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Hydrogen therapy from the initiation to its practical applications

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Abstract

Molecular hydrogen (H_2) has emerged as a therapeutic and prophylactic agent devoid of adverse effects. H_2 demonstrates multifaceted functionality across diverse cell types and organs, attributable to its interaction with oxidized hemes as a fundamental molecular mechanism. Given the abundance of various heme types both intracellularly and extracellularly, the broad-ranging effects of H_2 are comprehensible. Subsequent Pathways are mediated by end-or modified- products of lipid peroxide followed by free radical chain reactions. Notably, H_2 confers benefits not only to patients afflicted with diseases but also to individuals seeking to enhance health and wellness. The mission of hydrogen medicine encompasses addressing unresolved medical challenges, including cerebral infarction, post-cardiac arrest syndrome, advanced cancer, metabolic syndrome, and dementia. Transitioning from animal experiments to clinical studies is imperative to confront these formidable diseases effectively.

Key words: adverse effect; Alzheimer's disease; cancer; cardiac arrest; clinical trial; heme; hydrogen medicine; lipid peroxide; metabolic syndrome; multiple functions; oxidation; porphyrin; signal transduction; quarity-of-life.

Conflict of interests. The author is serving directors of the hydrogen related companies, H_2 water Japan, Inc., (Tokyo, Japan), Mitos, Co. Ltd. (Kawasakii, Japan), and H_2 Global Group s.r.o. (Ostrava, Czech Republic), and a patent holder related with hydrogen.

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Historically, molecular hydrogen (H_2), also known as dihydrogen, was perceived as biologically inert without the presence of a catalyst, given mammals' lack of genes encoding hydrogenases, enzymes pivotal for H_2 metabolism in certain bacteria [1, 2]. Consequently, H_2 was deemed non-functional in mammalian cells. However, our exploration into H_2's therapeutic potential commenced in January 2005, culminating in the seminal publication "Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals" in Nature Medicine in 2007 [3]. This pivotal work challenged prevailing notions and laid the groundwork for the burgeoning field of "hydrogen medicine and agriculture." Subsequently, global interest surged, leading to an extensive array of investigations spanning over 17 years, yielding more than 2,500 publications worldwide [4].

The multifaceted benefits of H_2 soon became evident, characterized by its diverse functions and minimal adverse effects [5]. These observations catalyzed a multitude of clinical inquiries, buoyed by H_2's safety profile. In 2016, the Japanese government endorsed H_2 therapy as an advanced treatment for post-cardiac arrest syndrome. Furthermore, H_2 demonstrated potential in enhancing the quality of life across various domains, including healthcare, sports, and beauty, while also ameliorating diverse pathological conditions. The recognition of H_2's safety by the US Food and Drug Administration (FDA) in 2014, designating it as Generally Recognized as Safe (GRAS), facilitated the marketing of H_2-infused water, known as H_2 water or H_2-rich water, as a beverage. This regulatory acknowledgment underscored H_2's beneficial effects on both healthy individuals and patients grappling with various ailments. Moreover, H_2's positive impact extends beyond humans to encompass higher plants, hinting at its potential significance in agriculture [6]. Indeed, numerous studies exploring the effects of H_2 on agricultural products have emerged, with some products already available in commercial markets.

Here, I would like to summarize the initiation of hydrogen medicine and the progress of hydrogen toward practical applications in various fields, focusing on our studies.

Methods of hydrogen administration, pharmacokinetics and safety

Transport mechanisms for H_2 into cells are notably absent. Due to its unique physical properties – being the smallest molecule, non-ionic, non-polar, and non-magnetic – H_2 can diffuse across biological membranes independently.

There are several routes for H_2 administration into the body. Inhalation of H_2 gas, facilitated by ventilator circuits, facemasks, or nasal cannulas, offers a direct and efficacious method. Upon inhalation, H_2 is absorbed by the lungs and swiftly disseminated throughout the body via arterial blood flow. Subsequently, H_2 permeates most tissues by traversing peripheral blood vessels [7]. Inhalation emerges as a preferred method for combating acute oxidative stress, with effective concentrations ranging from 1 – 4% (v/v), resulting in blood concentrations of 8 – 32 μM. Notably, these concentrations fall within physiologically beneficial ranges, contrasting with explosive concentrations of H_2 (4 – 75%).

Drinking H_2-infused water represents another viable option, owing to its ease of consumption. H_2 readily dissolves in water, achieving concentrations of up to 0.8 mM (1.6 mg/L) under atmospheric pressure and room temperature, without altering pH levels. Upon ingestion, H_2 traverses from the stomach to the portal vein via the jejunal vein, with subsequent transfer occurring within 10 minutes. Notably, H_2 concentration remains functionally significant in the liver, maintained at 10 – 20 μM for one to two hours, akin to concentrations achieved through inhalation of 1.2 – 4% H_2 gas [8].

Administration via intravenous or intraperitoneal routes, employing H_2 dissolved in saline (H_2-rich saline) has been demonstrated in animal models and patients [9]. Additionally, H_2-loaded eye drops, comprising H_2 dissolved in saline, offer a direct ocular delivery method [10]. A clinical trial showed that eye drops protect the cornea during cataract surgery (*K.Igarashi et al.*, 2019). Furthermore, H_2 incorporation into organs can be facilitated through H_2-supplemented water baths during cold organ preservation before organ transplantation. The permeability of H_2 through the skin allows for its widespread distribution, suggesting the feasibility of incorporating H_2 into daily life via warm H_2 baths.

Notably, H_2 exhibits no cytotoxicity even at high concentrations, as confirmed by various studies. Safety standards for inhaling high-pressure H_2 gas have been validated, notably in deep-diving gas mixtures to prevent decompression sickness and arterial gas thrombi [11]. Clinical trials have further affirmed the safety profile of H_2 [12], attributed to its inert nature, rendering its lack of toxic effects readily understandable and acceptable.

Selective reduction of reactive oxygen species

H_2 exhibits a remarkable selectivity in reducing highly oxidative reactive oxygen species (ROS), specifically hydroxyl radicals (•OH) and peroxynitrite ($ONOO^-$), while remaining inert towards superoxide ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), and nitric oxide (NO•) [3]. The cytoprotective potent of H_2 against •OH is evident (Figure 1). The efficacy of reducing •OH has been demonstrated not only in cultured cells but also in various tissues, including those involved in testicular radioprotection, hematopoietic stem cell damage induced by total body irradiation, and instances of hyperoxia, lung hypoxia/reoxygenation, retinal ischemia-reperfusion, and retinal sonication [13].

Despite significant advancements in hydrogen medicine, a fundamental question has persisted for over 15 years regarding the mechanism underlying the reduction of •OH. The reaction rate of •OH with H_2 in aqueous solutions is considerably slower ($0.35 \times 10^{-8}\,M^{-1}\,s^{-1}$) compared to that observed in living cells [14]. Notably, H_2 typically requires a metal catalyst for reaction, yet there are no metals such as Cu, Fe, Ni, and Pt within living cells. Additionally, the absence of an organo-catalyst for H_2 further complicates the understanding of these reactions. This disparity between reactions in homogeneous aqueous solutions and living cells has long been a subject of debate.

A recent study by Prof. *Qianjun He's* group in Shanghai and Shenzhen, published in Nano Research, sheds light on this phenomenon. They identified an oxidized form of Fe-porphyrin, referred to as "hematin", as the primary molecular target/biosensor of H_2 [15]. Here, we employ the term "heme" by a broad sense in place of "porphyrin". The hydroxy group ($^-$OH) conjugated with Fe(III)-containing heme can be replaced with hydrogen ($^-$H) through a reaction with H_2. The atomic H of the $^-$H group acts as a hydride, effectively scavenging hydroxyl radicals (•OH), as depicted by the chemical equation.

Heme-Fe(III)-H + •OH → Heme-Fe(II) + H_2O.

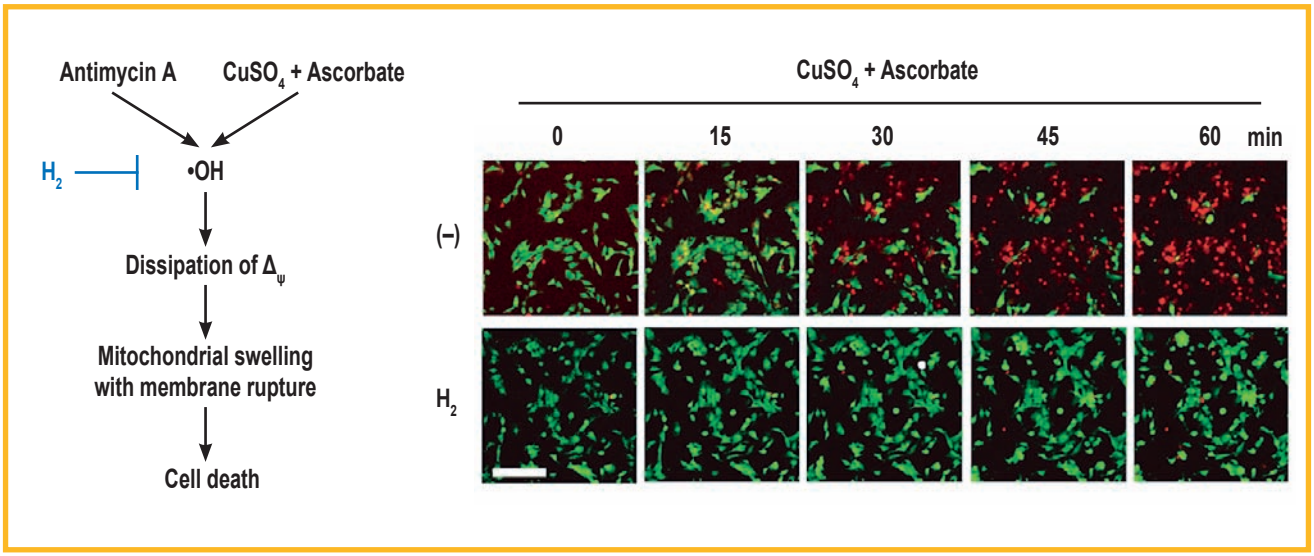

Figure 1. Protective effect of molecular hydrogen. Hydroxyl radicals were generated in cultured cells via the Fenton reaction (the left panel). In the right panel, green and red dots represent live and dead cells, respectively. In the absence of molecular hydrogen in the culture medium, within an hour, a majority of cells succumbed to hydroxyl radicals due to their highly oxidizing nature and cell-destructive properties. Molecular hydrogen in the medium conferred cell survival against hydroxyl radicals
Note: •OH, hydroxyl radicals; Δ_ψ, transmembrane difference of electrochemical potentials.

Furthermore, it has been demonstrated that heme with Fe(II) serves as a catalyst for a series of reactions, facilitating the reduction of free radicals and the restoration of oxidized forms to their reduced states. These catalytic reactions play a pivotal role in repairing oxidative damage and maintaining cellular homeostasis [16].

Heme-related multifunctionality of molecular hydrogen

Given the diverse cellular functions of H_2, it might have been speculated that H_2 exerts one effect by interacting with one specific target, potentially implying a multitude of targets to accommodate its various functions. However, the abundance of diverse heme types, each with its distinct roles, suggests that H_2 may achieve its multifunctionality by acting on different heme variants belonging a single heme group.

Heme is ubiquitously distributed throughout the body, residing both intracellularly and extracellularly. It plays critical roles in oxygen transport and utilization as seen in hemoglobin and myoglobin within blood and muscle tissues, respectively. Moreover, heme functions as a component of cytochromes in the electron transport chain of mitochondria, facilitating electron transfer. Within the intracellular cytosol, essential antioxidant enzymes such as catalase, peroxidase, P450, and nitric oxide (NO) synthase rely on heme for their functionality (Figure 2). These heme-containing enzymes, bearing Fe(II), serve diverse functions, primarily mediating redox reactions and are prone to oxidative damage due to exposure to oxidative stress [17].

H_2 exhibits the capability to restore various oxidized forms of hemes, such as Heme-Fe(III)-OH, to their functional reduced states, such as Heme-Fe(II), through the following specific reactions:

$$\text{Heme-Fe(III)-OH} + H_2 \rightarrow \text{Heme-Fe(III)-H} + H_2O, \quad (1)$$

$$\text{Heme-Fe(III)-H} + \bullet X \rightarrow \text{Heme-Fe(II)} + \text{H-X}, \quad (2)$$

where $\bullet X$ represents oxidative free radicals like $\bullet OH$.

Crucially, H_2 targets the oxidized form of heme, which is dysfunctional due to oxidation. Thus, H_2 operates specifically under pathological (oxidized) conditions, with no action on functional and reduced heme [17].

Additionally, several transcription factors, such as NPAS2 and the Bach family, contain heme [18 – 20]. Therefore, H_2 could potentially affect transcriptional regulation by modifying oxidized heme to express various phenotypes.

It is noteworthy that other medical gases, such as nitric oxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO), also target heme-containing molecules, indicating a commonality in their mechanisms of action.

Subsequent pathways mediated by end-products of lipid peroxide followed by free radical chain reactions

We now transition to the subsequent pathway initiated by the reduction of free radicals, leading to signal transduction and the manifestation of multiple phenotypes [13]. Lipid

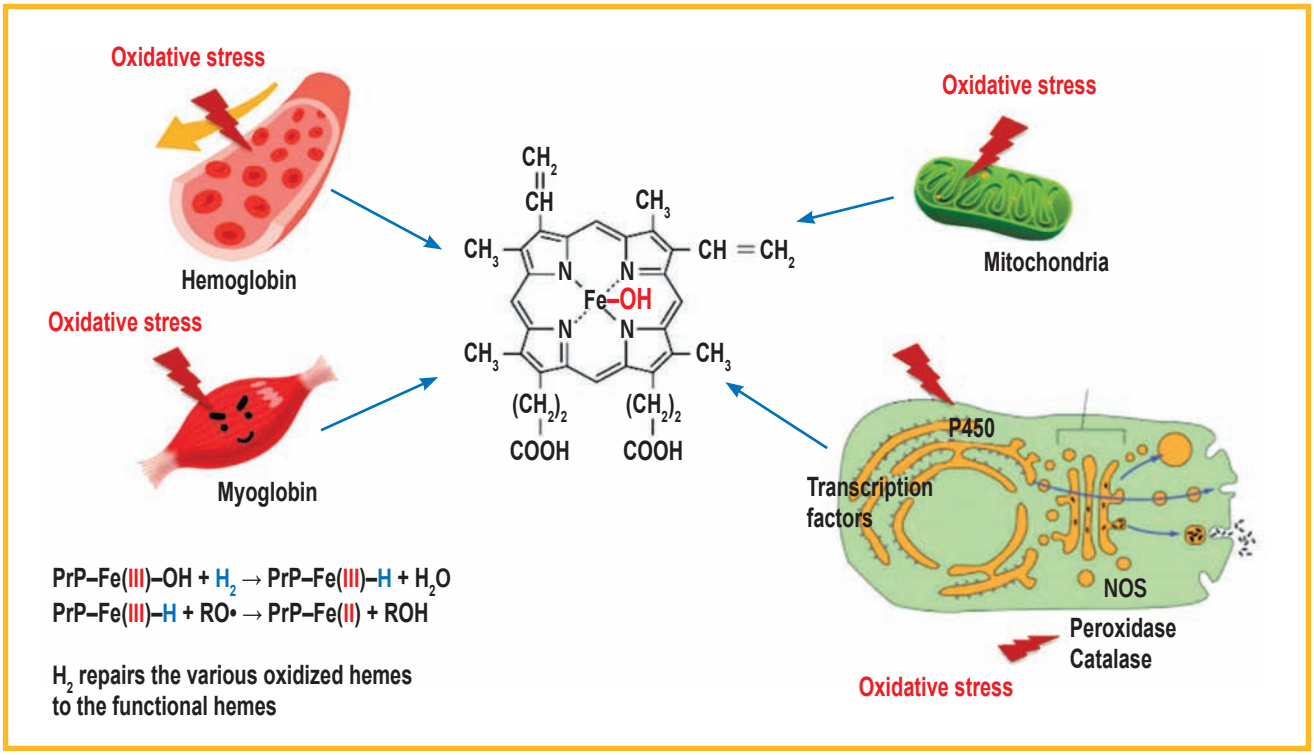

Figure 2. Molecular hydrogen targets oxidized heme, explaining its diverse effects. Heme, abundant in the body, serves various functions including as hemoglobin in blood, myoglobin in muscles, mitochondrial components, P450 detoxifying enzymes, NO synthase, antioxidant enzymes, and transcription factors in the nucleus. These heme molecules function in highly oxidative environments, and oxidized heme loses its functional capacity
Note: P450, enzymes of the P450 family; NOS, NO synthase.

peroxides (LPOs) accumulate as a result of free radical chain reactions. In the initiation phase, • OH radicals extract hydrogen atoms from polyunsaturated fatty acids, forming lipid radicals. These lipid radicals undergo further conversion into lipid peroxy radicals and subsequently lipid hydroperoxides during the free radical chain reaction, ultimately resulting in peroxide accumulation (LPO). LPO is known to induce ferroptosis [21]. Therefore, H_2 can mitigate this type of cell death by inhibiting LPO accumulation [22].

In signal transduction pathways, end-products derived from LPOs, such as 4-hydroxy-2-nonenal (4-HNE), often function as second messengers. Decreased levels of 4-HNE induce PGC-1α via the subsequent Akt/FoxO1 signaling pathway [23]. Notably, the multifunctionality of PGC-1α can further contribute to the diverse functions of H_2, including its role as an energy metabolism stimulator.

Considering an alternative pathway involving H_2, oxidized phospholipids (OxPLs) are known to exert various biological effects on different cell types, including the activation of Ca^{2+} signaling. During OxPL formation, H_2 may modify OxPLs, with the modified H-OxPLs potentially acting as antagonists. Consequently, Ca^{2+} signaling is suppressed by this antagonist, thereby linking H_2 to Ca^{2+} signaling and the Ca^{2+}-dependent transcription factor NFAT [24]. NFAT transcribes the following genes involved in inflammation: transcription factors (EGR-1, KLF2, ATF3, JUNB, and NFKB2), cytokines (TNF-α and IL-8), and enzymes (cyclooxygenase-2 (COX-2)) [24]. Therefore, H_2 can suppress inflammation by decreasing the expression of pro-inflammatory factors [13].

Figure 3 illustrates the pathways that H_2 exerts the multiple functions.

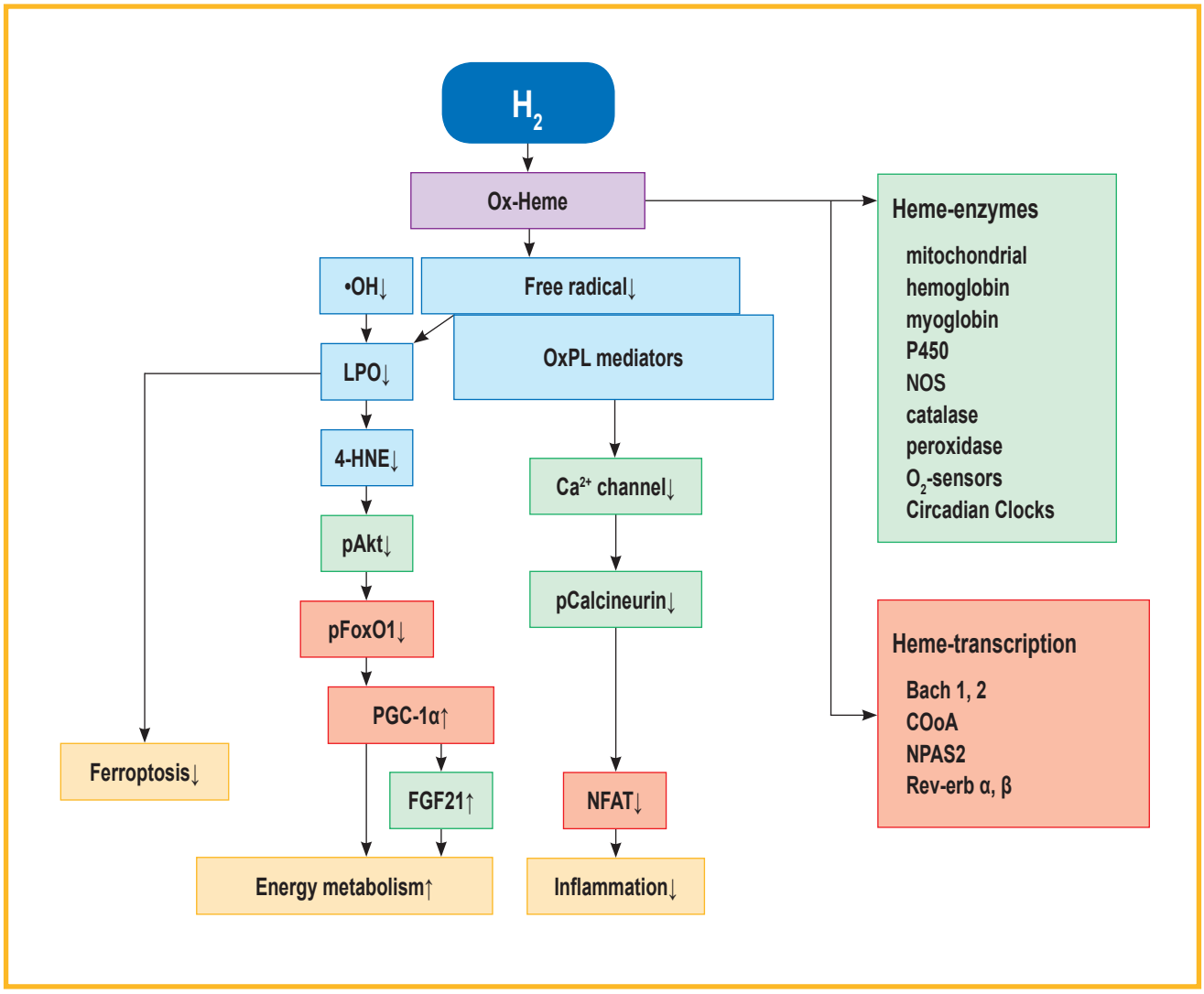

Figure 3. Molecular hydrogen mediates multiple functions via various pathways. Heme-Fe(III) containing H catalyzes reactions with free radicals, modifying them and suppressing ferroptosis by reducing lipid peroxide accumulation. Alternatively, the modified mediators contribute to enhanced energy metabolism and inflammation suppression. Hydrogen facilitates the repair of oxidized heme, thereby activating various heme-containing enzymes and transcription factors

Note: Ox-Heme, oxidized heme; OxPL mediators, oxidized phospholipid mediators; pCalcineurin, phosphorylated calcineurin; NOS, NO synthase; LPO, lipid peroxidation products; 4-HNE, 4-hydroxy-2-nonenal; NFAT, nuclear factor of activated T-cells; pAkt, phosphorylated protein kinase B; pFoxO1, phosphorylated FoxO1 protein (Forkhead family protein); PGC-1α, a coactivator of peroxisome proliferator-activated receptor γ-receptor 1α; FGF21, fibroblast growth factor 21; Rev-erb α,β, nuclear receptors Rev-erb α, β; COoA, CO-sensitive transcription activator; Bach 1,2, proteins of the Bach 1 and 2 family.

Indirect hormonal regulation by molecular hydrogen

Hormones play crucial roles in regulating various functions within the body. H_2 has been shown to modulate hormones and cytokines in specific tissues, affecting target cells even when it doesn't directly reach them at necessary concentrations. This suggests that H_2 can exert beneficial effects through indirect mechanisms, possibly involving second messenger systems under hormonal regulation.

Ghrelin is a hormone produced in the stomach that plays a role in appetite regulation and energy balance. H_2 has been found to increase the expression of ghrelin hormone. This suggests that H_2 may influence appetite and energy balance by modulating ghrelin levels, potentially affecting functions in the brain [25].

FGF21 is a protein hormone that plays a role in regulating energy metabolism, particularly in response to fasting and dietary conditions. H_2 has been shown to stimulate energy metabolism by increasing the expression of FGF21. This suggests that H_2 may have metabolic effects through its modulation of FGF21 levels [26].

As mentioned, H_2 has been shown to decrease the expression of pro-inflammatory cytokines, thereby reducing inflammation. This suggests that H_2 may have potential therapeutic benefits in conditions characterized by inflammation.

From animal experiments to clinical studies

H_2 has been examined in 200 animal models, yielding positive results and paving the way for transition from animal experiments to clinical trials [27, 28].

Health and wellness

H_2 represents a novel approach in the domains of health, wellness, and beauty. Ongoing research is exploring its multifaceted potential benefits, encompassing enhanced exercise capacity, improved liver function, cardiovascular health, mental well-being, and mitigation of oxidative stress and aging. Continued investigation is imperative to fully elucidate the broad spectrum of health advantages offered by H_2 water.

The beneficial effects of H_2 on the daily lives of healthy individuals were initially examined by administering H_2 water. Consumption of H_2 water was found to ameliorate mood, anxiety, and autonomic function in routine daily life situations without undue stress [29].

The impact of H_2 on exercise has been substantiated through numerous animal experiments and clinical studies involving ingestion of H_2 water and inhalation of hydrogen gas. Evidence has demonstrated various benefits, including reduction of post-exercise fatigue, improvement in motor function, and mitigation of muscle damage [30 – 33]. While achieving consistent results across all studies is challenging due to variations in exercise capacity among individuals, a meta-analysis has shown statistically significant reductions in fatigue following exercise [34]. Through meticulous research, hydrogen is anticipated to continue contributing to enhancing athletic performance among professional athletes and promoting the health of the general populace.

H_2 facilitates alcohol metabolism [35], and clinical trials have revealed that consuming H_2 suppresses hangovers [36].

The effects of H_2 on the skin, including atopic conditions, have been acknowledged [37]. Moreover, H_2 is garnering attention not only for its therapeutic applications in skin diseases but also for its potential in beauty treatments [38].

A series of studies demonstrating the positive impact of drinking H_2 water on quality of life has been compiled into a Systematic Review Article [39].

Ischemia-reperfusion injury

Ischemia-reperfusion injury occurs when blood supply to organs is restricted, followed by subsequent reperfusion and re-oxygenation, leading to severe oxidative stress. Conditions such as cardiac or cerebral infarction, cardiac arrest, organ transplantation, and liver resection can induce ischemia-reperfusion injury upon restoration of blood flow.

Our initial study in Nature Medicine utilized a cerebral infarction model to demonstrate the in vivo effects of H_2. Inhalation of 2% H_2 during reperfusion after cerebral infarction suppressed nerve cell death and subsequently led to improvements in body temperature and nerve function [3].

Subsequently, a randomized clinical trial was conducted on cerebral infarction patients. Twenty-five patients received inhaled 3% hydrogen gas, while 25 patients received conventional medicine alone. Improvement was observed in NIH Stroke Clinical Scale scores and MRI results. Additionally, rehabilitation proceeded smoothly with hydrogen gas inhalation. Positive effects were also observed in clinical trials involving patients with cardiac infarction [40].

Cardiac arrest also induces ischemia-reperfusion injury, particularly impacting the brain. Rats subjected to cardiopulmonary arrest were treated with 3% H_2 gas inhalation upon heart rate restoration, resulting in improved brain protection and pathological determination, leading to enhanced memory and motor function [41].

Typically, research begins with small animals, followed by studies in larger animals such as dogs or pigs, and in some cases, monkeys. Clinical trials are the final step. However, due to the significant brain protection observed, H_2 was certified by the Japanese Minister of Health, Labour, and Welfare as an advanced therapy B for post-cardiac arrest syndrome.

The multicenter, randomized, placebo-controlled, double-blind trial was conducted. The patients inhaled 2% H_2 with O_2 in addition to thermoregulatory therapy, and mortality and neurological outcomes were investigated. Strikingly, the 90-day mortality of H_2 plus thermoregulatory therapy was less than half of that receiving only the thermoregulatory (39% to 15%), and 46% of the H_2 group was recovered without sequelae, whereas only 21% of the control group was recovered without sequelae. These results strongly suggest that practical use of hydrogen therapy will save many lives and livelihoods, underscoring the profound impact of hydrogen on life and death [42] (Figure 4).

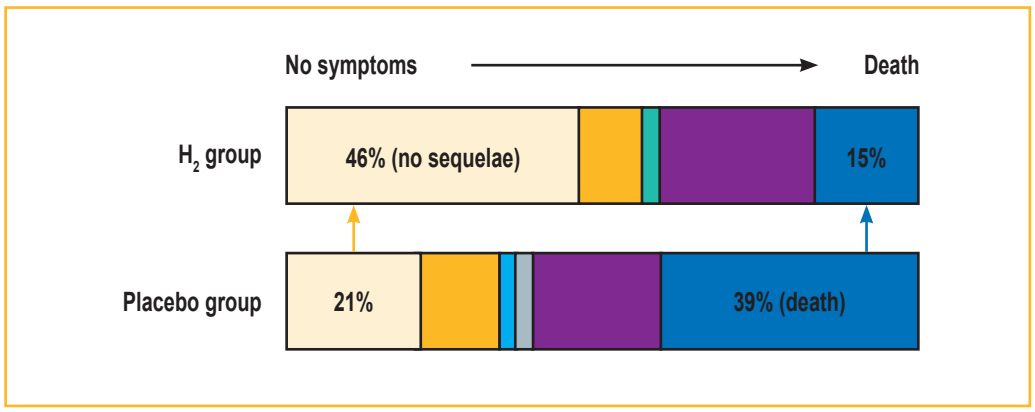

Figure 4. Hydrogen gas reduces mortality and improves patient outcomes. A multicenter, randomized, placebo-controlled, double-blind trial demonstrated the significant impact of hydrogen gas. Mortality rates were halved, while the number of patients without sequelae doubled. Hydrogen gas had a profound effect on patient survival

Metabolic syndrome

Metabolic syndrome is characterized by at least three of the following medical conditions: abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol, increasing the risk of developing cardiovascular disease and type 2 diabetes. Atherosclerotic cardiovascular and cerebrovascular diseases are major contributors to global morbidity and mortality [43].

Utilizing db/db mice as models for obesity and diabetes, characterized by uncontrolled appetite leading to overeating and subsequent obesity and diabetes, we observed that consumption of H_2 water resulted in reductions in body fat, blood glucose levels, insulin levels, and blood triglycerides. Notably, hydrogen water intake did not affect food or water intake or motor activity compared to control mice, indicating potential enhancement of energy metabolism [26] (Figure 5).

In a randomized, double-blind, placebo-controlled clinical trial, with sub-analyses conducted in the oxidative stress enhancement group, hydrogen water consumption was associated with reductions in body mass index, total fat area, and hip and waist circumferences.

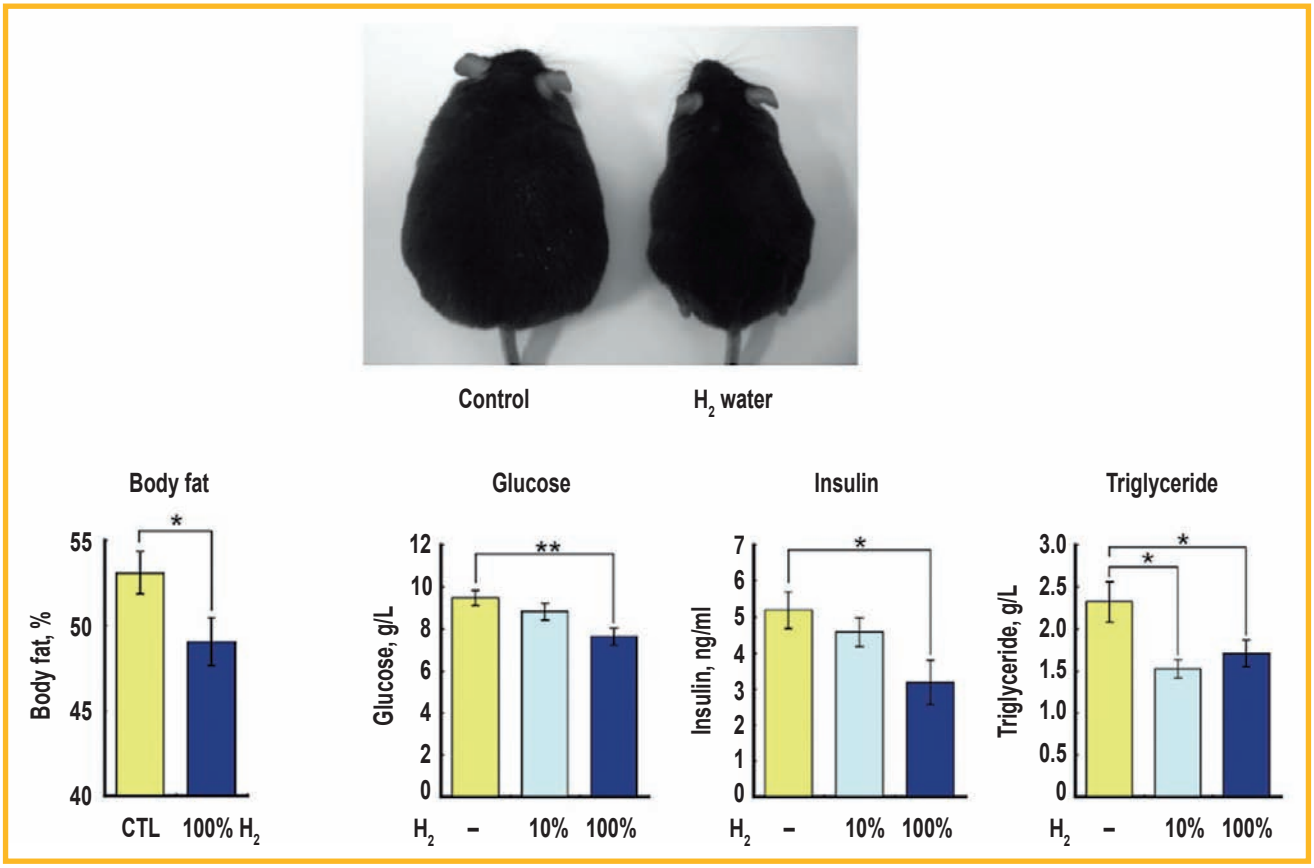

Figure 5. Hydrogen water suppresses obesity in db/db mutant mice. Control and hydrogen water-treated mice exhibited similar food and water intake and locomotor activity. However, drinking hydrogen water led to reductions in body fat, blood sugar levels, insulin levels, and blood triglycerides

We demonstrated the suppression of arteriosclerosis with H_2 water consumption in a murine model of arteriosclerosis [44], and ongoing clinical trials are further investigating this effect [43].

Regarding metabolic syndrome, a meta-analysis of eligible studies confirmed that drinking hydrogen water leads to reductions in blood lipids and cholesterol levels [45].

Dementia, Alzheimer's disease

Alzheimer's disease presents a formidable challenge, particularly due to its strongest risk factor, aging, which implicates multiple causative factors in its onset. Conversely, H_2 offers a multifaceted approach, encompassing antioxidant, anti-neuroinflammatory, anti-cell death, and energy metabolism-stimulating properties. Consequently, H_2 holds potential for prophylactic effects against Alzheimer's disease. In addition, H_2 has the advantage to reach the brain by crossing the blood-brain barrier (BBB) by gaseous diffusion without a specific drug delivery system.

Our attention was drawn to the observation that when animals are confined to small spaces and subjected to physical stress, oxidative stress accumulates in the brain, leading to impaired memory function. Upon administering H_2 water to physically stressed mice, we observed a suppression of the decline in memory function [46].

Next, to investigate the potential for suppress the decline of memory ability, we employed genetic manipulation to create dementia model mice, administering hydrogen water over six months from 14 to 18 months of age. Cognitive assessments utilizing Y-maze analysis revealed that hydrogen water mitigated memory decline and suppressed neurodegeneration in the hippocampus [47] (Figure 6).

Subsequently, a randomized, placebo-controlled clinical trial targeting subjects with mild cognitive impairment, a precursor to dementia, was conducted. Participants consumed 300 mL of hydrogen water daily for one year, with cognitive status assessed using the ADAS-cog scale [48]. Subgroup analysis focusing on subjects with APOE4 [49], a significant dementia risk factor, demonstrated significant symptom improvement with hydrogen treatment, surpassing the efficacy of approved medications [47].

In a clinical study involving eight severe Alzheimer's disease patients, inhalation of 3% hydrogen gas twice daily for six months yielded notable cognitive enhancement, assessed by ADAS-cog, persisting for an additional six months post-treatment cessation. Additionally, tensor diffusion imaging via MRI [50] revealed increased neuronal activity [51, 52]. Concurrently, a Korean study demonstrated reduced Alzheimer's disease markers with inhaled hydrogen gas [53], while a Chinese study reported symptomatic improvement in Alzheimer's patients [54].

The potential of H_2 for improving or slowing-down Alzheimer's disease is expected from various aspects [55].

Cancer management

We have demonstrated H_2's potential in alleviating adverse effects induced by chemotherapy and radiotherapy by animal experiments and clinical studies [56, 57].

Inhalation of H_2 gas has shown promise in improving outcomes for patients with advanced cancer, possibly mediated by two mechanisms: firstly, by reducing PD-1 expression on $CD8^+$ T-cells, thus enhancing immune function; and secondly, by enhancing mitochondrial activation via the 4-HNE/Akt/FoxO1 pathway, thereby mitigating mitochondrial dysfunction and boosting immune activity [58, 59].

H_2 emerges as a promising therapy for cancer treatment, supported by a systematic review encompassing 27 articles [60].

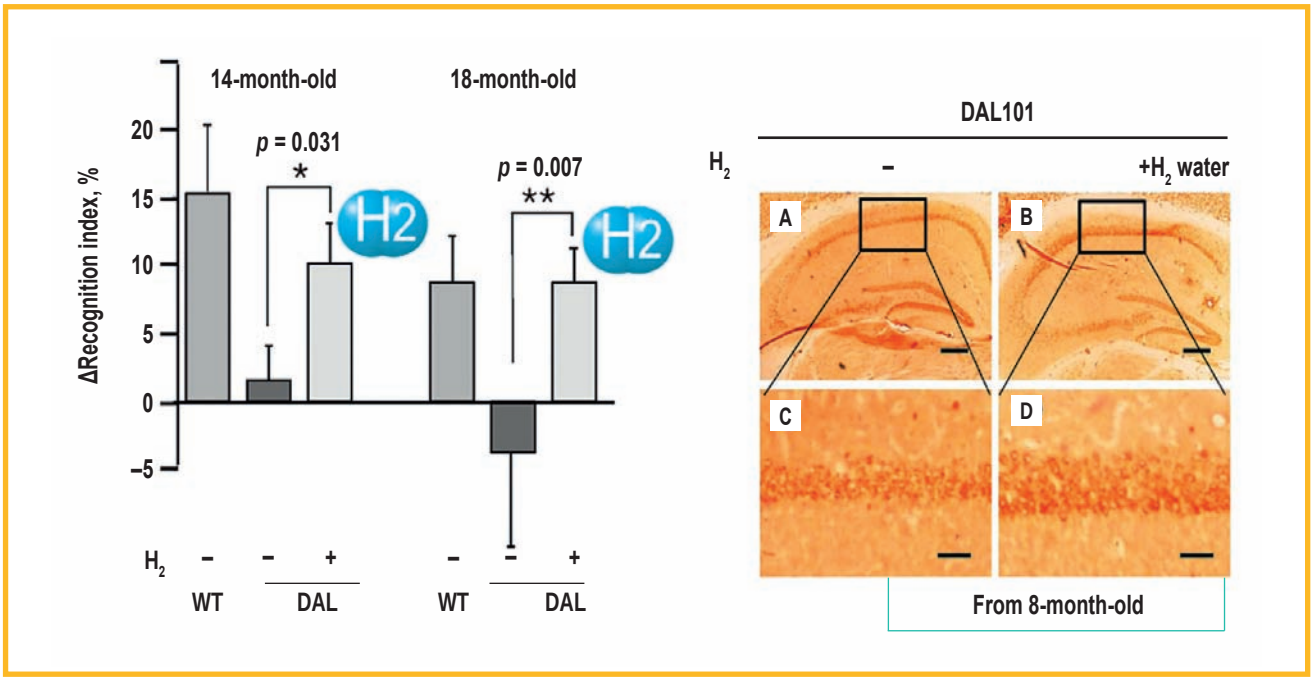

Figure 6. Molecular hydrogen mitigates age-dependent dementia in mice. Dementia model mice were provided with hydrogen water and subjected to cognitive assessments using Y-maze analysis. Administration of hydrogen water for six months, from 14 to 18 months of age, suppressed memory decline and neurodegeneration in the hippocampus

Conclusion

H_2 potentially presents remarkable therapeutic potential, benefiting patients with various severe ailments and promoting health and well-being in diverse populations. Hydrogen therapy may be a simple and low-cost treatment with minimum adverse effects, and may contribute to solving many of the serious problems facing today's society, so its mission is to receive public approval and to put it into practical use in the real world. However, further large-scale clinical studies are warranted to fully validate its efficacy and address current limitations, with the ultimate goal of curing sever diseases and enhancing quality of life across numerous medical conditions.

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