THE APPLICABILITY OF MOLECULAR HYDROGEN IN THE TREATMENT OF NEURODEGENERATIVE DISEASES: A BIBLIOGRAPHICAL REVIEW

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Abstract: Introduction: This article discusses the growing research on the use of molecular hydrogen (H2) in the treatment of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Amyotrophic Lateral Sclerosis (ALS). H2 stands out for its antioxidant and anti-inflammatory properties, which can reduce oxidative stress and inflammation in the brain, key factors in the progression of these diseases. Objective: To review current studies on the applicability of molecular hydrogen as a neuroprotective therapy, exploring its effects and possible benefits in the treatment of neurodegenerative diseases. Methodology: A literature review was carried out based on scientific articles published in the last 10 years in the PubMed, Scielo and ScienceDirect databases. Inclusion criteria included clinical and preclinical studies investigating molecular hydrogen as a therapeutic agent. Discussion: Studies indicate that H2 can act in the neutralization of free radicals, modulation of the cellular redox state and reduction of inflammation, which contributes to neuroprotection. Several administration methods are analyzed, such as inhalation, H2-enriched water, and injections. Clinical trials suggest improvements in cognitive function and reduction in the progression of neurodegenerative diseases, but research is still needed to establish optimal doses and more detailed mechanisms of action. Conclusion: Molecular hydrogen has great therapeutic potential for neurodegenerative diseases, being safe and low-cost. However, more clinical studies are needed to validate its efficacy and define treatment protocols.

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Keywords: Molecular hydrogen, neuroprotection, oxidative stress.

Introduction

In the last decade, research on therapies for neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS), has expanded significantly due to the increasing prevalence of these diseases in the world population (FALCO, 2016). Although pharmacological treatments exist, most have limited efficacy and adverse effects that are sometimes not tolerated by patients, greatly reducing the cost-benefit of treatment. Molecular hydrogen (H2), due to its antioxidant and anti-inflammatory properties, emerges as a promising alternative for complementary treatments. (SARAMAGO, 2018).

Molecular hydrogen (H_2) has emerged as a therapy with great potential in the treatment of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Amyotrophic Lateral Sclerosis (ALS). Its application in neurodegenerative conditions has been intensively studied, as H_2 has significant antioxidant and anti-inflammatory properties that can protect the brain from damage caused by oxidative stress and chronic inflammation — common and aggravating processes in many of these diseases.

In terms of mechanism of action, it is a flammable, colorless, odorless, and water-insoluble gas, which can easily cross cell membranes, including the blood-brain barrier, allowing its direct arrival to brain tissue. (CAMPUS, 2018). One of the main ways of its action is the neutralization of

free radicals, such as the hydroxyl radical and the superoxide anion, which are highly reactive and toxic to neuronal cells.

In addition, H_2can modulate the cellular redox state, increasing the expression of endogenous antioxidants and improving the balance between the pro and antioxidant systems, which is essential for the protection of neural cells. (BARBOSA, 2010)

In addition to antioxidant action, molecular hydrogen also exerts anti-inflammatory effects by reducing the release of pro-inflammatory cytokines such as TNF-α and IL-6, which are often elevated in neurodegenerative diseases. This helps decrease chronic brain inflammation, which contributes to the progressive death of neurons and cognitive decline. (CAPITA, 2024)

Methods of applying molecular hydrogen in therapies include its inhalation, oral administration through H_2-enriched water, and injections, depending on the clinical need and the desired degree of absorption. Preclinical studies and trials early clinical findings indicate that molecular hydrogen administration may contribute to improved cognitive function, decreased motor symptoms, and slowed the progression of neurodegenerative diseases, especially when integrated with other therapeutic approaches. (FALCO, 2016)

Inhalation of H_2 gas is the simplest and most widely used form. Inhaled H_2 diffuses into the alveoli of the lungs and is transported by blood throughout the body. On the other hand, the ingestion of water dissolved in H_2 (HW)* is considered safer and more convenient. Studies have shown that drinking water saturated with H_2 can prevent arteriosclerosis in animal models. However, the injection of H_2-dissolved saline (HS) is used in specific clinical settings and varies depending on the disease.

Studies so far suggest that the administration of H_2 has significant clinical potential for the prevention, treatment, and mitigation of neurological disorders such as neurodegenerative diseases and ischemic brain injuries. No adverse effects of H_2 have been reported, and it is considered relatively easy to use, cost-effective, and effective in daily medical practice. However, more research is still needed to establish the optimal dose and route of administration for each disease, as well as elucidate the mechanisms molecular effects that underpin the biological effects of H_2. (IKETANI, 2017)

This paper aims to review current studies on molecular hydrogen, addressing its therapeutic properties and its applicability in neuroprotection.

Methodology

For the construction of this review, a search was carried out in the main scientific databases (PubMed, Scielo, ScienceDirect) using the terms: "molecular hydrogen", "neurodegenerative diseases", "Alzheimer's", "Parkinson's", "neuroprotection". The inclusion criteria were clinical and preclinical studies published in the last 10 years, which addressed molecular hydrogen as a therapeutic agent. We excluded opinion articles and studies of poor methodological quality.

Discussion

The use of molecular hydrogen (H_2) as a treatment for degenerative diseases such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS) has attracted increasing attention in scientific research due to its potential antioxidant and anti-inflammatory properties. However, it is important to note that despite initial promises, widespread implementation and clinical use are still in the early stages. (TORRÃO, 2012)

According to SEO, the study investigated the effects of consuming hydrogen-rich water (HW) compared to ordinary water (PW) on biological antioxidant potential (BAP) and markers of oxidative damage in humans. The research is motivated by growing evidence that oxidative stress

It plays a crucial role in various diseases and molecular hydrogen may have antioxidant properties.

Consumption of hydrogen-rich water can increase biological antioxidant potential and reduce oxidative damage in humans, especially in individuals aged 30 years and older. These results suggest that hydrogen-rich water may be an effective intervention to improve antioxidant health.

Ingestion of 1.5 L of H2 water for 4 weeks reduced cell death and inflammatory responses by modulating the transcriptional networks of TLR-NFκB signaling. In addition, it may promote biological antioxidant capacity in adults > 30 years older than in younger individuals. (YES, 2020)

Alzheimer's and Parkinson's

In the case of Alzheimer's and Parkinson's, several experimental and clinical studies have explored H_2 for its neuroprotective properties. Studies have suggested that H_2 may help reduce oxidative stress, a key factor in the progression of these diseases. H_2 has shown potential in animal model studies and in preliminary clinical trials. In the treatment of Alzheimer's, some studies indicate that H_2 may have a protective effect on neurons, potentially helping to reduce inflammation and oxidation in the brain.

The mechanism of action of molecular hydrogen H_2 is quite interesting and multifaceted, acting mainly as an antioxidant, helping to neutralize free radicals in the body, which are unstable molecules that can cause oxidative stress and cell damage. Specifically, H_2 has the ability to selectively reduce the most toxic free radicals, such as hydroxyl radicals (•OH) and hydrogen peroxide (H_2O_2), without affecting beneficial free radicals that play important roles in physiological processes.

In addition to its antioxidant properties, H_2 may also influence several cell signaling pathways. Studies suggest that it may regulate the expression of genes related to oxidative stress and inflammation, promoting a healthier cellular environment. For example, hydrogen gas inhalation has shown positive effects in models of neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, possibly through the reduction of oxidative stress and modulation (JOHNSEN, 2023)

In the treatment of Parkinson's, H_2 has shown promise in reducing oxidative stress in dopaminergic neurons, which are characteristically affected by Parkinson's. Research shows that H_2 exerts neuroprotective effects, particularly in models of cerebral ischemia-reperfusion. The administration of H_2 was associated with reduced neuronal damage, due to its ability to inhibit the

production of ROS and reactive nitrogen species (RNS), preserving cellular integrity. (LI, 2020)

According to YORITAKA ET AL, 2013 a pilot study was a randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy of water dissolved in molecular hydrogen (H2) in Japanese patients with Parkinson's disease (PD) medicated with levodopa. Participants were 18 patients, with a mean age of 62.7 years, 11 of whom were women. Participants were divided into two groups: one group received 1,000 mL/day of H_2 water and the other group received placebo water for 48 weeks. The group that consumed H_2 water showed a significant improvement in the total scores of the Unified Parkinson's Disease Rating Scale (UPDRS), with a median of -21.0 and a mean of -25.7±8.4. The placebo group showed worsening in the total UPDRS scores, with a median of 4.5 and a mean of 4.1±9.2. The difference between the groups was statistically significant ($P<0.05$).

H2 water intake was safe and well tolerated. There was a significant improvement in total UPDRS scores in the group that consumed H2 water, indicating a potential therapeutic benefit for PD patients.

The study participants were taking the following antiparkinsonian medications:

Drug	Number of patients using the medication
Levodopa (L-dopa)	
Dopamine agonists	7 patients in the placebo group and 5 in the H_2 group
Anticholinergic agents	2 patients in each group
Selegiline	1 patient in the placebo group and 4 in the H_2 group
Entacapona	2 patients in the placebo group and none in the H_2 group
Amantadine	1 patient in each group
Zonisamide	1 patient in the placebo group and 5 in the H_2 group

None of the patients changed treatment with L-dopa or other antiparkinsonian drugs during the study period.

The study suggests that longer trials with larger numbers of participants are needed to confirm these findings.

Amyotrophic Lateral Sclerosis (ALS)

In the context of ALS, some experimental studies suggest that H_2 may help reduce neuronal cell death, a mechanism that occurs in ALS, due to its ability to neutralize free radicals. However, despite some initial trials being promising, the amount of clinical data and large-scale studies is still small. (BARBOSA, 2010)

Although the exact mechanisms of action of molecular hydrogen are not completely understood, its ability to cross the blood-brain barrier and reach the central nervous system is an important differentiator. The modulation of oxidative stress and anti-inflammatory activity suggest that H_2 may be beneficial as an adjunct treatment in neurodegenerative diseases. However, the heterogeneity of the studies, the variable dosages, and the different methodologies limit the comparability of the results, highlighting the need for more robust clinical trials to confirm the effects in humans.

The results of the randomized controlled trial that looked at consuming 2 liters per day of alkaline ionized water for 8 weeks showed a decrease in markers of oxidative stress, as well as improvements in participants' quality of life and physical performance. However, it is essential to note that the concentration of molecular hydrogen (H2) has not been reported, only the oxidation-reduction potential (ORP), which is not a reliable indicator of dissolved H2 concentration. This means that it is not possible to determine whether the positive results were actually attributed to the consumption of water with a high concentration of H_2 or if they were influenced by other factors. (CHEN, 2021)

Furthermore, in another study that tested the effects of different pH levels on diabetic patients, it was observed that only the group that consumed water with a high concentration of H2 showed significant benefits, while the group with a low concentration of H2, despite having an alkaline pH, did not show positive results. This highlights the importance of measuring H_2 concentration to validate the biological effects of ERW and avoid misinterpretations of the data. Therefore, the results suggest that the effectiveness of ERW is closely linked to the concentration of H_2 present in the water consumed. (LeBaron, 2022)

Conclusion

Molecular hydrogen presents a promising therapeutic profile for the treatment of neurodegenerative diseases, offering the potential to improve the quality of life of patients and reduce the progression of symptoms. However, more research is needed to establish administration protocols, effective dosages, and understand the specific mechanisms of action in the central nervous system. Thus, molecular hydrogen emerges as a complementary, safe, and low-cost treatment option that can potentially improve quality of life and slow the progression of neurodegenerative diseases.

However, more research is needed to define optimal dosages, treatment timing, and protocols to ensure their efficacy and safety in different patient populations. However, larger, long-term clinical trials are needed to confirm these findings and determine whether it may be a viable treatment option. However, the results are still inconclusive and more studies are needed to confirm the efficacy and safety of H_2 in these cases. In terms of statistics, the clinical use of H_2 for the treatment of these diseases is still limited.

Most studies are in the preclinical investigation phase or small clinical trials, with few H_2-based therapies being officially approved by regulatory agencies in large markets, such as the FDA (USA) or EMA (European Union). There are some alternative hydrogen-based therapies, such as H_2 inhalers or hydrogenated water, but widespread use and clinical acceptance are still a long way off. According to some scientific societies, such as the International Society for Molecular Hydrogen Therapy (IHMS), although research is growing, H_2 as a clinical treatment for neurodegenerative diseases still needs more robust evidence to become an established practice.

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