Molecular hydrogen: a therapeutic antioxidant and beyond

Lei Huang1, 2,*

1 Department of Anesthesiology, Loma Linda University, Loma Linda, CA, USA
2 Department of Basic Sciences, Division of Physiology, Loma Linda University, Loma Linda, CA, USA
*Correspondence to: Lei Huang, M.D., lhuang@llu.edu.

Abstract

Molecular hydrogen (H₂) medicine research has flourished since a landmark publication in Nature Medicine that revealed the antioxidant and cytoprotective effects of hydrogen gas in a focal stroke model. Emerging evidence has consistently demonstrated that molecular hydrogen is a promising therapeutic option for a variety of diseases and the underlying comprehensive mechanisms is beyond pure hydroxyl radicals scavenging. The non-toxicity at high concentrations and rapid cellular diffusion features of molecular hydrogen ensure the feasibility and readiness of its clinical translation to human patients.

Key words: hydrogen-saturated water/saline; hydrogen gas; free radical scavenger; anti-inflammation; anti-apoptosis; biological effect; clinical application; hydrogen-oxygen nebulizer machine

doii: 10.4103/2045-9912.196904

How to cite this article: Huang L (2016) Molecular hydrogen: a therapeutic antioxidant and beyond. Med Gas Res 6(4):219-222.

Open access statement: This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

INTRODUCTION

Molecular hydrogen (H₂), the most lightweight gas, is routinely used as a component of exotic breathing gas mixture, namely hydreliox (49% H₂, 50% helium and 1% O₂) for deep water divers to prevent decompression sickness (Abraini et al., 1994; Ohta, 2011). Therapeutic application of H₂ as a free radical catalyzer debuted in 1970s. A 2-week treatment of hyperbaric 97.5% H₂ gas in the absence of explosion risk caused a significant regression of skin tumor or leukemia in animals (Dole et al., 1975; Roberts et al., 1978). It was postulated that the underlying mechanism was through hydroxyl radicals scavenging by exthermic reaction of H₂ + ·OH = H₂O + H· followed by H· + O₂⁻ = HO₂⁻ reaction (Dole et al., 1975). In 2001, Gharib et al. (2001) confirmed the similar treatment efficacy of hyperbaric hydrogen against parasite-induced mice liver inflammation, consistently suggesting the protective mechanism at least in part by the reaction of molecular hydrogen with hydroxyl radicals. Five years later, Ohsawa et al. (2007) intensively elucidated the selective antioxidant feature of normobaric 2% H₂ gas (below the 4% explosion level) and its cytoprotective benefit against reperfusion oxidative injury using cell culture in vitro and a rat model of focal stroke in vivo. The finding added hydrogen as an innovative approach into a collection of therapeutic strategies against stroke (Dock et al., 2015; Li et al., 2015; Lioutas et al., 2015; Merali et al., 2015; Pena and Borlongan, 2015; Ploughman et al., 2015; Qi et al., 2015; Reuter et al., 2015; Schlunk et al., 2015; Soliman et al., 2015; Zhu et al., 2015). The antioxidant advantages of H₂ gas included: 1) its high biomembrane penetration and intracellular diffusion capability which enable it to reach subcellular compartments like mitochondria; and 2) selectively scavenging the deleterious hydroxyl radical while preserving other important reactive oxygen and nitrogen species for normal signaling regulation. It is superior to some antioxidant supplements with strong reductive activity such as vitamin C or vitamin E to avoid the increased risk of mortality (Ohsawa et al., 2007). Since this landmark publication

© 2016 Medical Gas Research | Published by Wolters Kluwer - Medknow
in *Nature Medicine*, research on the molecular hydrogen medicine has blossomed worldwide. Emerging evidence has demonstrated the pleiotropic therapeutic effects of molecular hydrogen in a variety of animal disease models and some human patients (Huang et al., 2010; Ohta, 2011; Dixon et al., 2013; Ishibashi et al., 2015; Kurokawa et al., 2015), which are comparable to what has been found with other traditional therapeutic gases regimens including hyperbaric/normobaric oxygen (Harch, 2015; Hu et al., 2015; Parra et al., 2015; Stoller, 2015; Weaver and Liu, 2015; Yan et al., 2015) and hydrogen sulfide (H,S) (Herrera et al., 2015; Langston and Toombs, 2015). H$_2$ is now considered as a signaling gaseous molecule with physiological functions similar to that of nitric oxide (NO), carbon monoxide (CO), and H$_2$S (Kajimura et al., 2012). Indeed, H$_2$ has no cytotoxicity even at high concentration, which ensures the safety privilege compared to the other gases (Ohta, 2011).

**Administration and Biological Benefit of Molecular Hydrogen**

Three administration forms of molecular hydrogen, namely 1–4% hydrogen gas inhalation, hydrogen-rich saline intraperitoneal injection/ intravenous infusion and oral intake of hydrogen-saturated water, have been commonly used in hydrogen medical research (Kurokawa et al., 2015; Wang et al., 2015). H$_2$ concentrations in the tissues depend on the administered H$_2$ concentration and specific tissue H$_2$ uptake is related to the difference in administration route, indicating the importance to choosing most efficient delivery route and hydrogen dose for each disease or tissue (Liu et al., 2014). The therapeutic effect of molecular hydrogen H$_2$ has been demonstrated in the central nervous system, cardiovascular system, lung, kidney, liver, pancreas, skin, eye, bone and reproduction system which have the underlying pathological conditions of ischemia-reperfusion injury (including organ transplantation) and the predominant oxidative stress-mediated diseases (Huang et al., 2010; Ohta, 2011, 2015; Ichihara et al., 2015; Nakata et al., 2015; Iketani and Ohsawa, 2016). In a comprehensive review in 2015, Ichihara et al. have nicely summarized the biological benefit of molecular hydrogen in all organs covering 31 disease categories that can be subdivided into 166 disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants (Ichihara et al., 2015). Although the underlying mechanisms were initially proposed as selective extinctions of hydroxyl radical and peroxynitrite, the signaling pathway regulation effect of molecular hydrogen by modulating a various molecules expressions/activities, gene expression and microRNA may also account for the ultimate effects of anti-reperfusion injury, anti-inflammation, anti-apoptosis, anti-metabolic disorders, anti-allergy, anti-radiation injury, anti-dementia as well as anti-aging (Ichihara et al., 2015; Hara et al., 2016; Li et al., 2016; Shao et al., 2016).

**Clinical Applications of Molecular Hydrogen**

Up to date, the clinical applications of molecular hydrogen to human patients has been conducted. The small cohort patients studies or case reports revealed the safety or some promising benefits of therapeutic hydrogen in the a variety range of diseases and pathological status such as post-cardiac syndrome, Parkinson’s disease, acute cerebral ischemia, metabolic syndrome, rheumatoid arthritis, hemodylisis and postpsoriasis (Ichihara et al., 2015; Nakata et al., 2015; Tamura et al., 2016). More large-scale prospective clinical studies on Parkinson’s disease, acute post-cardiac arrest syndrome and myocardial infarction as well as cerebral infarction are currently ongiong (Ichihara et al., 2015).

**Conclusion**

Overall, the impact of molecular hydrogen in medicine is extraordinary. The non-toxic and rapid intracelluar diffusion features of this biological gas ensure the feasibility and readiness for its clinical translation. Future preclinical studies are warranted to further elucidate the upstream master regulator(s) that drive molecular hydrogen-induced modifications of downstream effectors. It is also of importance to clarify the best administration modality and the optimal hydrogen dose regimen for each disease model preclinically and subsequently in sepcific patient population. A newly developed hydrogen-oxygen nebulizer machine (AMS-H-01, Asclepius Meditec Co., Ltd., Shanghai, China) is able to produce 66% hydrogen gas without the risk of spontaneous combustion. Given a dose-dependent benefit of hydrogen observed in the previous preclinical studies (Ohta, 2011; Ichihara et al., 2015), the therapeutic efficacy of such high hydrogen concentration deserves full investigation. Moreover, the well-designed multi-center clinical trials are expected to provide more solid evidences regarding to the effects of hydrogen in human patients.

**Author contributions**

LH conceived and wrote the manuscript as well as gathered the references. The author read and approved the final manuscript.
References

Abraini JH, Gardette-Chauffour MC, Martinez E, Rostain JC, Lemaire C (1994) Psychophysiological reactions in humans during an open sea dive to 500 m with a hydrogen-helium-oxygen mixture. J Appl Physiol 76:1113-1118.

Dixon BJ, Tang J, Zhang JH (2013) The evolution of molecular hydrogen: a noteworthy potential therapy with clinical significance. Med Gas Res 3:10.

Dock H, Theodorsson A, Theodorsson E (2015) DNA methylation inhibitor zebularine confers stroke protection in ischemic rats. Transl Stroke Res 6:296-300.

Dole M, Wilson FR, Fife WP (1975) Hyperbaric hydrogen therapy: a possible treatment for cancer. Science 190:152-154.

Gharib B, Hanna S, Abdallah OM, Lepidi H, Gardette B, De Reggi M (2001) Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation. C R Acad Sci III 324:719-724.

Hara F, Tatebe J, Watanabe I, Yamazaki J, Ikeda T, Morita T (2016) Molecular hydrogen alleviates cellular senescence in endothelial cells. Circ J 80:2037-2046.

Harch PG (2015) Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res 5:9.

Herrera BS, Coimbra LS, da Silva AR, Teixeira SA, Costa SK, Wallace JL, Spolidorio LC, Muscara MN (2015) The H,S-releasing naproxen derivative, ATB-346, inhibits alveolar bone loss and inflammation in rats with ligature-induced periodontitis. Med Gas Res 5:4.

Hu Q, Manaenko A, Guo Z, Huang L, Tang J, Zhang JH (2015) Hyperbaric oxygen therapy for post concussion symptoms: issues may affect the results. Med Gas Res 5:10.

Huang CS, Kawamura T, Toyoda Y, Nakao A (2010) Recent advances in hydrogen research as a therapeutic medical gas. Free Radic Res 44:971-982.

Ichihara M, Sobue S, Ito M, Ito M, Hirayama M, Ohno K (2015) Beneficial biological effects and the underlying mechanisms of molecular hydrogen—comprehensive review of 321 original articles. Med Gas Res 5:12.

Iketani M, Ohsawa I (2016) Molecular hydrogen as a neuroprotective agent. Curr Neuropharmacol doi: 10.2174/1570159X146661 60607205417.

Ishibashi T, Ichikawa M, Sato B, Shibata S, Hara Y, Nairiomi Y, Okazaki K, Nakashima Y, Iwamoto Y, Koyanagi S, Hara H, Nagao T (2015) Improvement of psoriasis-associated arthritis and skin lesions by treatment with molecular hydrogen: A report of three cases. Mol Med Rep 12:2757-2764.

Kajimura M, Nakanishi T, Takenouchi T, Morikawa T, Hishiki T, Yokutake Y, Suematsu M (2012) Gas biology: tiny molecules controlling metabolic systems. Respir Physiol Neurobiol 184:139-148.

Kurokawa R, Seo T, Sato B, Hirano S, Sato F (2015) Convenient methods for ingestion of molecular hydrogen: drinking, injection, and inhalation. Med Gas Res 5:13.

Langston JW, Toombs CF (2015) Defining the minimally effective dose and schedule for parenteral hydrogen sulfide: long-term benefits in a rat model of hindlimb ischemia. Med Gas Res 5:5.

Li L, Tao Y, Tang J, Chen Q, Yang Y, Feng Z, Chen Y, Yang L, Yang Y, Zhu G, Feng H, Chen Z (2015) A cannabinoid receptor 2 agonist prevents thrombin-induced blood-brain barrier damage via the inhibition of microglial activation and matrix metalloproteinase expression in rats. Transl Stroke Res 6:467-477.

Li Q, Yu P, Zeng Q, Luo B, Cai S, Hui K, Yu G, Zhu C, Chen X, Duan M, Sun X (2016) Neuroprotective effect of hydrogen-rich saline in global cerebral ischemia/reperfusion rats: up-regulated tregs and down-regulated miR-21, miR-210 and NF-kappaB expression. Neurochem Res 41:2655-2665.

Lioutas VA, Alfaro-Martinez F, Bedoya F, Chung CC, Pimentel DA, Novak V (2015) Intranasal insulin and insulin-like growth factor 1 as neuroprotectants in acute ischemic stroke. Transl Stroke Res 6:264-275.

Liu C, Kurokawa R, Fujino M, Hirano S, Sato B, Li XK (2014) Estimation of the hydrogen concentration in rat tissue using an airtight tube following the administration of hydrogen via various routes. Sci Rep 4:5485.

Merali Z, Leung J, Mikulis D, Silver F, Kassner A (2015) Longitudinal assessment of imatinib’s effect on the blood-brain barrier after ischemia/reperfusion injury with permeability MRI. Transl Stroke Res 6:39-49.

Nakata K, Yamashita N, Noda Y, Ohsawa I (2015) Stimulation of human damaged sperm motility with hydrogen molecule. Med Gas Res 5:2.

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

Ohta S (2011) Recent progress toward hydrogen medicine: potential of molecular hydrogen for preventive and therapeutic applications. Curr Pharm Des 17:2241-2252.

Ohta S (2015) Molecular hydrogen as a novel antioxidant: overview of the advantages of hydrogen for medical applications. Methods Enzymol 555:289-317.

Parr RS, Lopes AH, Carreira EU, Feitosa MR, Cunha FQ, Garcia SB, Cunha TM, da Rocha JJ, Feres O (2015) Hyperbaric oxygen therapy ameliorates TNBS-induced acute distal colitis in rats. Med Gas Res 5:6.

Pena I, Borlongan CV (2015) Translating G-CSF as an adjunct therapy to stem cell transplantation for stroke. Transl Stroke Res 6:421-429.

Ploughman M, Austin MW, Glynn L, Corbett D (2015) The effects of poststroke aerobic exercise on neuroplasticity: a systematic review of animal and clinical studies. Transl Stroke Res 6:13-28.

Qi Z, Dong W, Shi W, Wang R, Zhang C, Zhao Y, Ji X, Liu KJ, Luo Y (2015) Bel-2 phosphorylation triggers autophagy switch and reduces mitochondrial damage in limb remote ischemic conditioned rats after ischemic stroke. Transl Stroke Res 6:198-206.
Reuter B, Rodemer C, Grudzenski S, Meairs S, Bugert P, Hennerici MG, Fatar M (2015) Effect of simvastatin on MMPs and TIMPs in human brain endothelial cells and experimental stroke. Transl Stroke Res 6:156-159.

Roberts BJ, Fife WP, Corbett TH, Schabel FM Jr (1978) Response of five established solid transplantable mouse tumors and one mouse leukemia to hyperbaric hydrogen. Cancer Treat Rep 62:1077-1079.

Schlunk F, Schulz E, Lauer A, Yigitkanli K, Pfeilschifter W, Steinmetz H, Lo EH, Foerch C (2015) Warfarin pretreatment reduces cell death and MMP-9 activity in experimental intracerebral hemorrhage. Transl Stroke Res 6:133-139.

Shao A, Wu H, Hong Y, Tu S, Sun X, Wu Q, Zhao Q, Zhang J, Sheng J (2016) Hydrogen-rich saline attenuated subarachnoid hemorrhage-induced early brain injury in rats by suppressing inflammatory response: possible involvement of NF-kappaB pathway and NLRP3 inflammasome. Mol Neurobiol 53:3462-3476.

Soliman S, Ishrat T, Fouda AY, Patel A, Pillai B, Fagan SC (2015) Sequential therapy with minocycline and candesartan improves long-term recovery after experimental stroke. Transl Stroke Res 6:309-322.

Stoller KP (2015) All the right moves: the need for the timely use of hyperbaric oxygen therapy for treating TBI/CTE/PTSD. Med Gas Res 5:7.

Tamura T, Hayashida K, Sano M, Suzuki M, Shibusawa T, Yoshizawa J, Kobayashi Y, Suzuki T, Ohta S, Morisaki H, Fukuda K, Hori S (2016) Feasibility and safety of hydrogen gas inhalation for post-cardiac arrest syndrome-first-in-human pilot study. Circ J 80:1870-1873.

Wang JL, Zhang QS, Zhu KD, Sun JF, Zhang ZP, Sun JW, Zhang KX (2015) Hydrogen-rich saline injection into the subarachnoid cavity within 2 weeks promotes recovery after acute spinal cord injury. Neural Regen Res 10:958-964.

Weaver J, Liu KJ (2015) Does normobaric hyperoxia increase oxidative stress in acute ischemic stroke? A critical review of the literature. Med Gas Res 5:11.

Yan L, Liang T, Cheng O (2015) Hyperbaric oxygen therapy in China. Med Gas Res 5:3.

Zhu W, Casper A, Libal NL, Murphy SJ, Bodhankar S, Offner H, Alkayed NJ (2015) Preclinical evaluation of recombinant T cell receptor ligand RTL1000 as a therapeutic agent in ischemic stroke. Transl Stroke Res 6:60-68.