogen-rich saline was effective in preventing acute hearing loss due to transient cochlear ischemia.

Hydrogen Inhalation Protects against Ototoxicity Induced by Intravenous Cisplatin in the GuineaPig.

Fransson AE[1], Kisiel M[1], Pirttilä K[2], Pettersson C[2], Videhult Pierre P[3], Laurell GFE[1].

Author information

Abstract

Introduction: Permanent hearing loss and tinnitus as side-effects from treatment with the anticancer drug cisplatin is a clinical problem. Ototoxicity may be reduced by co-administration of an otoprotective agent, but the results in humans have so far been modest. **Aim:** The present preclinical *in vivo* study aimed to explore the protective

efficacy
of hydrogen (H_2) inhalation on ototoxicity induced by intravenouscisplatin. **Materials and Methods:** Albino guinea pigs were divided into four groups. The Cispt (*n* = 11) and Cispt+H_2 (*n* = 11) groups were given intravenous cisplatin (8 mg/kg b.w., injection rate 0.2 ml/min). Immediately after, the Cispt+H_2 group also received gaseous H_2 (2% in air, 60 min). The H_2 group (*n* = 5) received only H_2 and the Control group (*n* = 7) received neither cisplatin nor H_2. Ototoxicity was assessed by measuring frequency specific ABR thresholds before and 96 h after treatment, loss of inner (IHCs) and outer (OHCs) hair cells, and by performing densitometry-based immunohistochemistry analysis of cochlear synaptophysin, organic transporter 2 (OCT2), and copper transporter 1 (CTR1) at 12 and 7 mm from the round window. By utilizing metabolomics analysis of perilymph the change of metabolites in the perilymph was
assessed. **Results:** Cisplatin induced electrophysiological threshold shifts, hair cell loss, and reduced synaptophysin immunoreactivity in the synapse area around the IHCs and OHCs. H_2 inhalation mitigated all these effects. Cisplatin also reduced the OCT2 intensity in the inner and outer pillar cells and in the stria vascularis as well as the CTR1 intensity in the synapse area around the IHCs, the Deiters' cells, and the stria vascularis. H_2 prevented the majority of these effects. **Conclusion:** H_2 inhalation can reduce cisplatin-inducedototoxicity on functional, cellular, and subcellular levels. It is proposed that synaptopathy may serve as a marker for cisplatin ototoxicity. The effect of H_2 on the antineoplastic activity of cisplatin needs to be further explored.

Molecular Hydrogen Effectively Heals Alkali-Injured Cornea via Suppression of Oxidative Stress.

Cejka C[1], Kossl J[2], Hermankova B[2], Holan V[2], Cejkova J[1].

Author information

Abstract

The aim of this study was to examine the effect of molecular hydrogen (H_2) on the healing of alkali-injured cornea. The effects of the solution of H_2 in phosphate buffered saline (PBS) or PBS alone topically applied on the alkali-injured rabbit cornea with 0.25 M NaOH were investigated using immunohistochemical and biochemical methods. Central corneal thickness taken as an index of corneal hydration was measured with an ultrasonic pachymeter. Results show that irrigation of the damaged eyes with H_2 solution immediately after the injury and then within next five days renewed corneal

transparency lost after the injury and reduced corneal hydration increased after the injury to physiological levels within ten days after the injury. In contrast, in injured corneas treated with PBS, the transparency of damaged corneas remained lost and corneal hydration elevated. Later results-on day 20 after the injury-showed that in alkali-injured corneas treated with H_2solution the expression of proinflammatory cytokines, peroxynitrite, detected by nitrotyrosine residues (NT), and malondialdehyde (MDA) expressions were very low or absent compared to PBS treated injured corneas, where NT and MDA expressions were present. In conclusion, H_2 solution favorably influenced corneal healing after alkali injury via suppression of oxidative stress.

Hydrogen in drinking water attenuates noise-induced hearing loss in guinea pigs.

Lin Y[1], Kashio A, Sakamoto T, Suzukawa K, Kakigi A, Yamasoba T.

Author information

Abstract

It has been shown that molecular hydrogen acts as a therapeutic and preventive antioxidant by selectively reducing the hydroxyl radical, the most cytotoxic of the reactive oxygen species. In the present study, we tested the hypothesis that acoustic damage in guinea pigs can be attenuated by the consumption of molecular hydrogen. Guinea pigs received normal water or hydrogen-rich water for 14 days before they were exposed to 115 dB SPL 4-kHz octave band noise for 3h. Animals in each group underwent measurements for auditory brainstem response (ABR) or distortion-product otoacoustic emissions (DPOAEs) before the treatment (baseline) and immediately, 1, 3, 7, and 14 days after noise exposure. The ABR thresholds at 2 and 4 kHz were significantly better on post-noise days 1, 3, and 14 in hydrogen-treated animals when compared to the normal water-treated controls. Compared to the controls, the hydrogen-treated animals showed greater amplitude of DPOAE input/output growth functions during the recovery process, with statistical significance detected on post-noise days 3 and 7. These findings suggest that hydrogen can facilitate the recovery of hair cell function and attenuate noise-induced temporary hearing loss.

Hydrogen protects auditory hair cells from free radicals.

Kikkawa YS[1], Nakagawa T, Horie RT, Ito J.

Author information

Abstract

Reactive oxygen species (ROS) play a role in the degeneration of auditory hair cells because of aging, noise trauma, or ototoxic drugs. Hydrogenation is a fundamental reduction/de-oxidation reaction in living organisms. This study thus examined the potential of hydrogen to protect auditory hair cells from ROS-induced damage. To generate ROS, we applied antimycin A to explant cultures of auditory epithelia, and examined the effect of hydrogen on the protection of hair cells against ROS. Incubation with a hydrogen-saturated medium significantly reduced ROS generation and subsequent lipid peroxidation in the auditory epithelia, leading to increased survival of the hair cells. These findings show the potential of hydrogen to protect auditory hair cells from ROS-induced damage.

HEART

Hydrogen-rich solution against myocardial injury and aquaporin expression via the PI3K/Aktsignaling pathway during cardiopulmonary bypass in rats.

Song D[1], Liu X[2], Diao Y[3], Sun Y[3], Gao G[4], Zhang T[3], Chen K[5], Pei L[1].

Author information

Abstract

Myocardial ischemia, hypoxia and reperfusion injury are induced by aortic occlusion, cardiac arrest and resuscitation during cardiopulmonarybypass (CPB), which can severely affect cardiac function. The aim of the present study was to investigate the effects of hydrogen-rich solution (HRS) and aquaporin (AQP) on cardiopulmonary bypass (CPB)-induced myocardial injury, and determine the mechanism of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway. Sprague Dawley rats were divided into a sham operation group, a CPB surgery group and a HRS group. A CPB model was established, and the hemodynamic parameters were determined at the termination of CPB. The myocardial tissues were observed by hematoxylin and eosin, and Masson staining.

The levels of myocardial injurymarkers [adult cardiac troponin I (cTnI), lactate dehydrogenase (LDH), creatine kinase MB (CK-MB) and brain natriuretic peptide (BNP)], inflammatory factors [interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α)] and oxidative stress indicators [superoxide dismutase (SOD), malondialdehyde (MDA) and myeloperoxidase (MPO)] were determined by ELISA. Furthermore, H9C2 cells were treated with HRS following hypoxia/reoxygenation. Cell viability and cell apoptosis were investigated. The expression of apoptosis regulator Bcl-2 (Bcl-2), apoptosis regulator Bax (Bax), caspase 3, AQP-1, AQP-4, phosphorylated (p)-Akt, heme oxygenase 1 (HO-1) and nuclear factor erythroid 2-related factor 2 (Nrf2) were investigated using western blotting and quantitative-polymerase chain reaction of tissues and cells. Following CPB, myocardial cell arrangement was disordered, myocardial injury markers (cTnI, LDH, CK-MB and BNP), inflammatory cytokines (IL-1β, IL-6 and TNF-α) and MDA levels were significantly increased compared with the sham group; whereas the SOD levels were significantly downregulated following CPB compared with the sham group. HRS attenuated myocardial injury, reduced the expression levels of cTnI, LDH, CK-MB, BNP, IL-1β, IL-6, TNF-α, MDA and MPO, and increased SOD release. Levels of Bcl-2, AQP-1, AQP-4, p-Akt, HO-1 and Nrf2 were significantly increased following HRS; whereas Bax and caspase-3 expression levels were significantly reduced following CPB. HRS treatment significantly increased the viability of myocardial cells, reduced the rate of myocardial cell apoptosis and the release of MDA and LDH compared with the CPB group. A PI3K inhibitor (LY294002) was revealed to reverse the protective effect of HRS treatment. HRS was demonstrated to attenuate CPB-induced myocardial injury, suppress AQP-1 and AQP-4 expression following CPB treatment and protect myocardial cells via the PI3K/Akt signaling pathway.

Hydrogen gas improves left ventricular hypertrophy in Da hl rat of salt-sensitive hypertension.

Matsuoka H[1], Miyata S[2], Okumura N[1], Watanabe T[1], Hashimoto K[3], Nagahara M[4], Kato K[1], Sobue S[1], Takeda K[1], Ichihara M[1], Iwamoto T[1], Noda A[1].

Author information

Abstract

PURPOSE:
Hypertension is an important risk factor for death resulting from stroke, myocardial infarction, and end-stage renal failure. Hydrogen (H_2) gas protects against many diseases, including ischemia-reperfusion injury and stroke. The effects of H_2 on hypertension and its related left ventricular (LV) function have not been fully elucidated. The purpose of this study was to investigate the effects of H_2 gas on hypertension and LV hypertrophy using echocardiography.

METHODS:
Dahl salt-sensitive (DS) rats were randomly divided into three groups: those fed an 8% NaCl diet until 12 weeks of age (8% NaCl group), those additionally treated with H_2 gas (8% NaCl + H_2 group), and control rats maintained on a diet containing 0.3% NaCl until 12 weeks of age (0.3% NaCl group). H_2 gas was supplied through a gas flowmeter and delivered by room air (2% hydrogenated room air, flow rate of 10 L/min) into a cage surrounded by an acrylic chamber. We evaluated interventricular septal wall thickness (IVST), LV posterior wall thickness (LVPWT), and LV mass using echocardiography.

RESULTS:
IVST, LVPWT, and LV mass were significantly higher in the 8% NaCl group than the 0.3% NaCl group at 12 weeks of age, whereas they were significantly lower in the 8% NaCl + H_2 group than the 8% NaCl group. There was no significant difference in systolic blood pressure between the two groups.

CONCLUSION:
Our findings suggest that chronic H_2 gas inhalation may help prevent LV hypertrophy in hypertensive DS rats.

Molecular hydrogen potentiates beneficial anti-infarct effect of hypoxic postconditioning in isolated rat hearts: a novel cardioprotective intervention.

Zálešák M[1,1], Kura B[1,1], Graban J[1,1], Farkašová V[1,1], Slezák J[1,1], Ravingerová T[1,1].

Author information

Abstract

Generation of free radicals through incomplete reduction of oxygen during ischemia-reperfusion (I/R) is well described. On the other hand, molecular hydrogen (H_2) reduces

oxidative stress due to its ability to react with strong oxidants and easily penetrate cells by diffusion, without disturbing metabolic redox reactions. This study was designed to explore cardioprotective potential of hypoxic postconditioning (HpostC) against I/R (30 min global I - 120 min R) in isolated rat hearts using oxygen-free Krebs-Henseleit buffer (KHB). Furthermore, the possibility to potentiate the effect of HpostC by H_2 using oxygen-free KHB saturated with H_2 (H_2 + HpostC) was tested. HPostC was induced by 4 cycles of 1-minute perfusion with oxygen-free KHB intercepted by 1-minute perfusion with normal KHB, at the onset of reperfusion. H_2 + HPostC was applied in a similar manner using H_2-enriched oxygen-free KHB. Cardioprotective effects were evaluated on the basis of infarct size (IS, in % of area at risk, AR) reduction, post-I/R recovery of heart function, and occurrence of reperfusion arrhythmias. HPostC significantly reduced IS/AR compared with non-conditioned controls. H_2 present in KHB during HPostC further decreased IS/AR compared with the effectof HPostC, attenuated severe arrhythmias, and significantly restored heart function (vs. controls). Cardioprotection by HpostC can be augmented by molecular hydrogen infusion.

Efficacy of inhaled HYdrogen on neurological outcome following BRain Ischemia During post-cardiac arrest care (HYBRID II trial): study protocol for a randomized controlled trial.

Tamura T[1,2], Hayashida K[3,4], Sano M[4,5], Onuki S[4], Suzuki M[3,4].

Author information

Abstract

BACKGROUND:

Hydrogen gas inhalation (HI) improved survival and neurological outcomes in an animal model of post-cardiac arrestsyndrome (PCAS). The feasibility and safety of HI for patients with PCAS was confirmed in a pilot study. The objective of this study is to evaluate the efficacy of HI for patients with PCAS.

METHODS/DESIGN:

The efficacy of inhaled HYdrogen on neurological outcome following BRain Ischemia During post-cardiac arrest care(HYBRID II) trial is an investigator-initiated, randomized, double-blind, placebo-controlled trial designed to enroll 360 adult comatose (Glasgow Coma Scale score < 8) patients who will be resuscitated following an out-of-hospital cardiac arrest of a presumed cardiac cause. The patients will be randomized (1:1) to

either the HI or control group. Patients in the HI group will inhale 2% hydrogen with 24% to 50% oxygen, and those in the control group will inhale 24% to 50% oxygen for 18 h after admission via mechanical ventilation. Multidisciplinary post-arrest care, including targeted temperature management (TTM) between 33 °C and 36 °C, will be provided in accordance with the latest guidelines. The primary outcome of interest is the 90-day neurological outcome, as evaluated using the Cerebral Performance Categories scale (CPC). The secondary outcomes of interest are the 90-day survival rate and other neurological outcomes. This study will provide 80% power to detect a 15% change in the proportion of patients with good neurological outcomes (CPCs of 1 and 2), from 50% to 65%, with an overall significance level of 0.05.

DISCUSSION:

The first multicenter randomized trial is underway to confirm the efficacy of HI on neurological outcomes in comatose out-of-hospital cardiac arrest survivors. Our study has the potential to address HI as an appealing and innovative therapeutic strategy for PCAS in combination with TTM.

TRIALS REGISTRATION:

University Hospital Medical Information Network (UMIN), 000019820 . Registered on 17 November 2015.

The Effects of Hydrogen Gas Inhalation on Adverse Left Ventricular Remodeling AfterPercutaneous Coronary Intervention for ST-Elevated Myocardial Infarction - First Pilot Study in Humans.

Katsumata Y[1,2], Sano F[3], Abe T[3], Tamura T[4,2], Fujisawa T[1], Shiraishi Y[1], Kohsaka S[1], Ueda I[1], Homma K[4,2], Suzuki M[4,2], Okuda S[5], Maekawa Y[1], Kobayashi E[6,2], Hori S[4], Sasaki J[4], Fukuda K[1], Sano M[1,2].

Author information

Abstract

BACKGROUND:

Hydrogen gas inhalation (HI) reduced infarct size and mitigated adverse left ventricular (LV) remodeling in a rat model of acute myocardial infarction (AMI). We designed a prospective, open-label, rater-blinded clinical pilot study in patients experiencing ST-elevated MI (STEMI).Methods and Results:The 20 patients with an initial diagnosis of STEMI were

assigned to either an HI group (1.3% $H_2$with 26% oxygen) or a control group (26% oxygen). There were no HI-related severe adverse events. In the full analysis set, the cardiac salvage index as evaluated using cardiac magnetic resonance imaging at 7 days after primary percutaneous coronary intervention (PCI), showed no significant between-group difference (HI: 50.0±24.3%; control: 60.1±20.1%; P=0.43). However, the improvement from day 7 in the HI group was numerically greater than that in the control group in some of the surrogate outcomes at 6-month follow-up, including the LV stroke volume index (HI: 9.2±7.1 mL/m^2; control: -1.4±7.2 mL/m^2; P=0.03) and the LV ejection fraction (HI: 11.0%±9.3%; control: 1.7%±8.3%; P=0.11).

CONCLUSIONS:

The first clinical study has shown that HI during PCI is feasible and safe and may also promote LV reverse remodeling at 6 months after STEMI. The study was not powered to test efficacy and a further large-scale trial is warranted. (Clinical trials registration: UMIN00006825).

Treatment with hydrogen molecule attenuates cardiac dysfunction in streptozotocin-induceddiabetic mice.

Wu F[1], Qiu Y[1], Ye G[1], Luo H[1], Jiang J[2], Yu F[1], Zhou W[1], Zhang S[1], Feng J[3].

Author information

Abstract

INTRODUCTION:

Diabetic cardiomyopathy, a disorder of the heart muscle in diabetic patients, is one of the major causes of heart failure. The aim of present study was to investigate the therapeutic effect of hydrogen molecule on streptozotocin-induced diabetic cardiomyopathy in mice.

METHODS:

Diabetes was induced in adult male mice by consecutive peritoneal injection of streptozotocin (50 mg/kg/day) for 5 days. Then, they were treated with hydrogen water (1.3±0.2 mg/l) for 8 weeks (four groups, n=83-88 in each group).

RESULTS:

Although treatment of diabetic mice with hydrogen water did not significantly affect blood glucose level, it significantly attenuated cardiac hypertrophy and reduced expression of atrial natriuretic factor and β-myosin heavy chain; it

alleviated cardiac fibrosis and reduced expression of collagen I and III, transforming growth factor beta, alpha-smooth muscle actin, and osteopontin; it reduced cardiac caspase-3 activity and ratio of bax/bcl-2. Importantly, hydrogen water treatment improved cardiac function in streptozotocin-diabetic mice. Furthermore, it was found that hydrogen water treatment abated oxidative stress, suppressed inflammation, and attenuated endoplasmic reticulum stress in the hearts of streptozotocin-diabetic mice. In addition, hydrogen water treatment suppressed activation of Jun NH2-terminal kinase and p38 mitogen activated protein kinase signaling and nuclear factor κB signaling in the hearts of streptozotocin-diabetic mice.

CONCLUSION:
Treatment with hydrogen molecule attenuated cardiac dysfunction in streptozotocin-induced diabetic mice, which was independent of glycemic control.

SUMMARY:
Treatment with hydrogen molecule attenuated cardiac dysfunction in streptozotocin-induced type 1 diabetic mice. Molecular hydrogen could thus be envisaged as a nutritional countermeasure for diabetic cardiomyopathy.

Consumption of water containing over 3.5 mg of dissolved hydrogen could improve vascular endothelial function.

Sakai T[1], Sato B[2], Hara K[3], Hara Y[3], Naritomi Y[3], Koyanagi S[1], Hara H[3], Nagao T[4], Ishibashi T[5].

Author information

Abstract

BACKGROUND:
The redox imbalance between nitric oxide and superoxide generated in the endothelium is thought to play a pivotal role in the development of endothelial dysfunction. A third reactive oxygen species (ROS), H2O2, is known to have both beneficial and detrimental effects on the vasculature. Nonetheless, the influence of the hydroxyl radical, a byproduct of H2O2 decay, is unclear, and there is no direct evidence that the hydroxyl radical impairs endothelial function in conduit arteries. Molecular hydrogen (H2) neutralizes detrimental ROS, especially the hydroxyl radical.

OBJECTIVES:

To assess the influence of the hydroxyl radical on the endothelium and to confirm that a gaseous antioxidant, H2, can be a useful modulator of blood vessel function.

METHODS:

The efficacy of water containing a high concentration of H2 was tested by measuring flow-mediated dilation (FMD) of the brachial artery (BA). The subjects were randomly divided into two groups: the high-H2 group, who drank high-H2 water containing 7 ppm H2 (3.5 mg H2 in 500 mL water); and the placebo group. Endothelial function was evaluated by measuring the FMD of the BA. After measurement of diameter of the BA and FMD at baseline, volunteers drank the high-H2 water or placebo water immediately and with a 30-minute interval; FMD was compared to baseline.

RESULTS:

FMD increased in the high-H2 group (eight males; eight females) from 6.80%±1.96% to 7.64%±1.68% (mean ± standard deviation) and decreased from 8.07%±2.41% to 6.87%±2.94% in the placebo group (ten males; eight females). The ratio to the baseline in the changes of FMD showed significant improvement ($P<0.05$) in the high-H2 group compared to the placebo group.

CONCLUSION:

H2 may protect the vasculature from shear stress-derived detrimental ROS, such as the hydroxyl radical, by maintaining the nitric oxide-mediated vasomotor response.

Hydrogen-supplemented drinking water protects cardiac allografts from inflammation-associated deterioration.

Noda K[1], Tanaka Y, Shigemura N, Kawamura T, Wang Y, Masutani K, Sun X, Toyoda Y, Bermudez CA, Nakao A.

Author information

Abstract

Recent evidence suggests that molecular hydrogen has therapeutic value for disease states that involve inflammation. We hypothesized that drinking hydrogen-rich water (HW) daily would protect cardiac and aortic allograft recipients from inflammation-associated deterioration. Heterotopic heart transplantation with short-course tacrolimus immunosuppression and orthotopic aortic transplantation were performed in allogeneic

rat strains. HW was generated either by bubbling hydrogen gas through tap water (Bu-HW) or via chemical reaction using a magnesium stick [Mg + 2H(2) O → Mg (OH)(2) + H(2)] immersed in tap water (Mg-HW). Recipients were given either regular water (RW), Mg-HW, Bu-HW, or Mg-HW that had been subsequently degassed (DW). Graft survival was assessed by daily palpation for a heartbeat. Drinking Mg-HW or Bu-HW was remarkably effective in prolonging heart graft survival and reducing intimal hyperplasia in transplanted aortas as compared with grafts treated with RW or DW. Furthermore, T cell proliferation was significantly inhibited in the presence of hydrogen in vitro, accompanied by less production of interleukin-2 and interferon-γ. Hydrogen treatment was also associated with increased graft ATP levels and increased activity of the enzymes in mitochondrial respiratory chain. Drinking HW prolongs survival of cardiac allografts and reduces intimal hyperplasia of aortic allografts.

HUMAN STUDIES

Positive effects of hydrogen-water bathing in patients of psoriasis and parapsoriasis en plaques.

Zhu Q[1], Wu Y[2], Li Y[3], Chen Z[1], Wang L[1], Xiong H[1], Dai E[4], Wu J[5], Fan B[6], Ping L[3], Luo X[7].

Author information

Abstract

Psoriasis and parapsoriasis en plaques are chronic inflammatory skin diseases, both representing therapeutic challenge in daily practice and adversely affecting the quality of life. Reactive oxygen species (ROS) has been evidenced to be involved in the pathogenesis of the chronic inflammatory diseases. We now report that hydrogen water, an effective ROS scavenger, has significant and rapid improvement in disease severity and quality of life for patients with psoriasis and parapsoriasis en plaques. At week 8, our parallel-controlled trial revealed 24.4% of patients (10/41) receiving hydrogen-water bathing achieved at least 75% improvement in Psoriasis Area Severity Index

(PASI) score compared with 2.9% of patients (1/34) of the control group (Pc = 0.022, OR = 0.094, 95%CI = [0.011, 0.777]). Of patients, 56.1% (23/41) who received bathing achieved at least 50% improvement in PASI score compared with only 17.7%(6/34) of the control group (P = 0.001, OR = 0.168, 95%CI = [0.057, 0.492]). The significant improvement of pruritus was also observed ($P = 3.94 \times 10^{-4}$). Besides, complete response was observed in 33.3% of patients (2/6) of parapsoriasis en plaques and partial response in 66.7% (4/6) at week 8. Our findings suggested that hydrogen-water bathing therapy could fulfill the unmet need for these chronic inflammatory skin diseases.

Effects of Molecular Hydrogen Assessed by an Animal Model and a Randomized Clinical Studyon Mild Cognitive Impairment.

Nishimaki K[1], Asada T[2,3], Ohsawa I[1,4], Nakajima E[2], Ikejima C[2], Yokota T[1], Kamimura N[1], Ohta S[1,5].

Author information

Abstract

BACKGROUND:

Oxidative stress is one of the causative factors in the pathogenesis of neurodegenerative diseases including mild cognitiveimpairment (MCI) and dementia. We previously reported that molecular hydrogen (H2) acts as a therapeutic and preventive antioxidant.

OBJECTIVE:

We assess the effects of drinking H2-water (water infused with H2) on oxidative stress model mice and subjects with MCI.

METHODS:

Transgenic mice expressing a dominant-negative form of aldehyde dehydrogenase 2 were used as a dementia model. The mice with enhanced oxidative stress were allowed to drink H2-water. For a randomized double-blind placebo-controlled clinical study, 73 subjects with MCI drank ~300 mL of H2-water (H2-group) or placebo water (control group) per day, and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores were determined after 1 year.

RESULTS:

In mice, drinking H2-water decreased oxidative stress markers and suppressed the decline of memory impairment and neurodegeneration. Moreover, the mean lifespan in the H2-water group was longer than that of the control group. In MCI subjects, although there was no significant difference between the H2- and control groups in ADAS-cog score after 1 year, carriers of the apolipoprotein E4 (APOE4) genotype in the H2-group were improved significantly on total ADAS-cog score and word recall task score (one of the sub-scores in the ADAS-cog score).

CONCLUSION:

H2-water may have a potential for suppressing dementia in an oxidative stress model and in the APOE4 carriers with MCI.

Novel haemodialysis (HD) treatment employing molecular hydrogen (H_2)-enriched dialysissolution improves prognosis of chronic dialysis patients: A prospective observational study.

Nakayama M[1,2,3], Itami N[4], Suzuki H[5], Hamada H[4], Yamamoto R[6], Tsunoda K[7], Osaka N[8], Nakano H[9], Maruyama Y[10], Kabayama S[11,12], Nakazawa R[13], Miyazaki M[11,12], Ito S[11].

Author information

Abstract

Recent studies have revealed unique biological characteristics of molecular hydrogen (H_2) as an anti-inflammatory agent. We developed a novel haemodialysis (E-HD) system delivering an H_2 (30-80 ppb)-enriched dialysis solution by water electrolysis, and conducted a non-randomized, non-blinded, prospective observational study exploring its clinical impact.

Prevalent chronic HD patients were allocated to either the E-HD (n = 161) group or the conventional HD (C-HD: n = 148) group, and received the respective HD treatments during the study. The primary endpoint was a composite of all-cause mortality and development of non-lethal cardio-cerebrovascular events (cardiac disease, apoplexy, and leg amputation due to peripheral artery disease). During the 3.28-year mean observation period, there were no differences in dialysis parameters between the two groups; however, post-dialysis hypertension was ameliorated with significant reductions

in antihypertensive agents in the E-HD patients. There were 91 events (50 in the C-HD group and 41 in the E-HD group). Multivariate analysis of the Cox proportional hazards model revealed E-HD as an independent significant factor for the primary endpoint (hazard ratio 0.59; [95% confidence interval: 0.38-0.92]) after adjusting for confounding factors (age, cardiovascular disease history, serum albumin, and C-reactive protein). HD applying an H_2-dissolved HD solution could improve the prognosis of chronic HD patients.

28-Days Hydrogen-Rich Water Supplementation Affects Exercise Capacity in Mid-Age Overweight Women: 2942 Board #225 June 1 330 PM - 500 PM

Ostojic, Sergej, M.; Korovljev, Darinka; Stajer, Valdemar; Javorac, Dejan

Medicine & Science in Sports & Exercise: May 2018 - Volume 50 - Issue 5S - p 728–729

doi: 10.1249/01.mss.0000538402.25953.d2

F-62 Free Communication/Poster - Ergogenic Aids VI - Other Friday, June 1, 2018, 1:00 PM - 6:00 PM Room: CC-Hall B

- Author Information

Molecular hydrogen (H_2) improves body composition, metabolic profiles and mitochondrial function in overweight women, yet no studies so far evaluated the effectiveness of H_2 for improving exercise capacity in this population.

PURPOSE: To examine the effects of 28-days supplementation with 1 L per day of hydrogen-rich water (HRW) on exercise capacity and quality of life in overweight mid-age women.

METHODS: Twelve women (age 53.8 ± 13.0 years, BMI 28.8 ± 3.3 kg/m^2, VO2max 22.3 ± 3.7 ml/kg/min) participated in this randomized, placebo-controlled, cross-over, repeated-measure interventional study. All participants were allocated in a double-blind design to receive two randomly assigned trials: first group received 1 L per day of HRW (supplying ~ 9 ppm of H_2), while the second group received placebo (tap water). Participants were evaluated at baseline, and following 28 days of intervention. The primary endpoint was the change in cardiorespiratory endurance (VO_{2max}) assessed at baseline and at 28 days follow-up. Secondary outcomes included change from baseline to end of treatment in values for work capacity, impact of weight on quality of life

(IWQoL), and hematological biomarkers. Participants were asked to maintain their usual lifestyle, dietary intake and not to use other dietary supplements during the study.

RESULTS: HRW intervention significantly improved VO_{2max} as compared to placebo at 28-day follow-up (26.2 ± 4.8 ml/kg/min *vs.* 24.2 ± 4.1 ml/kg/min; $P = 0.03$). Differences were found for time to exhaustion and total work completed during an incremental exercise, with HRW resulting in improvement of both variables as compared to placebo ($P < 0.05$). IWQoL scores and hematological markers were not affected by either intervention ($P > 0.05$).

CONCLUSION: Results indicate that HRW can be used as an alternative hydration formulation to positively affect exercise performance in mid-age overweight women.

Supported by the Serbian Ministry of Education, Science and Technological Development (175037), the Provincial Secretariat for Higher Education and Scientific Research (114-451-710), the University of Novi Sad Faculty of Sport and PE (2017 Annual Award) and HRW Natural Health Products Inc, New Westminster, BC, Canada. Clinical trial registration http://www.clinicaltrials.gov, ID number NCT02832219.

Protective effect of hydrogen-rich water on liver function of colorectal cancer patients t reatedwith mFOLFOX6 chemotherapy.

Yang Q[1], Ji G[1], Pan R[1], Zhao Y[2], Yan P[3].

Author information

Abstract

The present study was conducted to investigate the protective effect of hydrogen-rich water on
the liver function of colorectal cancer (CRC) patients treated with mFOLFOX6 chemothe rapy. A controlled, randomized, single-blind clinical trial was designed. A total of 152 patients with CRC were recruited by the Department of Oncology of Taishan Hospital (Taian, China) between June 2010 and February 2016, among whom 146 met the inclusion criteria. Subsequently, 144 patients were randomized into the treatment (n=80) and placebo (n=64) groups. At the end of the study, 76 patients in the hydrogen treatment group and 60 patients in the placebo group were included in the final analysis. The changes in liver function after the chemotherapy, such as altered levels of alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, indirect bilirubin (IBIL) and direct bilirubin, were observed. The damaging effects of
the mFOLFOX6 chemotherapy on liver function were mainly represented by increased ALT, AST and IBIL levels. The hydrogen-rich water group exhibited no significant differences in liver function before and after treatment, whereas the placebo group

exhibited significantly elevated levels of ALT, AST and IBIL. Thus, hydrogen-rich water appeared to alleviate the mFOLFOX6-related liver injury.

Hydrogen-rich water for improvements of mood, anxiety, and autonomic nerve function in dailylife.

Mizuno K[1,2], Sasaki AT[1,3,4], Ebisu K[1,3], Tajima K[5,3], Kajimoto O[1,2], Nojima J[6], Kuratsune H[7], Hori H[1,3], Watanabe Y[1,8,4].

Author information

Abstract

Health and a vibrant life are sought by everyone. To improve quality of life (QOL), maintain a healthy state, and prevent various diseases, evaluations of the effects of potentially QOL-increasing factors are important. Chronic oxidative stress and inflammation cause deteriorations in central nervous system function, leading to low QOL. In healthy individuals, aging, job stress, and cognitive load over several hours also induce increases in oxidative stress, suggesting that preventing the accumulation of oxidative stress caused by daily stress and daily work contributes to maintaining QOL and ameliorating the effects of aging. Hydrogen has anti-oxidant activity and can prevent inflammation, and may thus contribute to improve QOL. The present study aimed to investigate the effects of drinking hydrogen-rich water (HRW) on the QOL of adult volunteers using psychophysiological tests, including questionnaires and tests of autonomic nerve function and cognitive function. In this double-blinded, placebo-controlled study with a two-way crossover design, 26 volunteers (13 females, 13 males; mean age, 34.4 ± 9.9 years) were randomized to either a group administered oral HRW (600 mL/d) or placebo water (PLW, 600 mL/d) for 4 weeks. Change ratios (post-treatment/pre-treatment) for K6 score and sympathetic nerve activity during the resting state were significantly lower after HRW administration than after PLW administration. These results suggest that HRW may reinforce QOL through effects that increase central nervous system functions involving mood, anxiety, and autonomic nerve function.

Effects of intravenous infusion of hydrogen-rich fluid combined with intra-cisternal infusion of magnesium sulfate in severe aneurysmal subarachnoid hemorrhage: study protocol for a randomized controlled trial.

Takeuchi S, Mori K, Arimoto H, Fujii K, Nagatani K, Tomura S, Otani N, Osada H, Wada K.

Abstract

BACKGROUND:
The failures of recent studies intended to prevent cerebral vasospasm have moved the focus of research into delayed cerebral ischemia away from cerebral artery constriction towards other mechanisms. Recent accumulating evidence has suggested that early brain injury is also involved in the development of delayed cerebral ischemia, and that hydrogen can prevent early brain injury. Therefore, we have established a combination therapy of intravenous hydrogen infusion and intra-cisternal magnesium sulfate infusion for the treatment of both early brain injury and cerebral vasospasm. The present randomized controlled clinical trial is designed to investigate the effects of this novel therapeutic strategy on the occurrence of cerebral vasospasm, delayed cerebral ischemia, and clinical outcomes after high-grade subarachnoid hemorrhage.

METHODS:
This study is a randomized, double-blind, placebo-controlled design to be conducted in two hospitals. A total of 450 patients with high-grade subarachnoid hemorrhage will be randomized to one of three arms: (i) Mg + H2 group, (ii) Mg group, and (iii) control group. Patients who are assigned to the Mg + H2 group will receive intra-cisternal magnesium sulfate infusion (2.5 mmol/L) at 20 mL/h for 14 days and intravenous hydrogen-rich fluid infusion (200 mL) twice a day for 14 days. Patients who are assigned to the Mg group will receive intra-cisternal magnesium sulfate infusion (2.5 mmol/L) at 20 mL/h for 14 days and intravenous normal glucose-electrolyte solution (200 mL) without added hydrogen twice a day for 14 days. Patients who are assigned to the control group will receive intra-cisternal Ringer solution without magnesium sulfate at 20 mL/h for 14 days and intravenous normal glucose-electrolyte solution (200 mL) without added hydrogen twice a day for 14 days. Primary outcome measures will be occurrence of delayed cerebral ischemia and cerebral vasospasm. Secondary outcome measures will be modified Rankin scale score at 3, 6, and 12 months and biochemical markers.

DISCUSSION:
The present protocol for a randomized, placebo-controlled study of intravenous hydrogen therapy with intra-cisternal magnesium infusion is expected to establish the efficacy and safety of this therapeutic strategy.

TRIAL REGISTRATION UMIN-CTR:
UMIN000014696.

Atomic hydrogen surrounded by water molecules, H(H2O)m, modulates basal and UV-induced gene expressions in human skin in vivo.

Shin MH[1], Park R, Nojima H, Kim HC, Kim YK, Chung JH.

Author information

Abstract

Recently, there has been much effort to find effective ingredients which can prevent or retard cutaneous skin aging after topical or systemic use. Here, we investigated the effects of the atomic hydrogen surrounded by water molecules, H(H2O)m, on acute UV-induced responses and as well as skin aging. Interestingly, we observed that H(H2O)m application to human skin prevented UV-induced erythema and DNA damage. And H(H2O)m significantly prevented UV-induced MMP-1, COX-2, IL-6 and IL-1β mRNA expressions in human skin in vivo. We found that H(H2O)m prevented UV-induced ROS generation and inhibited UV-induced MMP-1, COX-2 and IL-6 expressions, and UV-induced JNK and c-Jun phosphorylation in HaCaT cells. Next, we investigated the effects of H(H2O)m on intrinsically aged or photoaged skin of elderly subjects. In intrinsically aged skin, H(H2O)m application significantly reduced constitutive expressions of MMP-1, IL-6, and IL-1β mRNA. Additionally, H(H2O)m significantly increased procollagen mRNA and also decreased MMP-1 and IL-6 mRNA expressions in photoaged facial skin. These results demonstrated that local application of H(H2O)m may prevent UV-induced skin inflammation and can modulate intrinsic skin aging and photoaging processes. Therefore, we suggest that modifying the atmospheric gas environment within a room may be a new way to regulate skin functions or skin aging.

Hydrogen(H2) treatment for acute erythymatous skin diseases. A report of 4 patients with safety data and a non-controlled feasibility study with H2 concentration measurement on two volunteers.

Ono H[#1], Nishijima Y[#1], Adachi N[#1], Sakamoto M[#1], Kudo Y[#1], Nakazawa J[#1], Kaneko K[#1], Nakao A[#2].

Author information

Abstract

BACKGROUND:
We have treated 4 patients of acute erythematous skin diseases with fever and/or pain by H2 enriched intravenous fluid. We also added data from two volunteers for assessing the mode of H2 delivery to the skin for evaluation of feasibility of H2 treatment for this type of skin diseases.

METHODS:
All of the four patients received intravenous administration of 500 ml of H2 enriched fluid in 30 min for more than 3 days except in one patient for only once. From two volunteers (one for intravenous H2 administration and the other for H2 inhalation), blood samples were withdrawn serially and air samples were collected from a heavy duty plastic bag covering a leg, before, during and after H2 administration. These samples were checked for H2 concentration immediately by gas chromatography. Multiple physiological parameters and blood chemistry data were collected also.

RESULTS:
Erythema of these 4 patients and associated symptoms improved significantly after the H2 treatment and did not recur. Administration of H2 did not change physiological parameters and did not cause deterioration of the blood chemistry. The H2 concentration in the blood from the volunteers rapidly increased with H2 inhalation and slowly decreased with cessation of H2 particularly in the venous blood, while H2 concentration of the air from the surface of the leg showed much slower changes even after H2 inhalation was discontinued, at least during the time of sample collection.

CONCLUSION:
An improvement in acute erythemtous skin diseases followed the administration of H2 enriched fluid without compromising the safety. The H2 delivery study of two volunteers suggested initial direct delivery and additional prolonged delivery possibly from a slowly desaturating reservoir in the skin to the surface.

KIDNEY

Novel haemodialysis (HD) treatment employing molecular hydrogen (H_2)-enriched dialysis solution improves prognosis of chronic dialysis patients: A prospective observational study

Masaaki Nakayama,[1,2,3] Noritomo Itami,[4] Hodaka Suzuki,[5] Hiromi Hamada,[4] Ryo Yamamoto,[6] Kazumasa Tsunoda,[7] Naoyuki Osaka,[8] Hirofumi Nakano,[9] Yukio Maruyama,[10] Shigeru Kabayama,[1,2] Ryoichi Nakazawa,[11] Mariko Miyazaki,[1,2] and Sadayoshi Ito[1]

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Abstract

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Introduction

The combination of enhanced oxidative stress and inflammation in patients on chronic haemodialysis (HD) treatment plays a crucial role in the occurrence of excessive cardiovascular events and death[1,2]. The bio-incompatibility of the HD procedure is supposed to be involved with this pathology. HD may exaggerate leukocyte activation and injury[3–5], which enhance oxidative stress and inflammation. Therefore, we hypothesized that ameliorating the stress to leukocytes during HD may have a beneficial effect on patient outcomes.

Molecular hydrogen (H_2) is an inert gas with no known side effects. Recent studies have shown that H_2acts as an antioxidant and an anti-inflammatory agent, and ameliorates cellular and organ damage[6,7]. We therefore developed a novel HD system using highly dissolved H_2 water rendered by the water electrolysis technique[8–10]. Previous pilot studies, including ours, have reported that suppression of interleukin-6, high-sensitivity C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1)/chemokine (C-C motif) ligand 2 (CCL2), and myeloperoxidase (MPO), decrease oxidative injury of lymphocytes, improve the redox status of serum albumin, and ameliorate hypertension[8–14]. In reference to these findings, we conducted a non-randomized, non-blinded, prospective observational study to compare the outcomes between patients receiving haemodialysis using an H_2-enriched dialysis solution (E-HD group) and patients receiving conventional haemodialysis (C-HD group).

Go to:

Results

Patient registration and characteristics

Patients were recruited during April 2011 and October 2012. Of the 327 prevalent chronic HD patients who were pre-registered, 18 were excluded because of the lack of data and withdrawal. Ultimately, 148 patients were allocated to the C-HD group and 161 patients were allocated to the E-HD group (Fig. 1). The patients' characteristics in the two groups at baseline are shown in Table 1. All subjects were treated by the standard HD schedule (three sessions/week, 4–5 h/session), using high-performance

biocompatible dialyzers with fixed blood flow rate (QB) (200 mL/min) and dialysate flow rate (QD) (500 mL/min). Patients who had been treated by a vitamin-E coated dialyzer were excluded from this study. At baseline, there was no statistical difference between the groups in the blood urea nitrogen (BUN) reduction rate by HD (69.7 ± 6.9% in the C-HD group and 70.3 ± 8.4% in the E-HD group; p = 0.485).

Hydrogen-Rich Saline Attenuates Acute Kidney Injury After Liver Transplantation via Activating p53-Mediated Autophagy

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Original Basic Science—Liver

Background Acute kidney injury (AKI) impacts the survival of liver transplant recipients severely. To date, the related mechanism and effective therapy have not been rigorously explored. The present study aimed to explore the role of p53-mediated autophagy in the protective effect of hydrogen-rich saline (HRS) on AKI after orthotropic liver transplantation (OLT).

Methods Adult male Sprague-Dawley rats were randomly allocated into four groups: sham, OLT, OLT with HRS (6 ml/kg) pretreatment (HS), OLT with HRS and chloroquine pretreatment (60 mg/kg) group (CQ). All the samples were collected 6 hours after reperfusion. The renal function and oxidative stress level were measured by biochemical and histopathologic examinations. The formation of autophagosome was observed by transmission electron microscopy. The apoptotic rate was determined by terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labeling analysis. The expression of caspase-3, cytochrome c, p53, damage-regulated autophagy modulator, Becline-1, microtubule-associated protein light 3-II, p62, lysosome-associated membrane protein-2, and the phosphorylation of p53 were assayed by western blot assay.

Results Compared with the OLT group, HRS dramatically attenuated the histopathologic damage, restored the renal function, and decreased the oxidative stress level. Simultaneously, HRS significantly ameliorated apoptosis by decreasing the apoptotic rate and inhibiting the expression of caspase-3 and cytochrome c in rats subjected to OLT. The expression of Becline-1 and microtubule-associated protein light 3-II were upregulated with the inhibition of p62 and lysosome-associated membrane protein-2. The inhibition of autophagy by chloroquine counteracted the renoprotective effects of HRS.

Conclusions HRS is able to protect against AKI after liver transplantation partly by reducing apoptosis, which is possibly involved in the modulation of p53-mediated autophagy.

Acute kidney injury (AKI) is one of the common complications in the immediate postoperative period of liver transplantation and associated with significant morbidity and mortality. Over 30% to 50% recipients have experienced postoperative AKI.[1] A wide array of factors are responsible for the prevalence of AKI. Hypotension has been considered to be a crucial independent risk factor of renal ischemia-reperfusion (I/R) injury during perioperative period of liver transplantation.[2] Several pharmacologic agents with the potential to reduce I/R injury have been characterized so far,[3,4]but none has yet been translated into clinical application.

Although the mechanisms underlying I/R injury are complex, both apoptosis and autophagy play vital roles in the progression of cell death induced by I/R.[5,6] Although the comprehensive picture depicting apoptotic regulation has been well explored, the mechanism of autophagy is still unclear. Accumulating evidence reveals that the crosstalk between autophagy and apoptosis is considered to be the turning point of cell fate, and several pathways have been delineated to provide mechanistic insight into this connection.[7,8] In the network, some regulators, such as Bcl-2 family members and PI3K/Akt signaling proteins in the process of apoptosis, have been found to modulate autophagy simultaneously.[9,10] P53 is a crucial transcription factor which mediates the cell cycle arrest associated with I/R injury.[11] Intriguingly, several recent literatures have highlighted the functional connection of p53 between autophagy and apoptosis.[12]

The activation of autophagy by p53 is partly attributed to the inhibition of the negative regulator of autophagy (mammalian target of rapamycin) and the stimulation of AMP kinase or damage-regulated autophagy modulator (DRAM).[13] In several settings (in vitro and in vivo), pharmacological or genetic inhibition of p53-mediated autophagy contributed to apoptosis in response to diverse stresses, pointing to p53 appears to be a significant component in the network controlling apoptosis and autophagy.[14,15] Also, the activation of p53 was speculated to be therapeutically desirable for I/R treatment.

As a novel antioxidant, hydrogen possesses antioxidative property by selectively neutralizing cytotoxic reactive oxygen species, such as •OH and ONOO.[16,17] Ohsawa et al[18] demonstrated the protective effect of hydrogen against cerebral I/R injury via attenuating the production of cytotoxic reactive oxygen species. In addition, hydrogen could also suppress diseases induced by inflammation, such as acute peritonitis, intestinal injury, and so on.[19,20] However, the therapeutic mechanism underlying its protective effects in organ transplantation has not been completely elucidated.

Herein, the present study was aimed to explore the protective effect of hydrogen-rich saline (HRS) on AKI of rats after orthotropic liver transplantation (OLT) and to investigate the potential role of p53-mediated autophagy in hydrogen-offered protection.

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MATERIALS AND METHODS

Experimental Animals

Adult male Sprague-Dawley rats weighing 220 ± 10 g were obtained from the Laboratory Animal Center, The People's Liberation Army Military Academy of Medical Sciences, Beijing, China. All animal care and experimental procedures were strictly under obligations of Institutional Animal Care and Use Committee of Tianjin First Center Hospital. All efforts were made to minimize suffering. Acclimatized to the environment for 5 days, rats were randomly assigned into 4 groups: sham-operated (sham), OLT, OLT rats injected with 6 mL/kg HRS through infrahepatic vena cava 5 minutes before ischemia (HS), and OLT rats pretreated with 6 mL/kg HRS and chloroquine (60 mg/kg) intraperitoneally just before ischemia (CQ).

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Materials and Reagents

Chloroquine (Sigma, St. Louis, MO) was diluted in phosphate-buffered saline (PBS). Malondialdehyde (MDA) and superoxide dismutase (SOD) detection kits were purchased from Jiancheng Biotech (Jiangsu, China). The primers of caspase-3 and cytochrome c (cyt c) were purchased from Augct Biotech (Beijing, China). The antibodies against p53, p-p53, DRAM, Beclin1, microtubule-associated protein light 3-II (LC3-II), p62, caspase-3, cyt c, glyceraldehyde-3-phosphate dehydrogenase, and tubulin were purchased from Cell Signaling Technology (Beverly, MA). Lysosome-associated membrane protein-2 (LAMP-2) was purchased from Santa Cruz Biotechnology (Santa Cruz, CA).

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HRS Production

Hydrogen was dissolved in normal saline under the pressure of 0.5 MPa for 7 hours to reach the saturation by using the apparatus (Hydrovita Biotechnology Co, Beijing, China). Then, the saturated HRS was stored under atmospheric pressure at 4°C and then sterilized with γ radiation. The concentration of HRS was 0.6 mmol/L measured by gas chromatography. Hydrogen-rich saline would be prepared every week to maintain the saturated concentration.

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Establishment of Rat OLT Models

The OLT model was performed as described by Kamada et al.[21] Donor liver was harvested in a standardized procedure, which included dissecting the liver from the ligaments and vessels, cannulating the common bile duct with a 22G stent, retracting liver lobes in situ to minimize the harvest-dependent injury. Then, the graft was flushed with 4°C solution under a pressure of 10 cm H_2O before implantation. After removing from the original liver, the OLT operation was performed in the hepatectomized recipient rat by the following steps: anastomosing the suprahepatic vena cava with a running 7/0 polyproplene suture, inserting cuffs into the related vessels to reestablish the blood flow and connecting the bile duct with the splint technique. During the operation, the portal vein was clamped for 25 to 30 minutes. The rats were allowed to drink glucose water without any food. All the samples were collected 6 hours after reperfusion.

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The Assay of Mean Arterial Pressure

The right carotid artery was catheterized with a polyethylene catheter (outer diameter, 0.96 mm; inner diameter, 0.66 mm) to monitor mean arterial pressure (MAP),[22] the recording time points of which were as follows: before the OLT operation, before vascular clamped, the anhepatic phase (1 minute, 15 minutes), after portal vein unclamped (reperfusion, 1 minute, 15 minutes), before operation finished, and after operation for 10 minutes. The carotid artery was filled with heparinized saline (30 U/mL) to prevent the clot formation.

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Histopathologic Examination

The tissues were embedded in paraffin after fixation in 10% phosphate-buffered formalin for 12 hours. Then they were sectioned at 4-μm thick and stained with hematoxylin-eosin before the examination under light microscopy (Olympus BX51, Tokyo, Japan). Each sample was examined by the same pathologist in a blinded study. Morphological changes were scored from 0 to 4 to assess the degree of renal damage as described by Jablonski et al[23] (Table 1).

TABLE 1

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Determination of Renal Function

The renal function of rats after OLT was evaluated using the parameters of blood urea nitrogen (BUN) and serum creatinine (Cr), which were measured using an automated clinical chemistry analyzer (AU5400; Beckman Coulter).

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Assessment of Oxidative Stress Parameters

Each sample from different groups was homogenized and centrifuged for detecting the level of MDA and SOD by commercially available kits. The concentration of MDA was measured by the thiobarbituric acid method. The SOD activity was measured using the nitroblue tetrazolium method.

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Deoxynucleotide Transferase-Mediated Deoxyuridine Triphosphate Nick-End Labeling Assay

To identify the apoptotic nuclei quantitatively, the terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) was performed. Briefly, tissue sections were deparaffinized and rehydrated by heating at 65°C, followed by incubation in protease K (10 μg/mL) for 30 minutes at room temperature. After washing in PBS twice, the sections were exposed to the TUNEL reaction mixture for 1 hour at 37°C in a humidified atmosphere without light. The apoptotic cells stained with 4′,6-diamidino-2-phenylindole were examined by the fluorescence microscopy. The apoptotic index was calculated in a total of 10 representative fields (400× magnification) from each tissue section.

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Transmission Electron Microscopy

Kidney samples from each group were carefully immersed in the fixative solution (2.5% glutaraldehyde) overnight. Then, the tissues of approximately 1 mm^3 were washed with PBS for 3 times, fixed in 10% buffered glutaraldehyde and 1% osmic acid, dehydrated, embedded, and finally sliced. The ultrastructure of autophagosome was observed under a transmission electron microscope by the same histologist who was unaware of the group of each sample.

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Quantitative Real-Time Polymerase Chain Reaction

Total RNA was extracted from renal tissue using RNAeasy kit (Qiagen, Hilden, Germany). Also, 4 μg was reverse-transcribed into complementary (c)DNA by using the first-strand cDNA synthesis kit (Takara, Japan). The thermal cycling conditions were as follows: denaturation for 1 minute at 95°C, 40 cycles of 5 seconds at 95°C, 30 seconds at 58°C, and 30 seconds at 72°C, and dissolve curve analysis for 15 seconds at 95°C, 1

minute at 60°C, and 15 seconds at 95°C. The primer sequences used to amplify the desired cDNA were shown in Table 2. The polymerase chain reaction products were normalized to β-actin levels.

TABLE 2

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Western Blot Analysis

Kidney tissues were rapidly lysed in 200 μL of extraction protein buffer. After homogenization on ice for 30 minutes, the supernatant was centrifuged at 12 000*g* for 10 minutes, and the content would be calculated with Bradford assay. Then total protein were boiled in water for 5 minutes to denature the protein. Equal amounts of protein were loaded on 10% sodium dodecyl-sulfate-polyacrylamide gel electrophoresis and transferred to the polyvinylidene difluoride membrane. After being blocked in 5% (w/v) skimmed milk powder-Tris–buffered saline with 0.1% Tween 20 for 1 hour at 37°C, the membranes were probed with antibodies against p53, p-p53, DRAM, Beclin1, LC3-II, p62, LAMP-2, caspase-3, cyt c, glyceraldehyde-3-phosphate dehydrogenase and tubulin overnight at 4°C, respectively. Subsequently, the membranes were incubated with secondary peroxidase-conjugated antibodies at room temperature for 2 hours. Blots were quantified by Image-Pro Plus Software. The glyceraldehyde-3-phosphate dehydrogenase and tubulin were taken as endogenous control, and the densitometry values were used for normalizing the expression of different proteins.

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Statistical Analysis

Histologic damage scores were expressed as median ± interquartile range and the statistical significance was calculated by Kruskale-Wallis H test. Other data were expressed as mean ± SD and analyzed by 1-way analysis of variance. A *P*value less than 0.05 was considered to be statistically significant. All statistical tests were performed with SPSS20.0.

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RESULTS

The Levels of Rat MAP During OLT

According to Table 3, it shows a significantly lower value of MAP during the anhepatic phase. After the blood flow was reestablished, the MAP gradually recovered to the normal value. The results above indicated that blood reflux disorders including the severe hypotension during the anhepatic phase might be partly responsible for the AKI after OLT.

TABLE 3

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Effect of HRS Pretreatment on Renal Function of Rats Induced by OLT

To investigate the effect of HRS on renal damage after OLT, we checked the level of Cr and BUN in serum (Figures 1A, B). Orthotropic liver transplantation dramatically elevated the Cr and BUN levels compared with the sham-treated rats ($P < 0.05$). The increase in Cr and BUN values were reduced by administering HRS ($P < 0.05$). Pretreatment with chloroquine aggravated the renal damage compared with the HS group ($P < 0.05$). These findings suggest that HRS could improve the renal function of rats after OLT.

Consumption of hydrogen-rich water alleviates renal injury in spontaneous hypertensive rats.

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Author information

Abstract

In hypertensive animals and patients, oxidative stress represents the primary risk factor for progression of renal disease. Recently, it has been demonstrated that hydrogen, as a novel antioxidant, can selectively reduce hydroxyl radicals and peroxynitrite anion to exert therapeutic antioxidant activity. Herein, we investigated the protective effect of hydrogen-rich water (HW) against renal injury in spontaneously hypertensive rats (SHR). The 8-week-old male SHR and age-matched Wistar-Kyoto rats were randomized into HW-treated (1.3 ± 0.2 mg/l for 3 months, drinking) and vehicle-treated group. Although treatment with HW had no significant effect on blood pressure, it significantly ameliorated renal injury in SHR. Treatment with HW lowered reactive oxygen species formation, upregulated the activities of superoxide dismutase, glutathione peroxidase, glutathione-S-epoxide transferase, and catalase, and

suppressed NADPH oxidase activity. Treatment with HW in SHR depressed pro-inflammatory cytokines expression including TNF-α, IL-6, IL-1β, and macrophage chemoattractant protein 1, which might be mediated by suppressing nuclear factor-κB activation. In addition, treatment with HW had protective effect on mitochondrial function including adenosine triphosphate formation and membrane integrity in SHR. In conclusion, consumption of HW is a promising strategy to alleviate renal injury as a supplement for anti-hypertensive therapy.

Electrolysed-reduced water dialysate improves T-cell damage in end-stage renal disease patients with chronic haemodialysis.

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Author information

Abstract

BACKGROUND:

T-cell damage by increased oxidative stress in end-stage renal disease (ESRD) patients undergoing chronic haemodialysis (HD) led to the increased T-cell apoptosis and the alteration of surface markers and Th1/Th2 ratio in CD4(+) T lymphocytes. Antioxidant electrolysed-reduced water (ERW) was used as the dialysate in ESRD patients undergoing chronic HD to test for improved oxidative stress-related T-cell apoptosis, alterations of surface markers and intracellular cytokine profile.

METHODS:

We evaluated apoptosis formation by annexin V, CD25-related surface markers, and cytokine ratio of Th1/Th2 in CD4(+) T lymphocytes and Tc1/Tc2 in CD8(+) T lymphocytes of 42 ESRD patients haemodialysed with ERW for 1 year.

RESULTS:

In comparison to 12 healthy individuals, the ESRD patients had more T-cell apoptosis and less CD3(+), CD4(+) and CD8(+) T cells and CD25/CD69/CD94/CD3(+) phenotypes at baseline. Lower intracellular IL-2 and IFN-gamma levels in the Th1/CD4(+) and Tc1/CD8(+) cells and higher intracellular IL-4, IL-6 and IL-10 levels in the Th2/CD4(+) and Tc2/CD8(+) cells were also noted in the ESRD patients. After a 1-year ERW treatment, the patients had a decrease in T-cell apoptosis and increases in CD3(+), CD4(+) and CD8(+) cell numbers and CD25/CD69/CD94/CD3(+) phenotypes in

the T cells. The intracellular IL-2 and IFN-gamma levels in the Th1/Tc1 cells significantly ($P < 0.05$) increased and the intracellular IL-4, IL-6 and IL-10 levels in the Th2/Tc2 cells decreased. Furthermore, the Th1/Th2 and Tc1/Tc2 cytokine ratios were improved toward a normal status.

CONCLUSION:
One-year ERW treatment effectively ameliorated T-cell apoptosis, altered CD25-related surface markers and intracellular cytokine profile in the HD patients.

LIVER

Hydrogen-rich saline protects against small-scale liver ischemia-reperfusion injury by inhibiting endoplasmic reticulum stress☆

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Abstract

Aim

Our research investigated the role of Hydrogen-rich saline (HRS) on the Endoplasmic reticulum stress (ERS) pathway and the effect of HRS on tissue injury in small Bama pig model of hepatic ischemia-reperfusion combined with partial hepatectomy.

Main methods

Eighteen healthy Bama miniature pigs were randomly divided equally into three groups: Sham, IRI, and HRS. Laparoscopic technique was employed to establish the model of hepatic ischemia-reperfusion combined with partial hepatectomy. HRS (10 mL/kg) was

injected into the portal vein 10 min before perfusion. Histological examinations of the liver tissues were performed after HE staining. Additionally, transmission electron microscopywas performed to detect liver cell microstructure. Real-time PCR, Western blotting, and immunohistochemical staining were performed to analyze various ERS molecules including GRP78, p-eIF2α, XBP-1s, Full-length ATF6α, p-JNK, ATF4, and CHOP.

Key findings

We observed that HRS visibly improved ischemia-reperfusion injury (IRI) by reducing various parameters of ERS stress as evidenced by down-regulation of the mRNA as well as protein levels of GRP78, p-eIF2α, XBP-1s, p-JNK, and CHOP, and reducing the cleavage of Full-length ATF6α.

Significance

Our study demonstrates that HRS protects the liver from IRI by inhibiting ERS.

Effect of hydrogen-rich water on oxidative stress, liver function, and viral load in patients with chronic hepatitis B.

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Author information

Abstract

OBJECTIVE:

To investigate effects of hydrogen-rich water (HRW) on oxidative stress, liver function and HBV DNA in patients with chronic hepatitis B (CHB).

METHODS:

Sixty patients with CHB were randomly assigned into routine treatment group or hydrogen treatment group in which patients received routine treatment alone or additional oral HRW (1200-1800 mL/day, twice daily), respectively, for 6 consecutive weeks. Serum oxidative stress, liver function, and HBV DNA level were detected before and after treatment. Thirty healthy subjects served as controls.

RESULTS:

When compared with controls, oxidative stress was obvious in CHB patients, and the liver function also significantly impaired. After treatment, the oxidative stress remained unchanged in routine treatment group, but markedly improved in hydrogen treatment

group. The liver function was improved significantly and the HBV DNA reduced markedly after corresponding treatments. Although a significant difference was noted in the oxidative stress between two groups after treatment, the liver function and HBV DNA level were comparable after treatment and both had improved tendencies.

CONCLUSION:
HRW significantly attenuates oxidative stress in CHB patients, but further study with long-term treatment is required to confirm the effect of HRW on liver function and HBV DNA level.

Inhalation of hydrogen gas reduces liver injury during major hepatotectomy in swine.

Xiang L[1], Tan JW, Huang LJ, Jia L, Liu YQ, Zhao YQ, Wang K, Dong JH.

Author information

Abstract

AIM:
To study the effect of H2 gas on liver injury in massive hepatectomy using the intermittent Pringle maneuver in swine.

METHODS:
Male Bama pigs (n = 14) treated with ketamine hydrochloride and Sumianxin II as induction drugs followed by inhalation anesthesia with 2% isoflurane, underwent 70% hepatotectomy with loss of bleeding less than 50 mL, and with hepatic pedicle occlusion for 20 min, were divided into two groups: Hydrogen-group (n = 7), the pigs with inhalation of 2% hydrogen by the tracheal intubation during major hepatotectomy; contrast-group (n = 7), underwent 70% hepatotectomy without inhalation of hydrogen. Hemodynamic changes and plasma concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), hyaluronic acid (HA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and malondialdehyde (MDA) in liver tissue were measured at pre-operation, post-hepatotectomy (PH) 1 h and 3 h. The apoptosis and proliferating cell nuclear antigen (PCNA) expression in liver remnant were evaluated at PH 3 h. Then we compared the two groups by these marks to evaluate the effect of the hydrogen in the liver injury during major hepatotectomy with the Pringle Maneuver in the swine.

RESULTS:

There were no significant differences in body weight, blood loss and removal liver weight between the two groups. There was no significant difference in changes of portal vein pressure between two groups at pre-operation, PH 30 min, but in hydrogen gas treated-group it slightly decrease and lower than its in contrast-group at PH 3 h, although there were no significant difference (P = 0.655). ALT and AST in Hydrogen-group was significantly lower comparing to contrast-group (P = 0.036, P = 0.011, vs. P = 0.032, P = 0.013) at PH 1 h and 3 h, although the two groups all increased. The MDA level increased between the two group at PH 1 h and 3 h. In the hydrogen gas treated-group, the MDA level was not significantly significant at pre-operation and significantly low at PH 1 h and 3 h comparing to Contrast-group (P = 0.0005, P = 0.0004). In Hydrogen-group, the HA level was also significantly low to contrast-group (P = 0.0005, P = 0.0005) although the two groups all increased at PH 1 h and 3 h. The expression of cluster of differentiation molecule 31 molecules Hydrogen-group was low to Contrast-group. However, PCNA index (%) was not statistically significant between the two groups (P = 0.802). Microphotometric evaluation of apoptotic index (AI) in terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling-stained tissue after hepatotectomy for 3h, the AI% level in the hydrogen was significantly low to contrast-group (P = 0.012). There were no significant difference between Hydrogen-group and contrast-group at pre-operation (P = 0.653, P = 0.423), but after massive hepatotectomy, the TNF-α and IL-6 levels increase, and its in Hydrogen-group was significantly low compared with contrast-group (P = 0.022, P = 0.013, vs. P = 0.016, P = 0.012), respectively. Hydrogen-gas inhalation reduce levels of these markers and relieved morphological liver injury and apoptosis.

CONCLUSION:

H2 gas attenuates markedly ischemia and portal hyperperfusion injury in pigs with massive hepatotectomy, possibly by the reduction of inflammation and oxidative stress, maybe a potential agent for treatment in clinic.

Hydrogen from intestinal bacteria is protective for Concanavalin A-induced hepatitis.

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Author information

Abstract

It is well known that some intestinal bacteria, such as Escherichia coli, can produce a remarkable amount of molecular hydrogen (H(2)). Although the antioxidant effects of H(2) are well documented, the present study examined whether H(2) released from intestinally colonized bacteria could affect Concanavalin A (ConA)-induced mouse hepatitis. Systemic antibiotics significantly decreased the level of H(2) in both liver and intestines along with suppression of intestinal bacteria. As determined by the levels of AST, ALT, TNF-alpha and IFN-gamma in serum, suppression of intestinal bacterial flora by antibiotics increased the severity of ConA-induced hepatitis, while reconstitution of intestinal flora with H(2)-producing E. coli, but not H(2)-deficient mutant E. coli, down-regulated the ConA-induced liver inflammation. Furthermore, in vitro production of both TNF-alpha and IFN-gamma by ConA-stimulated spleen lymphocytes was significantly inhibited by the introduction of H(2). These results indicate that H(2) released from intestinal bacteria can suppress inflammation induced in liver by ConA.

Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation.

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Author information

Abstract

Molecular hydrogen reacts with the hydroxyl radical, a highly cytotoxic species produced in inflamed tissues. It has been suggested therefore to use gaseous hydrogen in a new anti-inflammatory strategy. We tested this idea, with the aid of the equipment and skills of COMEX SA in Marseille, a group who experiments with oxygen-hydrogen breathing mixtures for professional deep-sea diving. The model used was schistosomiasis-associated chronic liver inflammation. Infected animals stayed 2 weeks in an hyperbaric chamber in a normal atmosphere supplemented with 0.7 MPa hydrogen. The treatment had significant protective effects towards liver injury, namely decreased fibrosis, improvement of hemodynamics, increased NOSII activity, increased antioxidant enzyme activity, decreased lipid peroxide levels and decreased circulating TNF-alpha levels. Under the same conditions, helium exerted also some protective effects, indicating that hydroxyl radical scavenging is not the only protective mechanism. These findings indicate that the proposed anti-inflammatory strategy deserves further attention.