REVIEW

Molecular hydrogen: a therapeutic antioxidant and beyond

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Abstract

Molecular hydrogen (H_2) 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

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Introduction

Molecular hydrogen (H_2), the most lightweight gas, is routinely used as a component of exotic breathing gas mixture, namely hydreliox (49% H_2, 50% helium and 1% O_2) for deep water divers to prevent decompression sickness (Abraini et al., 1994; Ohta, 2011). Therapeutic application of H_2 as a free radical catalyzer debuted in 1970s. A 2-week treatment of hyperbaric 97.5% H_2 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 pospulated that the underlying mechansim was through hydroxyl radicals scanverging by exthermic reaction of $H_2 + \cdot OH = H_2O + H\cdot$ followed by $H\cdot + O_2^- = HO_2^-$ reaction (Dole et al., 1975). In 2001, Gharib et al. (2001) confirmed the similar treatment efficacy of hyperbaric hydrogen aganist 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 eluicdated the seletive antioxidant feature of normobaric 2% H_2 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 H_2 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

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 have 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 hyrogen sulfide (H_2S) (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_2S (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 adminstration 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-infammation, 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 clincal applications of molecular hydrogen to human patients has been conducted. The small cohert patients studies or case reports revealed the safety or some promising benefits of theraputic 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 stuides are warranted to further elucidate the upstream master regulator(s) that drive molecular hydorgen-induced modifications of downstream effectors. It is also of importance to clarify the best adminstration modality and the optimal hydrogen dose regimen for each disease model preclinically and subsquently 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.

Conflicts of interest

None.

Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

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