General characteristics of therapeutic molecular hydrogen

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Abstract

In recent years, interest in the use of molecular hydrogen, as a medical gas with possible therapeutic effects on the body, has increased. This applies primarily to the medical industry, but also to cosmetology. Molecular hydrogen as the smallest molecule in the Universe. In its gas form, it participates in numerous processes in living organisms. In the human body, molecular hydrogen plays the role of antioxidant. Directly, it neutralizes highly reactive oxidants and indirectly it reduces oxidative stress by regulating the expression of various genes. By regulating genes expression, molecular hydrogen functions as an anti-inflammatory, anti-allergic, and anti-apoptotic molecule, as much as stimulating energy metabolism. These properties are effectively used by scientists in innovative therapies, the effects of which are subject to research, in order to define the widest range of medical and cosmetological applications of hydrogen. The aim of this work is to describe the general characteristics of molecular hydrogen, touching upon the most up-to-date scientific literature in the field of medicine, as well as the descriptions of clinical trials on the therapeutic use of molecular hydrogen and chemical articles on the physicochemical properties of such element. This work defines the concept of molecular hydrogen and hydrogen-rich water, describing the history of therapeutic use of molecular hydrogen, the method of its administration to the human body, as well as methods for measuring the concentration of hydrogen molecules. This article is intended as an introduction to the presentation of specific possibilities of using therapeutic molecular hydrogen in various disciplines of medicine and cosmetology.

Key words:

molecular hydrogen, characteristics, therapy

Introduction

Hydrogen is one of the most widespread elements in the Universe. At standard temperature and pressure, it exists as a colourless, odorless, tasteless, diatomic gas with the molecular formula (H2) [1].

Because hydrogen atoms are covalently linked, they form a molecule. Therefore, H_2 is referred to as a molecular or «free hydrogen» (also, dihydrogen, or hydrogen gas). The hydrogen molecule contains two protons and two electrons, making it a neutrally charged molecule. It is a colourless, odorless, tasteless, non-metallic, flammable gas and it becomes explosive if mixed with air in concentration above 4.6%. The hydrogen molecule is also 14.4 times lighter than air. This form of hydrogen has precise therapeutic effects on organisms [2].

Characteristics of hydrogen

The two hydrogen atoms combine with a sigma bond [3]. During the formation of this bond, 436 kJ / mol (104 kcal / mol) of energy is released. The reaction product is more stable than the substrate, because 436 kJ / mol of energy, to bind H-H, would have to be provided to break the H_2 molecule into two H atoms [2].

On Earth, free hydrogen is relatively rare. Most of the hydrogen found on our planet is found in water and organic compounds. It is highly reactive in the presence of certain catalysts and/or heat [2]. One of more spectacular examples of its reactivity was shown in 1937, when Zeppelin Hindenburg, using hydrogen as the lifting gas, caught fire and was destroyed in less than a minute as a result of a fire. This is one of the reasons why the use of hydrogen as a therapeutic agent was not intuitively obvious [4].

Hydrogen ions are protons. In addition to the common isotope – protium (^1H), hydrogen occurs as a stable deuterium (^2H) isotope and unstable radioactive isotope tritium (^3H) [1].

Hydrogen in its atomic form (H•) is neutral and contains an unpaired electron. This free radical form is rare because it is unstable and quickly bonds with a second hydrogen atom. During electrolysis it is observed that H• starts to be the source of forming molecular hydrogen (H• + H• → H2). Atomic hydrogen has probably been incorrectly translated from Japanese into English as "active hydrogen"[5].

Hydrogen in the oxidation stage -1 forms an ion (H^-), known as "hydride", which is unstable in the presence of water. It contains one proton and two electrons. It is not a free radical unless it contains an unpaired electron. Water oxidizes it to free hydrogen: $H^- + H_2O \rightarrow H_2 + OH^-$ [6].

Hydrogen under natural conditions does not occur in the form of independent positively charged hydrogen ion (also named "proton", H^+), formed by the detachment of the electron from the H atom, and thus does not occur in the form of a free proton. In water, the proton undergoes solvation [7]. H^+ is responsible for the pH found in water [8], and it plays an important role in proton ATPases, those are used by cells to transport protons against the electrochemical gradient by harnessing the energy of ATP hydrolysis [9].

In 1975, one of the first publications on hydrogen as a medical gas was published, the authors of which were Dole and colleagues from the University of Baylor and Texas A&M. Researches have shown that hyperbaric hydrogen therapy effectively reduces melanoma tumors in mice by placing nude mice suffering from squamous cell carcinoma in a chamber with 2.5% oxygen and 97.5% hydrogen at 8 atm [10].

In 1994, it was noticed that hydrelix – a mixture consisting of 49% hydrogen, 50% helium, and 1% oxygen, effectively prevents decompression sickness and nitrogen narcosis of divers working below 500 meters below sea level [11].

In 2001, anti-inflammatory effects of hyperbaric hydrogen on animal organisms afflicted with chronic hepatitis were observed. Infected animals stayed for two weeks in a hyperbaric chamber in an atmosphere supplemented with 0.7 MPa of molecular hydrogen. The treatment had a significant impact on liver regeneration, namely reduction of fibrosis, improvement in hemodynamics, increase in antioxidant enzymes, reduction of lipid peroxidation and reduction of TNFa circulation [12].

In 2002, an article was published in which Yuping Li and associates described how electrolysed water exerts antioxidant activity against ROS and protects beta-cell cells from pancreatic-induced damage to cells [13].

In 2005, the pioneering work of Tomoyuki Yanagihara and associates, describing how rich in neutral hydrogen (with a pH value close to 7) appeared, the water that was produced by the electrolysis device reduced the oxidative stress in rats. Researchers have for the first time proved that it is molecular hydrogen, not the alkaline pH of electrolyzed alkaline water, that has therapeutic effects [14].

However, interest in hydrogen started relatively recently after 2007, when it was discovered that the administration of hydrogen gas by inhalation (at levels below the flammability limit of 4.6% by volume) or the intake of aqueous solution containing dissolved molecular hydrogen can also exert therapeutic biological effects. Inhalation of 2-4% molecular hydrogen significantly reduces the volume of focal encephalocele in a study of rats in which ischemia-reperfusion injury was induced by closure of the middle cerebral artery. Hydrogen was more effective than edarinavone (a clinically approved drug administered in cases of cerebral infarction) and had no negative toxic effects. The authors also showed that dissolved hydrogen in cultured cell media in biologically significant concentrations lowers the level of toxic hydroxyl radicals (•OH), does not react with other physiologically important reactive oxygen species (e.g., peroxides, nitric oxide, hydrogen peroxide) [15]. "Since most drugs specifically act on their specific targets, H_2 seems to differ from conventional pharmaceutical drugs. Owing to its great efficacy and lack of adverse effects, H^2 has potential clinical applications for many diseases" – wrote M. Ichihara in "Medical Gas Research" [16].

The unique physicochemical properties of molecular hydrogen, such as hydrophobicity, neutrality, size, mass, etc., provide excellent ability to penetrate biomembranes (e.g., cell membranes, blood-brain barrier, placenta and blood-testicle barrier) and reach the intercellular compartments (e.g. mitochondria, cell nuclei, etc.), where it can exert its therapeutic effect [17].

Molecular hydrogen can be administered to the human body, including the previously mentioned method of hyperbaric treatment [10] [12] and inhalation [15][18], via ingestion of solubilized hydrogen-rich solutions [19], hydrogen-rich hemodialysis solution [20], intravenous injection of hydrogen-rich saline [21], topical administration of hydrogen-rich media (e.g. bath, shower and creams) [17], ingestion of hydrogen-producing material upon reaction with gastric acid [21], or ingestion of non-digestible carbohydrates as prebiotic to hydrogen-producing intestinal bacteria [22].

The most commonly used methods are inhalations and drinking hydrogen-rich water (hydrogen water). The pharmacokinetics of each method is still under investigation, but it depends on the dosage and time [23].

In the case of inhalation, a 2-4% hydrogen mixture is most common because it is below the flashpoint; however, some studies use 66.7% H_2 and 33.3% O_2, which is a mixture of non-toxic and effective, but flammable. Inhaled hydrogen reaches the maximum plasma level (i.e., the balance based on Henry's law) in about 30 minutes, and after inhalation, the return to the baseline takes place in about 60 minutes. Molecular hydrogen gas can be inhaled through the ventilation circuit, face mask or nasal cannula. Just as inhaled molecular hydrogen works quickly, it can be used as an emergency treatment for acute oxidative stress [24].

Inhalation of molecular hydrogen gas is impractical in the case of daily consumption of molecular hydrogen for preventive purposes. On the other hand, hydrogen-rich water may be beneficial because it is administered in a safe and easy-to-use manner [25].

Hydrogen-rich water can be produced by several methods: by introducing molecular hydrogen gas into water under high pressure, by electrolysing water to form molecular hydrogen and by reacting magnesium metal or its hydride with water. These methods can be used not only in contact with water, but can also be used with other solvents. It is worth remembering that molecular hydrogen penetrates the glass and plastic walls of any vessel in a short time, while aluminum containers can stop molecular hydrogen for a long time [24].

Drinking hydrogen rich water causes a peak increase in plasma and H_2 concentration within 5-15 minutes in a dose-dependent manner. The increase in the amount of hydrogen in the exhaled air indicates that the hydrogen diffuses into the circulatory system,

and then it is expelled from the lungs. This increase in H_2 in blood and breath returns to baseline within 45-90 minutes, depending on the dosage used [26].

Molecular hydrogen is injected intravenously or intraperitoneally as a hydrogen-rich physiological saline (dissolved molecular hydrogen in physiological saline, *further* – H_2-saline), which allows the delivery of molecular hydrogen with high efficiency in animal models [27]. Kimihiro Nagatani and associates conducted an open, prospective, non-randomized study of intravenous administration of molecular hydrogen in 38 patients, hospitalized for acute cerebral infarction. All patients received intravenous solution H2, immediately after the diagnosis of acute cerebral infarction. Data from this study indicate that intravenous solution of molecular hydrogen is safe for patients with acute cerebral infarction, including patients treated with a tissue-plasminogen activator (marker of inflammation) [28].

Eye drops filled with molecular hydrogen can be prepared by dissolving H_2 in saline and directly administering them to the surface of the eye [29]. Molecular hydrogen easily penetrates the skin and is distributed throughout the body by the blood. Therefore, taking a warm bath with dissolved molecular hydrogen, H_2 can be delivered to the body every day. It takes just 10 minutes to spread it all over the body, according to the assessment of molecular hydrogen gas measurement when exhaling. Powders that can be used to make H_2 baths are available on the Japanese market [30].

There are several methods for measuring hydrogen gas concentration, but the most useful is measuring by gas chromatography. In addition, the concentration of H_2 dissolved in the solution can be measured using this method. For example, the molecular hydrogen in the blood may be monitored by the following method: venous or arterial blood (e.g., 5 ml) is collected in a sealed aluminum pouch without dead space, and then a specific volume of air (e.g., 1 ml) is added to the pouch. After complete transfer of molecular hydrogen gas from the blood to the air in a sealed pouch, H_2 can be measured by gas chromatography. The inhalation of molecular hydrogen actually increases the molecular hydrogen dissolved in arterial blood in a concentration-dependent manner of hydrogen, and the venous hydrogen levels in venous blood were lower than in arterial blood; a different level between arterial and venous blood indicates the amount of molecular hydrogen incorporated and consumed by the tissues [15].

In a clinical study conducted by Hirohis Ono and associates in 2012, the difference in molecular hydrogen concentrations between arterial and venous blood was also demonstrated [31]. The molecular hydrogen concentration can be measured using a H_2 electrode, which is used primarily to detect molecular hydrogen; however, it is also slightly sensitive to hydrogen sulphide. For this reason, when the solution is contaminated with hydrogen sulfide, the possible effects should be taken into account. Molecular hydrogen can be measured in tissues using a needle H_2 sensor. The electrode current was measured using a picoammeter connected to the recorder. The negative current obtained from the H_2 sensor was converted into a regional H_2 concentration by means of a calibration curve generated from known levels saturated with molecular hydrogen of saline [24].

Hydrogen-rich water

The concept of hydrogen-rich is used to describe the so-called "hydrogen water", which we can observe by reading scientific articles [32] [33] [34]. The very concept of "hydrogen water" is described on the website of the Molecular Hydrogen Institute [35]. The concentration of H2 gas in water or air is presented as ppm (mg/L, weight/volume) or % (volume/volume) [36]. Because flow devices are capable of producing a liter or more of water with the same H_2 concentration, the measured water concentration of this class of equipment will typically be representative of the number of milligrams of molecular hydrogen that will be consumed after drinking one liter of water [37].

Interpreting the measurement of H_2 water produced by other technologies (tablets, sticks, cartridges, etc.) than flow ones, the ppm measurement must be converted to mg / L, adjusting it to the volume of water rich in hydrogen in the test tube. Only after this conversion it could be determined, how much

molecular hydrogen will be consumed after drinking the entire contents of the sampled container [38].

The titration method using colloidal methylene-platinum blue reagent is effective in determining the concentration of hydrogen gas in an aqueous solution [39].

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