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Molecular-Hydrogen, a Natural Resource for Health, in the Context of Modern Life

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Abstract: Objectives. The aims of this paper is to highlight the importance of molecular hydrogen (MH) as a natural resource for health, in the context of modern life. **Prior Work**. Hydrogen is an essential chemical element present in our universe. Scientific studies have suggested that MH may have beneficial effects on different conditions and diseases, such as inflammatory, neurodegenerative, metabolic disorders, tissue damage due to ischemia-reperfusion. **Approach**. Oxygen, a molecule essential to life, is likely to cause damage in the body via the formation of free radicals, also called activated oxygen species. Hydrogen exists in several forms but we find it mainly in the molecular form of hydrogen also called diatomic form, or dihydrogen. **Results.** Due to its small size MH can easily penetrate cells and act directly on free radicals. Unlike many other antioxidants, it does not neutralize reactive species necessary for essential cellular functions, making it an antioxidant without unwanted side effects. MH is easily accessible, it can be inhaled, dissolved in water or administered intravenously, which allows various options for use, especially as an antioxidant. **Value**. Overall, this paper presents some important antioxidative mechanisms of MH, forms and methods of use and its benefits as an antioxidant.

Keywords: molecular hydrogen; health; oxidative stress; antioxidant

1. Introduction

Molecular hydrogen (MH) is a colorless, tasteless, odorless, highly flammable molecule that become an increasingly popular research topic for its potential in reducing oxidative stress and improving athletic performance (Sies & Cadenas, 1985).

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MH is the smallest molecule and therefore can easily penetrate the cell membrane, such as the blood-brain barrier (BBB) so quickly diffuse into the organelles and act at various sites in the body (Ostojic, 2018).

Compared to other medical gases, MH is not cytotoxic, while medical gases such as hydrogen sulfide (MHS), carbon monoxide (CO), and •NO are highly toxic molecules and play important roles as signaling molecules (Kimura, 2010; Motterlini & Otterbein, 2010).

2. MH Actions and Effects in Different Pathologies

Animal experiments and clinical studies have demonstrated the protective effects of MH on many organs and systems. MH has various mechanisms of action, such as modulating oxidative stress, inflammation, autophagy, the aging process. Most studies have reported the effects of MH on diseases such as tumors, stroke, diabetes disease (Ge, et. al, 2017).

The additional transport of MH to various organs and tissues ensures the development of systemic effects, which include organoprotective effects, minimization of the consequences of ischemia-reperfusion injuries, limitation of systemic inflammatory responses, anti-tumor effects, anti-aging effects, increasing the body's resistance to stress factors, improved tolerance to effort (Huang, et. al, 2010).

MH has multiple indications for use, such as anti-allergic, anti-apoptotic, anti-inflammatory and antioxidant representing a potential therapeutic benefit for both prophylaxis and remediation (Jurcău, et. al, 2023). Thus, is evidence for the modulatory effect of molecular hydrogen on various types of metabolism, in particular, lipid, protein and carbohydrate metabolism (Iuchi, et. al, 2016).

We present some examples of *MH action in different conditions*:

a) In hypertension, MH regulates the RAAS and sympathetic system by penetrating the BBB to attenuate NLRP3-mediated inflammation (Socha, et. al, 2020).

b) In type 2 diabetes, MH inhibits the activation of NLRP3 and caspase-1 in the NLRP3 inflammasome pathway and prevents the translocation of NF-KB caused by the activation of TLR2 and TLR4 (Ding, et. al, 2019).

c) In Hepatitis, MH controls NLRP3 activation in liver cells to prevent chronic inflammation in the liver (Mridha, et. al, 2017).

d) In chronic kidney disease, MH controls the activation of NLRP3 inflammasomes to prevent chronic inflammation in the kidneys (Kim, et. al, 2019).

e) In Parkinson's disease, MH prevents mitophagy and activation of microglia cells by controlling the activation of NLRP3 inflammasomes in dopaminergic neurons (Qin, et. al, 2021).

3. MH and Oxidative Stress

The antioxidant action of MH has attracted considerable attention and many studies have reported its benefits. MH acts as a powerful selective antioxidant, having the ability to neutralize free radicals without affecting other reactive oxygen species (ROS) necessary for normal cell signaling. MH directly reduces hydroxyl radicals in cultured cells, indicating its antioxidant activity at the cellular level (Buxton, et. al, 1988).

It is believed that MH can selectively reduce hydroxyl and peroxynitrite radicals and does not affect physiologically reactive species (Sies & Cadenas, 1985). Although MH was considered to be an inert gas in living bodies for many years, an animal study reported that inhalation of gaseous molecular hydrogen decreased oxidative stress and brain injury caused by ischemia and reperfusion injury due to its antioxidant action (Ohsawa, et. al, 2007).

By reducing oxidative stress, molecular hydrogen can indirectly attenuate inflammatory responses by modulating inflammatory signaling pathways such as NF-κB and MAPK pathways, thus suppressing the production of pro-inflammatory cytokines and inhibiting apoptosis in various cell types, an effect that could be mediated of its antioxidant properties, as oxidative stress is a common trigger of apoptosis (Terasaki, et. al, 2011). MH prevents the uncontrolled leakage of electrons from the electron transport chain thus improving mitochondrial dysfunction and regenerates cell dysfunction (Tian, et. al, 2021).

MH also reduces the expression of intercellular adhesion molecules and chemokines and thus decreases the infiltration of neutrophils and macrophages (Chen, et. al, 2018). The effects of MH administration may vary depending on the context, thus it could trigger protective responses, such as upregulation of cytoprotective proteins or activation pathways such as NF-κB/Bcl-xL (Ohta, 2014).

4. MH in Relation to Physical Exercise

Fatigue. The use of specific biomarkers for oxidative stress (such as the level malondialdehyde, lipid peroxidation, or antioxidant enzyme activity) can be used to measure the impact of MH, alongside the assessment of parameters related to athletic performance, such as recovery time, endurance, or fatigue reduction (Sies & Cadenas, 1985). Also it was observed that the consumption of MH before physical effort caused a post-exercise reduction in blood lactate levels and an improvement in muscle fatigue after acute exercise (Aoki, et. al, 2012).

Intense physical effort. Intense or irregular exercise has similarities to disease models in terms of pathological factors, such as ROS, inflammation, and metabolic changes; studies in rats have shown that administration of MH can be as effective as exercise in protecting against myocardial injury induced by acute myocardial infarction (Ichihara, et. al, 2015). Administration of MH may mimic some benefits of exercise and restore redox homeostasis, attenuating inflammation and preventing pathological changes induced by extreme exercise. It is suggested that MH may have protective and therapeutic effects against harmful forms of exercise (Ostojic, 2015). Unlike conventional antioxidants, MH does not scavenge all reactive oxygen species (ROS), but selectively reduces excessive levels and this property recommends it for research as a potential safe and effective medical gas for clinical management and potential mitigation of the adverse effects of vigorous exercise (Halliwell & Gutteridge, 2015).

The use of MH in sports was done in different forms of administration and in *various forms of physical effort*, of which we present some important ones.

a) Recreationally trained soccer players using 30 min pedaling effort and maximal knee extension exercises - adequate hydration with MH-rich water before exercise was found to reduce blood lactate and improve muscle function (Aoki, et. al, 2012).

b) Exercise cycling in untrained participants - drinking MH water had antioxidative effects during consecutive days of intense exercise helping to prevent accumulated muscle fatigue (Dobash, et. al, 2020).

c) Treadmill and jump squats 5 × 10 repetitions - inhalation of MH gas during the post-exercise recovery period results in reduced oxidative damage and consequently improves exercise performance (Shibayama, et. al, 2020).

d) Cycling to exhaustion test - continuous MH water supplementation potentially increases aerobic capacity, leading to improved aerobic exercise performance and physical health (Hori, et. al, 2020).

5. Routes of MH Administration and their Characteristics

MH can be administered in different ways, having different effects (Fu & Zhang, 2022).

a) Hydrogen gas, by inhalation is a simple method with rapid action;

b) Hydrogen water, by oral intake or bath is portable, safe, and convenient;

c) Hydrogen saline, by peritoneal injection, intravenous injection, intrathecal injection or eye drops, provides highly accurate hydrogen doses; produces neuro-protectipe effects an d may treat eye diseases;

d) Hydrogen nanocrystals, by oral intake or injection, gas highly targeted effects.

6. Conclusion

Hydrogen is an essential chemical element present in our universe. MH is a gas that has multiple beneficial effects due to which it can be used in numerous conditions. It has small size MH, so it can easily penetrate cells, it is easily accessible, it can be inhaled, dissolved in water or administered intravenously, which allows various options for use, especially as an antioxidant. Overall, MH is a natural resource for health which deserves attention and practical application in the context of modern life.

Conflict of interests

Nothing to declare.

References

Aoki, K.; Nakao, A.; Adachi, T.; Matsui, Y. & Miyakawa, S. (2012). Pilot study: Effects of drinking hydrogen-rich water on muscle fatigue caused by acute exercise in elite athletes. *Medical Gas Research*, Vol. 2.

Buxton, G. V.; Greenstock, C. L.; Helman, W. P. & Ross, A. B. (1988). Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals (OH/O-) in aqueous solution. *Journal of Physical and Chemical Reference Data*, Vol. 17(2), pp. 513-886.

Chen, M.; Zhang, J.; Chen, Y.; Qiu, Y.; Luo, Z. & Zhao, S. et al. (2018). Hydrogen protects lung from hypoxia/re-oxygenation injury by reducing hydroxyl radical production and inhibiting inflammatory responses. *Scientific Reports*, Vol. 8.

Ding, S.; Xu, S.; Ma, Y.; Liu, G.; Jang, H. & Fang, J. (2019). Modulatory Mechanisms of the NLRP3 Inflammasomes in Diabetes. *Biomolecules,* Vol. 9(12).

Dobashi, S.; Takeuchi, K. & Koyama, K. (2020). Hydrogen-rich water suppresses the reduction in blood total antioxidant capacity induced by 3 consecutive days of severe exercise in physically active males. *Medical Gas Research*, Vol. 10(1), pp. 21-26.

Fu, Z. & Zhang, J. (2022). Molecular hydrogen is a promising therapeutic agent for pulmonary disease. *Journal of Zhejiang University-Science B,* Vol. 23(2), pp. 102-122.

Halliwell, B. & Gutteridge, J. M. C. (2015). *Free Radicals in Biologiy & Medicine*. 5th Edition. Auflage. New York: Oxford University Press.

Hori, A.; Sobue, S.; Kurokawa, R.; Hirano, S. I.; Ichihara, M. & Hotta, N. (2020). Two-week continuous supplementation of hydrogenrich water increases peak oxygen uptake during an incremental cycling exercise test in healthy humans: a randomized, single-blinded, placebo-controlled study. *Medical Gas Research,* Vol. 10(4), pp. 163-169.

Ichihara, M.; Sobue, S.; Ito, M.; Ito, M.; Hirayama, M. & Ohno, K. (2015). Beneficial biological effects and the underlying mechanisms of molecular hydrogen - comprehensive review of 321 original articles. *Medical Gas Research*, Vol. 5(1).

Jurcău, R.N.; Jurcău, I.M. & Colceriu, N.A. (2023). Molecular hydrogen, a therapeutic gas with antioxidant effects, general aspects and mechanisms. *Health, Sports & Rehabilitation Medicine*, Vol. 24(1), pp. 32-37.

Kim, Y. G.; Kim, S. M.; Kim, K. P.; Lee, S. H. & Moon, J. Y. (2019). The Role of Inflammasome-Dependent and Inflammasome-Independent NLRP3 in the Kidney. *Cells,* Vol. 8(11).

Kimura, H. (2010). Hydrogen sulfide: from brain to gut. *Antioxid Redox Signal,* Vol. 12(9), pp. 1111-1123.

Motterlini, R. & Otterbein, L. E. (2010). The therapeutic potential of carbon monoxide. *Nature Reviews Drug Discovery,* Vol. 9(9), pp. 728-743.

Mridha, A. R.; Wree, A.; Robertson, A. A. B.; Yeh, M. M.; Johnson, C. D.; Van Rooyen, D. M.; Haczeyni, F.; Teoh, N. C.; Savard, C.; Ioannou, G. N.; Masters, S. L.; Schroder, K.; Cooper, M. A.; Feldstein, A. E. & Farrell, G. C. (2017). NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *Journal of Hepatology,* Vol. 66(5), pp. 1037-1046.

Ohta, S. (2014). Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. *Pharmacology & Therapeutics*, Vol. 144(1), pp. 1-11.

Ostojic, S. M. (2015). Molecular hydrogen in sports medicine: new therapeutic perspectives. *International Journal of Sports Medicine*, Vol. 36(4), pp. 273-279.

Ostojic, S.M. (2018). Inadequate Production of H 2 by Gut Microbiota and Parkinson Disease. *Trends in Endocrinology & Metabolism*, Vol. 29(5), pp. 286-288.

Qin, Y.; Qiu, J.; Wang, P.; Liu, J.; Zhao, Y.; Jiang, F. & Lou, H. (2021). Impaired autophagy in microglia aggravates dopaminergic neurodegeneration by regulating NLRP3 inflammasome activation in experimental models of Parkinson’s disease. *Brain, Behavior and Immunity*, Vol. 91, pp. 324-338.

Shibayama, Y.; Dobashi, S.; Arisawa, T.; Fukuoka, T. & Koyama, K. (2020). Impact of hydrogen-rich gas mixture inhalation through nasal cannula during post-exercise recovery period on subsequent oxidative stress, muscle damage and exercise performances in men. *Medical Gas Research,* Vol. 10(4), pp. 155-162.

Socha, M. W.; Malinowski, B.; Puk, O.; Dubiel, M. & Wiciński, M. (2020). The NLRP3 Inflammasome Role in the Pathogenesis of Pregnancy Induced Hypertension and Preeclampsia. *Cells,* Vol. 9.

Tian, Y.; Zhang, Y.; Wang, Y.; Chen, Y.; Fan, W.; Zhou, J.; Qiao, J. & Wei, Y. (2021). Hydrogen, a Novel Therapeutic Molecule, Regulates Oxidative Stress, Inflammation, and Apoptosis. *Frontiers in Physiology,* Vol. 12.