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Beneficial biological effects and the underlying mechanisms of molecular hydrogen - comprehensive review of 321 original articles -

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Abstract

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Therapeutic effects of molecular hydrogen for a wide range of disease models and human diseases have been investigated since 2007. A total of 321 original articles have been published from 2007 to June 2015. Most studies have been conducted in Japan, China, and the USA. About three-quarters of the articles show the effects in mice and rats. The number of clinical trials is increasing every year. In most diseases, the effect of hydrogen has been reported with hydrogen water or hydrogen gas, which was followed by confirmation of the effect with hydrogen-rich saline. Hydrogen water is mostly given *ad libitum*. Hydrogen gas of less than 4 % is given by inhalation. The effects have been reported in essentially all organs covering 31 disease categories that can be subdivided into 166 disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants with a predominance of oxidative stress-mediated diseases and inflammatory diseases. Specific extinctions of hydroxyl radical and peroxynitrite were initially presented, but the radical-scavenging effect of hydrogen cannot be held solely accountable for its drastic effects. We and others have shown that the effects can be mediated by modulating activities and expressions of various molecules such as Lyn, ERK, p38, JNK, ASK1, Akt, GTP-Rac1, iNOS, Nox1, NF-κB p65, IκBα, STAT3, NFATc1, c-Fos, and ghrelin. Master regulator(s) that drive these modifications, however, remain to be elucidated and are currently being extensively investigated.

Keywords: Molecular hydrogen, Ischemia-reperfusion injury, Inflammatory diseases

Introduction

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It has been 8 years since Ohsawa and colleagues reported the astonishing therapeutic effects of molecular

hydrogen on a rat model of cerebral infarction in *Nature Medicine* in 2007 [1]. Inhalation of 1–4 % hydrogen gas markedly reduced the sizes of cerebral infarction in rats. They also demonstrated that hydrogen specifically scavenges hydroxyl radical and peroxynitrite but not hydrogen peroxide or superoxide. Their paper ignited interest in the effect of molecular hydrogen in various diseases and has been cited 533 times as of July 2015. Similarly, the number of original articles demonstrating the effect of molecular hydrogen adds up to more than 300. This review summarizes research articles published in these past 8 years and addresses possible molecular mechanisms underlying the effects of hydrogen.

Molecular hydrogen research before 2007

Even before the publication by Ohsawa and colleagues in 2007 [1], biological effects of molecular hydrogen had been investigated in a small scale, as shown below. Dole and colleagues first reported the hydrogen effect in *Science* in 1975 [2]. They placed nude mice carrying squamous cell carcinoma in a chamber with 2.5 % oxygen and 97.5 % hydrogen under 8-atmospheric pressure and observed prominent reduction in the size of the tumors. A similar effect of hyperbaric hydrogen on leukemia was reported in 1978 [3]. Hydreliox, which contained 49 % hydrogen, 50 % helium, and 1 % oxygen, was reported to be effective to prevent decompression sickness and nitrogen narcosis for divers working below 500 meters under sea level [4]. An anti-inflammatory effect of hyperbaric hydrogen on a mouse model of schistosomiasis-associated chronic liver inflammation was also reported in 2001 [5]. Hyperbaric hydrogen may be effective for some diseases, but only a limited number of studies have been published. The difference between hyperbaric and normobaric hydrogen has not been directly compared to date.

Following a small number of studies with hyperbaric hydrogen, the effect of electrolytically alkaline water has been reported. Shirahata and colleagues hypothesized that the hydrogen atom, which they called active hydrogen, is generated in electrolysis and proposed that active hydrogen scavenges reactive oxygen species (ROS) [6]. Although it is unlikely that atomic hydrogen is able to exist for a substantial time in our bodies, molecular hydrogen does exist in electrolyzed water and the effects of electrolyzed water have been reported thereafter. Li and colleagues reported that electrolyzed water scavenged ROS and protected a hamster pancreatic beta cell line from alloxan-induced cell damage [7]. Similarly, reduced hemodialysis solution produced by an electrolysis device (Nihon Trim Co. Ltd.) ameliorated oxidative stress in hemodialysis patients [8]. In 2005, researchers in Tohoku University Graduate School of Medicine and Nihon Trim started cooperative clinical studies and established the Association of Electrolyzed Water-Hemodialysis Study Group in 2008. According to personal communications with this group, they now believe that the effects of electrolyzed water are likely due to dissolved hydrogen molecules.

In 2005, Yanagihara and colleagues at Miz Co. Ltd. reported that hydrogen-rich neutral water that was produced with their unique electrolysis device reduced oxidative stress in rats [9]. This was a pioneering work, because they explicitly proved that molecular hydrogen but not alkaline in the electrolyzed alkaline water exerts therapeutic effects.

Molecular hydrogen research in and after year 2007

As stated in the introduction, the *Nature Medicine* paper in 2007 [1] spurred interest in hydrogen research. Figure 1 shows 321 original articles up to June 2015 in the MEDLINE database, which demonstrate the effects of molecular hydrogen on disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants. Most studies were conducted in Japan, China, and the USA, with a predominance of China since 2010 (Fig. 1A). About three-quarters of the articles show the effects in mice and rats (Fig. 1B), but the number of human studies is increasing every year (1 article each in 2008–2009; 2 in 2010; 3 in 2011; 5 in 2012; 9 in 2013; 6 in 2014; and 6 in 2015). In addition, the effects of hydrogen have been reported in plants in 13 articles, which suggest a wide range of effects over various species not restricted to mammals. The effects of molecular hydrogen on plants may warrant application of hydrogen to increase agricultural production. Modalities of hydrogen administration are shown in Fig. 1C. Hydrogen-

rich saline, which is almost exclusively used in China, dominates over the others. Hydrogenized saline is administered either by intraperitoneal injection or drip infusion. Hydrogen water is mostly given *ad libitum*. Hydrogen gas is usually given by inhaling 1–4 % hydrogen gas, which is below the explosion level (4 %). There is a single report, in which hydrogen gas was injected intraperitoneally [10].

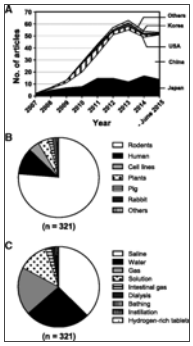


Fig. 1

Profiles of 321 original articles up to June 2015 showing therapeutic effects of molecular hydrogen. **a** Temporal profile of countries where the studies are reported from 2007 to June 2015. **b** Biological species used in the studies. **c** Modalities of hydrogen **...**

Among the various routes of hydrogen administration shown in Fig. 1C, the best method still remains uncertain. This is partly because only a few reports have addressed the difference of effects among administration methods. We previously showed that drinking hydrogen water, but not continuous hydrogen gas exposure, prevented development of 6-hydorxydopamine-induced Parkinson's disease in rats [11]. In addition, we recently showed that continuous exposure to hydrogen gas and *ad libitum per os* administration of hydrogen water modulated signaling pathways and gene expressions in different manners in mice [12]. We demonstrated that hydrogen-responsive genes are divided into four groups: genes that respond favorably to hydrogen gas, those that respond exclusively to hydrogen water, those that respond to both hydrogen gas and water, and those that respond only to the simultaneous administration of gas and water (Fig. 2). As hydrogen gas and water increase the hydrogen concentrations in the rodent body to a similar level [12], the difference in the organs exposed to a high concentration of hydrogen, the rise time of hydrogen concentration, and/or the area under the curve of hydrogen concentration may account for the difference in the modulated genes. On the other hand, a collation of hydrogen reports indicate that a similar degree of effects can be observed with different modalities of administration. For example, the marked effect of hydrogen on a mouse model of LPS-induced acute lung injury has been reported by four different groups with three different modalities: hydrogen gas [13, 14], hydrogen water [15], and hydrogen-rich saline [14, 16]. Similarly, the dramatic effect of hydrogen on animal models of acute myocardial infarction has been reported by eight different groups with two different modalities: hydrogen gas [17–20] and hydrogen-rich saline [21–24]. To clarify the difference of hydrogen's effects with different modalities of administration, each research group should scrutinize the difference of the effects between hydrogen gas, hydrogen water, and hydrogen-rich saline. This would uncover the best modality for each disease model, if any, and also the optimal hydrogen dose.

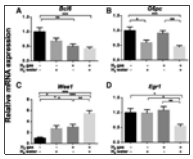


Fig. 2

Four groups of genes that show different responses to hydrogen gas and/or water [12] . **a** *Bcl6* responds to hydrogen gas more than hydrogen water. **b** *G6pc* responds only to hydrogen water. **c** *Wee1* responds to both hydrogen water and gas. **d** *Egr1* responds **...**

Table 1 summarizes disease categories for which the effects of hydrogen have been reported. Ohsawa and colleagues reported the hydrogen effect in cerebral infarction [1] and many subsequent studies also showed its effect in ischemia-reperfusion injuries including organ transplantations. Following the initial report by Ohsawa and colleagues, the specific hydroxyl radical scavenging effect of hydrogen has been repeatedly proposed in oxidative stress-mediated diseases including inflammatory diseases and metabolic diseases.

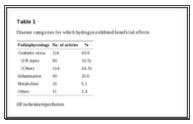


Table 1

Disease categories for which hydrogen exhibited beneficial effects

Table 2 shows the details of organs and diseases for which the effects of hydrogen have been reported. Table 2 is an update of our previous review article in 2012 [25]. We have now classified the organs and diseases into 31 categories and showed the effects in 166 disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants. Hydrogen is effective in essentially all organs, as well as in plants.

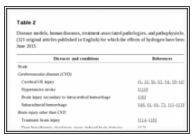


Table 2

Disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants (321 original articles published in English) for which the effects of hydrogen have been reported from 2007 to June 2015

Molecular mechanisms of the effects of hydrogen

Collation of the 321 original articles reveals that most communications address the anti-oxidative stress, anti-inflammatory, and anti-apoptotic effects. Specific scavenging activities of hydroxyl radical and peroxynitrite, however, cannot fully explain the anti-inflammatory and anti-apoptotic effects, which should involve a number of fine-tuned signaling pathways. We have shown that hydrogen suppresses signaling pathways in allergies [26] and inflammation [27] without directly scavenging reactive oxygen/nitrogen species. Signaling molecules that are modulated by hydrogen include Lyn [26, 28], Ras [29], MEK [29, 30], ERK [12, 24, 29–37], p38 [12, 16, 24, 27, 30, 32, 33, 35–41], JNK [13, 24, 27, 30, 32, 33, 35–38, 40, 42–47], ASK1 [27, 46], Akt [12, 29, 36, 37, 48, 49], GTP-Rac1 [36], iNOS [27, 34, 36, 50–52], Nox1 [36], NF-κB p65 or NF-κB [12, 14, 27, 35–38, 40, 41, 43, 49, 53–75], IκBα [27, 40, 41, 54, 60, 62, 69, 73, 76], STAT3 [65, 77, 78], NFATc1 [12, 36, 78], c-Fos [36], GSK-3β [48, 79], ROCK [80]. Activities and expressions of these molecules are modified by hydrogen. Master regulator(s) that drive these modifications remain to be elucidated.

The anti-oxidative stress effect of hydrogen was first reported to be conferred by direct elimination of hydroxyl radical and peroxynitrite. Subsequent studies indicate that hydrogen activates the Nrf2-Keap1 system. Hydrogen activates Nrf2 [36, 81–87] and its downstream heme oxygenase-1 (HO-1) [36, 51, 52, 65, 71, 81, 82, 84–93]. Kawamura and colleagues reported that hydrogen did not mitigate hyperoxic lung injury in *Nrf2*-knockout mice [82]. Similarly, Ohsawa and colleagues reported that hydrogen enhanced mitochondrial functions and induced nuclear translocation of Nrf2 at the Symposium of Medical Molecular Hydrogen in 2012 and 2013. They proposed that hydrogen induces an adaptive response against oxidative stress, which is also known as a hormesis effect. These studies indicate that the effect of hydrogen is mediated by Nrf2, but the mechanisms of how Nrf2 is activated by hydrogen remain to be solved.

Another interesting mechanism is that hydrogen modulates miRNA expressions [64, 94]. Hydrogen regulates expressions of miR-9, miR-21, and miR-199, and modifies expressions of IKK-β, NF-κB, and PDCD4 in LPS-activated retinal microglia cells [64]. Similarly, analysis of miRNA profiles of hippocampal neurons during I/R injury revealed that hydrogen inhibits I/R-induced expression of the miR-200 family by reducing ROS production, which has led to suppression of cell death [94]. However, modulation of miRNA expression cannot solely explain all the biological effects mediated by hydrogen. In addition, mechanisms underlying modulated miRNA expressions remain to be elucidated.

Matsumoto and colleagues reported that oral intake of hydrogen water increased gastric expression and secretion of ghrelin and that the neuroprotective effect of hydrogen water was abolished by the ghrelin receptor-antagonist and by the ghrelin secretion-antagonist [95]. As stated above, we have shown that

hydrogen water, but not hydrogen gas, prevented development of Parkinson's disease in a rat model [11]. Prominent effect of oral hydrogen intake rather than hydrogen gas inhalation may be partly accounted for by gastric induction of ghrelin.

Recently, Ohta and colleagues showed at the 5th Symposium of Medical Molecular Hydrogen at Nagoya, Japan in 2015 that hydrogen influences a free radical chain reaction of unsaturated fatty acid on cell membrane and modifies its lipid peroxidation process. Furthermore, they demonstrated that air-oxidized phospholipid that was produced either in the presence or absence of hydrogen *in vitro*, gives rise to different intracellular signaling and gene expression profiles when added to the culture medium. They also showed that this aberrant oxidization of phospholipid was observed with a low concentration of hydrogen (at least 1.3 %), suggesting that the biological effects of hydrogen could be explained by the aberrant oxidation of phospholipid under hydrogen exposure. Among the many molecules that are altered by hydrogen, most are predicted to be passengers (downstream regulators) that are modulated secondarily to a change in a driver (master regulator). The best way to identify the master regulator is to prove the effect of hydrogen in an *in vitro* system. Although, to our knowledge, the study on lipid peroxidation has not yet been published, the free radical chain reaction for lipid peroxidation might be the second master regulator of hydrogen next to the radical scavenging effect. We are also analyzing other novel molecules as possible master regulators of hydrogen (in preparation). Taken together, hydrogen is likely to have multiple master regulators, which drive a diverse array of downstream regulators and achieve beneficial biological effects against oxidative stress, inflammation, apoptosis, and dysmetabolism to name a few (Fig. 3).

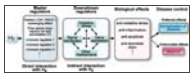


Fig. 3
Schematic summary of molecular mechanisms of hydrogen

These studies all point to the notion that hydrogen modulates intracellular signal transduction systems and regulates the downstream gene expressions to mitigate disease processes. In general, biologically active substances that modulate signaling molecules have both beneficial and noxious effects on our bodies. Hydrogen may also have undisclosed toxic effects, although none have been reported to date to the best of our knowledge. Understanding the exact molecular mechanisms of the effects of hydrogen will elucidate its master regulator(s) and clarify the pros and cons of hydrogen therapy, which will also potentially lead to the development of another therapeutic modality to modulate the master regulator(s). We summarized in Table 3 original articles that addressed biological effects and *in vivo* kinetics of hydrogen, which were not directly relevant to disease models or human diseases. It is essential to elucidate detailed pharmacokinetics of hydrogen *in vivo* from the viewpoint of clinical application of hydrogen, although we have accumulated vast knowledge about the effects and not the kinetics of hydrogen in disease models and human diseases. Through these analyses, promising outcomes are expected for more effective administration regimen of hydrogen therapy.

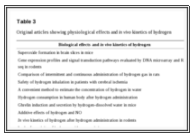
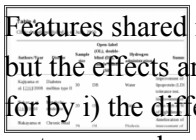


Table 3
Original articles showing physiological effects and *in vivo* kinetics of hydrogen

Clinical studies of molecular hydrogen

As stated in the introduction, the number of clinical trials has been increasing since 2011. About half of human studies have been conducted in Japan. Dependable studies recruiting more than ten patients or employing double-blind studies are summarized in Table 4.

Table 4
Clinical trials published as of June, 2015



Features shared in these clinical studies are that hydrogen exhibits statistically significant effects in patients but the effects are usually not as conspicuous as those observed in rodent models. These can be accounted for by i) the difference in species, ii) technical difficulty in preparing a high concentration of hydrogen water every day for the patients, and iii) the difference between acute and chronic diseases. Further large-scale and long-term clinical studies are expected to prove the effects of hydrogen in humans.

Table 5 shows clinical studies currently registered in Japan. Researchers in Juntendo University have started a large-scale clinical trial of Parkinson's disease after they have shown the effects of molecular hydrogen in a small number of patients in a short duration [96]. Being prompted by the prominent effects of hydrogen for mouse models with ischemia reperfusion injuries, clinical trials for acute post cardiac arrest syndrome and myocardial infarction have started at Keio University. Similarly, a clinical trial for cerebral infarction has started at the National Defense Medical College.

Table 5

Clinical trials registered in Japan as of June, 2015

Conclusions

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The number of original articles showing the effects of hydrogen are increasing yearly after 2007, and an extensive review of these articles are getting more and more difficult. Some of these articles, however, are a repetition of previous studies with insignificant novel findings. We suppose that almost all disease models and almost all modalities by which hydrogen is administered have been already examined. Large-scale controlled human studies and elucidation of molecular mechanisms underlying the effects of hydrogen are the next steps that must be pursued.

A dose–response effect of hydrogen is observed in drinking hydrogen-rich water [94, 97]. A similar dose–response effect is also observed in inhaled hydrogen gas [1, 17, 98]. However, when hydrogen concentrations in drinking water and in inhaled gas are compared, there is no dose–response effect. Hydrogen-rich water generally shows a more prominent effect than hydrogen gas, although the amount of hydrogen taken up by hydrogen water is ~100 times less than that given by hydrogen gas [11]. Gastric secretion of ghrelin may partly account for this difference [95]. Another factor that accounts for the effects of hydrogen is the temporal profile of hydrogen administration. Intermittent inhalation, but not continuous inhalation, of hydrogen is protective against a rat model of Parkinson's disease, which is against a dose-responsiveness of hydrogen [11]. The prominent effects of molecular hydrogen in a variety of disease models, human diseases, treatment-associated pathologies, and pathophysiological conditions of plants have been disclosed in these 8 years, but unsolved conundrums still challenge us.

Acknowledgements

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Footnotes

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Competing interests

We have no competing interest to disclose.

Authors' contributions

MI[1] collated and scrutinized all hydrogen papers. SS, MI[2], MI[3], and MH made critical comments on hydrogen papers. MI[1] and KO wrote the paper. All authors read and approved the final manuscript.

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