ISSN: 2980-3063 (online) Review

Rats
2023; 1(1): 11-13
Doi: 10.5281/zenodo.8143351
https://ratsjournal.com

Recent knowledge of hydrogen therapy: Cases of rat

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Recevied: 18.05.2023 Accepted: 05.06.2023 Published: 13.07.2023

Abstract
Hydrogen therapy, which originated in Japan, is gaining popularity and expanding its reach to other Asian countries as well as the USA. The rise in the number of centenarians in Japan has been linked to the elevated levels of hydrogen gas detected in their breath. Subsequently, extensive research, consisting of thousands of studies focusing on numerous diseases, has been conducted. Owing to its non-toxic nature and numerous advantageous characteristics, molecular hydrogen has been proposed for applications in areas such as food, agriculture, pharmaceuticals, and medicine. This review highlights recent advancements in hydrogen research using rat models.
Keywords: *Molecular hydrogen, hydrogen therapy, health, rat.*

1. Introduction

Over the past two decades, the interest of researchers has steadily grown towards hydrogen therapy. The distinctive attributes of hydrogen, particularly its environmentally friendly qualities and its wide range of beneficial and therapeutic functions, have motivated numerous research centers and medical institutions to investigate the potential applications of hydrogen in treating various diseases. In 2007, Ohsawa and co-workers were the first to evaluate the therapeutic use of hydrogen as an antioxidant, in a rat model of ischemia.[1] Afterward, several laboratories and research centers especially in Japan, China, Korea, and the USA lanced new plans to explore the potential therapeutic uses of hydrogen. Since 2007, 78 Randomized Controlled Trials, 101 Clinical Trials, 25 meta-analyses, and 161 review papers have been published according to the database of PubMed and Web of Science. 503 research has been conducted on hydrogen therapy on rats according to the database of PubMed. In this paper, we will discuss the last reports on the use of hydrogen therapy in rat models.

2. Molecular hydrogen stimulates Coenzyme Q and improves the mitochondrial function of Rats

Mitochondria is the energy center of the cell producing ATP necessary for different physiological needs. Mitochondria plays an important role in the function of the heart where it forms about 38% of the cell volume.[2] Excessive production of free radicals causes oxidative damage to mitochondria. Antioxidant therapy may be helpful in this pathological process. Molecular Hydrogen (H_2) has been shown to possess selective antioxidant activity, especially against the most aggressive ones i.e. hydroxyl radical and peroxynitrite.[3]

In a study performed on rats, Gvozdjáková and co-workers revealed that the long-term administration of hydrogen-rich water (45 days) significantly stimulated CoQ9-OX concentration in the rat myocardium tissue by 31.80% and decreased plasma malondialdehyde concentration.[2] This study showed that short and prolonged intake of hydrogen-rich water can provide a positive effect on coenzyme Q9 concentration and respiratory chain function of mitochondria of rat hearts.

3. Molecular hydrogen intake lowers blood pressure in a rat model of hypertension

Hypertension is one of the most common diseases with about 1.13 billion people worldwide. It forms a risk factor for other diseases such as cardiovascular and chronic kidney diseases. A study has been performed to evaluate the possible effect of hydrogen on hypertension. Rats were exposed to a hydrogen-including gas mixture (1.3% H_2 + 21% O_2 + 77.7% N_2) at a 10 L/min flow rate for 1 h per day for 4 weeks using an anesthetic box.[4] Results showed that hydrogen significantly reduced blood pressure in 5/6 nephrectomy rats in the chronic phase. These results showed that hydrogen possesses an anti-hypertensive effect independent of its anti-inflammatory properties during the perioperative phase. Additionally, hydrogen exhibited an anti-hypertensive effect not only during daytime rest but also during night-time activities.

4. Molecular hydrogen intake modifies the physiological function of rats

Molecular hydrogen possesses not only therapeutic advantages but also a multitude of nutritional and physiological properties. A study was performed on healthy rats to evaluate the effect of hydrogen intake on their body and serum parameters.[5] Sprague–Dawley rats were subjected to two types of hydrogen therapy: hydrogen-rich water intake and hydrogen inhalation for 6 months The hydrogen rich water (HRW) group was provided access to HRW by oral intake for 1 h each time, two times per day; while the inhalation group was pla-

How to cite this article: Alwazeer D. Recent knowledge of hydrogen therapy: Cases of rats. Rats, 2023; 1(1): 11-13. Doi: 10.5281/zenodo.8143351

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ced in an inhalation chamber (4% H_2, 96% air containing 21% O_2) for 1 h each time, and two times a day. The hydrogen therapy of rats allowed for a significant decrease in the following serum biochemical parameters: body weight (BW), uric acid (UA), serum triglycerides (TG), serum total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), serum aspartate aminotransferase (AST), serum total bile acid (TBA), lactic dehydrogenase (LDH), α-hydroxybutyric dehydrogenase (HDB), creatine kinase (CK) and its isoenzyme creatine kinase-MB (CK-MB). However, no effect on the fasting blood glucose (FBG), or serum alanine aminotransferase (ALT) levels, has been shown after the six months. There were slight differences between the two intervention methods regarding the change in biochemical parameters with a more significant effect shown for HI than HRW for the majority of parameters.

5. Hydrogen gas inhalation improves delayed brain injury in rats

Aneurysmal subarachnoid hemorrhage (SAH) is a common disease that is divided into early brain injury (EBI) and delayed brain injury (DBI). DBI known as focal neurological deficits and/or cognitive deficits is considered the main cause of mortality and morbidity after SAH. Sprague–Dawley rats were subjected to 1.3% H2 gas (1.3% H_2, 30% O_2, 68.7% N_2) inhalation.[6] The study showed that early brain injury (EBI), reactive astrogliosis, and delayed brain injury (DBI) were ameliorated in the hydrogen inhalation group. Due to the nontoxic effects of hydrogen gas inhalation, in the future, the inhalation of hydrogen gas before coiling surgery and in patients with suspected SAH in the ambulance before arrival at the hospital might reduce the brain damage of the patient.

6. Hydrogen therapy reduces oxidative stress and renal fibrosis in rats

Free radicals cause oxidative stresses that are responsible for the occurrence of inflammatory conditions such as unilateral ureteral obstruction (UUO). UUO generally induces renal fibrosis through ROS accumulation. In a recent study, UUO rats were administered hydrogen-rich water for 2 weeks post-surgery [7]UUO kidneys were found to have widened interstitial spaces and tubular dilatation. Compared with the UUO + DW group, HW administration attenuated tubulointerstitial injury and reduced interstitial fibrotic area, causing a substantial decline in the frequency of α-SMA-, ED-1-, and TGF-β1-positive cells in the UUO + HW group. The decrease in the klotho mRNA expression in the UUO + HW group was less pronounced than that in the UUO + DW group. Conclusion: Oral HW intake reduced oxidative stress and prevented interstitial fibrosis in UUO kidneys, potentially involving klotho in the underlying mechanism. Impact: Oral intake of hydrogen-rich water (HW. The study showed that HRW administration alleviated tubulointerstitial injury and decreased interstitial fibrotic area, allowing a substantial decline in the frequency of α-SMA-, ED-1-, and TGF-β1-positive cells. The study concluded that intaking HRW can reduce oxidative stress and prevent interstitial fibrosis in UUO kidneys.

7. Molecular hydrogen reprograms the liver metabolism in rats

The liver is known as the metabolic center that connects many organs and has the ability to accumulate the highest hydrogen levels [8]molecular data to support therapeutic functions attributed to the biological activities of H2 remain elusive. Here, using transcriptomic and metabolomic approaches coupled with biochemistry and micro-CT technics, we evaluated the effect of long-term (6 months. In a study, two types of hydrogen administration i.e. hydrogen-rich water intake (rats were given access to HRW for 1 h, twice a day) and hydrogen gas inhalation (rats were exposed to 4% hydrogen gas for 1 h and twice a day) were tested for evaluating the effect of hydrogen administration on liver function in the rat [8]molecular data to support therapeutic functions attributed to the biological activities of H2 remain elusive. Here, using transcriptomic and metabolomic approaches coupled with biochemistry and micro-CT technics, we evaluated the effect of long-term (6 months.

The study showed that rats exposed two hours daily to hydrogen either by drinking HRW or by breathing 4% H_2 gas showed a reduction in lipogenesis and an increase in lipolysis in the liver, which was linked with an apparent loss of visceral fat and brown adipose tissue as well as a reduced level of serum lipids. The hydrogen treatment seems to trigger lipid and amino acid catabolism in the liver to provide energy and building blocks for purine nucleotides and carbohydrates biosynthesize reactions by modulating pathways involving the redox couple NADP/NADPH.

8. Molecular hydrogen improves type 2 diabetes in rats

Type 2 diabetes mellitus is a hyperglycemia metabolic disorder disease that is considered a chronic inflammatory state.

Diabetic Sprague-Dawley rats were provided with 500 µL saturated hydrogen saline by intragastric injection for 80 days.[9] The study showed that hydrogen administration could decrease fasting blood glucose levels and increase hepatic glycogen synthesis and improve insulin sensitivity. Hydrogen administration could also increase serum superoxide dismutase (SOD) levels while decreasing serum malondialdehyde (MDA). Additionally, the hydrogen treatment could alleviate the pathological changes exhibited by pancreatic islets and kidneys during type 2 diabetes mellitus by improving hyperglycemia and inhibiting oxidative stress. The study concluded that hydrogen therapy can be administrated against type 2 diabetes mellitus. Another study evaluated the impact of *ad libitum* drinking hydrogen-rich water by type 2 diabetes db/db obesity model mice lacking the functional leptin receptor. The study revealed that drinking H_2-rich water decreased hepatic oxidative stress, and alleviated fatty liver and high fat-diet-induced fatty liver, and decreased levels of plasma glucose, insulin, and triglyceride allowing to significantly controlled fat and body weights.[10]

9. Hydrogen therapy alleviates inflammation in spinal cord damage in rats

Post-traumatic spinal cord injury is considered a common cause of severe physical disability. It is believed that free radicals play a role in the secondary injury developed after spinal cord damage. In a recently published study, spinal cord injury rats were subjected to hydrogen-rich saline (HRS) treatment for 7 days after laminectomy at T7–T10.[11] The study revealed that IL-6

and TNF-α levels as well as apoptosis were decreased in spinal cord injury rats treated with HRS. The study concluded that the hydrogen administration effect may be clinically useful as adjuvant therapy after spinal cord injury.

10. Molecular hydrogen alleviates nuclear electromagnetic pulse-induced brain damage in rats

Exposure to irradiation can cause negative impacts on the body including the central nervous system. In a recently published study, rats were exposed to nuclear electromagnetic pulse (NEMP) causing severe brain injury.[12] Rats were provided access to hydrogen-rich water 3 days before NEMP exposure. Results of the study showed that NEMP-exposed rats exhibited anxiety-like behavior, and hydrogen treatment could alleviate it. Additionally, the NEMP-Hydrogen group showed a significant impact on the neuroactive ligand-receptor interaction, synaptic vesicle cycle, and synapse.

11. Conclusion

After about fifteen years of the first paper revealing the potential therapeutic properties of hydrogen due to its selective antioxidant activity in rat models, the number of research papers on hydrogen therapy is still increasing trend. One of the key advantages of hydrogen therapy is its "green" notes. The intake of hydrogen by hydrogen-rich water and other beverages provides one of the simple methods of hydrogen supplementation. This trend of hydrogen-rich products will increase in the future due to the positive results of scientific research papers on different physiological parameters of the body, lifestyle, and health.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

This situation does not exist.

Funding statement

This study has not received any financial support from any institution.

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