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MOLECULAR HYDROGEN AND NEURAL PLASTICITY: EMERGING EVIDENCE IN REGENERATION AND COGNITIVE PERFORMANCE

Zaika Capita
Corresponding author: dracapitta@gmail.com
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ABSTRACT

Introduction: Molecular hydrogen has emerged as a bioactive molecule capable of modulating key processes involved in neural integrity, including oxidative stress, neuroinflammation, and synaptic plasticity. Recent studies suggest that its use may contribute to neural regeneration and improve cognitive performance in a variety of clinical and experimental contexts. **Objective:** To analyze scientific evidence published since 2020 on the effects of molecular hydrogen on neural plasticity and cognitive performance, identifying mechanisms of action, therapeutic benefits, and potential clinical applications. **Methods:** An integrative review was conducted in the PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and SciELO databases, selecting studies published between 2020 and 2025. Experimental studies, clinical trials, and reviews evaluating the effects of molecular hydrogen on cognitive parameters and neural mechanisms were included. Data were organized into an analytical matrix and synthesized into thematic categories. **Results:** Twenty studies met the eligibility criteria. Findings demonstrated that molecular hydrogen reduces oxidative stress and neuroinflammation, protects the blood–brain barrier, stimulates neurogenesis, preserves synaptic integrity, and improves multiple cognitive domains. Clinical evidence showed benefits in memory, attention, processing speed, and attenuation of mild cognitive impairment progression. **Conclusion:** Molecular hydrogen shows relevant therapeutic potential for promoting neural plasticity and improving cognitive performance. Although promising, the evidence highlights the need for larger, standardized, and long-term clinical trials to support its incorporation into clinical practice.

Keywords (MeSH): Hydrogen; Neuroplasticity; Cognition; Oxidative Stress; Neurodegenerative Diseases.

INTRODUCTION

Molecular hydrogen (H_2) has emerged as one of the most promising therapeutic innovations in applied neuroscience and regenerative medicine. Its ability to act as a selective antioxidant, neutralizing highly toxic reactive oxygen species such as the hydroxyl radical and peroxynitrite, has stimulated growing interest in its use within the central nervous system. Experimental and clinical evidence indicates that H_2 exerts anti-inflammatory, antiapoptotic, and cell-signaling modulatory effects involved in neural homeostasis, positioning it as a molecule with the potential to enhance neuronal plasticity and functional recovery across different neurological conditions [1,19].

Neural plasticity, defined as the capacity of the nervous system to reorganize its structure and function in response to internal and external stimuli, is fundamental to learning, memory, tissue repair, and cognitive maintenance throughout life. In various clinical conditions, including neurodegenerative diseases, inflammatory encephalopathies, ischemic injury, and age-related brain decline, there is a significant increase in oxidative stress and neuroinflammation. These processes compromise synaptic integrity and reduce the efficiency of cognitive circuits. The introduction of molecular hydrogen as a therapeutic intervention has shown direct benefits on these pathological mechanisms, including reduced inflammatory cytokines, decreased microglial activation, improved mitochondrial function, and preservation of neuronal morphology [1,4,6].

Animal studies demonstrate that H_2 increases the expression of neurotrophic factors such as BDNF, promotes neurogenesis, and supports the maintenance of dendritic spines, which are essential for synaptic plasticity. In neurodegenerative disease models, including Alzheimer's disease, H_2 treatment reduced beta-amyloid deposition, tau hyperphosphorylation, and synaptic loss, resulting in improved performance in behavioral tests of memory and learning [3,17]. In contexts of systemic inflammation and sepsis-associated encephalopathy, H_2 preserved the blood–brain barrier and reduced hippocampal damage, a region central to declarative memory processes [4,5].

Beyond preclinical evidence, clinical studies have begun to reveal the potential impact of molecular hydrogen on human cognitive performance. In sleep-deprived young adults, ingestion of hydrogen-rich water improved attention, processing speed, and alertness [2]. Among older adults over 70 years of age, continuous use of H_2 over six months led to improvements in neuronal metabolic biomarkers such as N-acetylaspartate, suggesting potential support for neural functioning [11]. Other pilot studies indicate benefits in specific cognitive domains, including working memory and executive functions, particularly in individuals with mild cognitive impairment [10,20].

Taken together, these findings indicate that molecular hydrogen exhibits relevant biological properties for the maintenance and restoration of neural plasticity. The breadth of experimental and clinical models analyzed shows that its effects extend from molecular pathways to behavioral improvements associated with cognition. Considering the global

rise in neurodegenerative diseases and the impact of cognitive dysfunction in aging populations, investigating the role of molecular hydrogen as a therapeutic strategy represents an emerging scientific and social priority.

In this context, the present study aims to integratively analyze recent scientific literature (published from 2020 onward) regarding the effects of molecular hydrogen on neural plasticity and cognitive performance, identifying evidence, underlying mechanisms, and potential clinical applications resulting from interventions using this gaseous molecule.

METHODOLOGY

This integrative review was conducted in accordance with the methodological principles proposed by Whittemore and Knafl, encompassing the stages of problem identification, definition of eligibility criteria, systematic search, critical evaluation, and synthesis of the included studies. This method enables the integration of evidence from different research designs, expanding understanding of the effects of molecular hydrogen on neural plasticity and cognitive performance.

Search Strategy

The search was performed in the PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and SciELO databases, in addition to consultation of the open-access repository PubMed Central (PMC). Articles published between January 1, 2020, and January 2025 were selected, a period chosen due to the recent advancements in research involving molecular hydrogen and neuroscience.

Controlled descriptors and free-text keywords were combined using Boolean operators, including: "molecular hydrogen", "hydrogen-rich water", "hydrogen inhalation", "brain", "hippocampus", "cognition", "memory", "synaptic plasticity", "neurogenesis", "neuroinflammation", "oxidative stress", and "neuroprotection", as well as their equivalents in Portuguese.

Example of the PubMed search strategy: (molecular hydrogen OR hydrogen-rich water OR hydrogen inhalation) AND (cognition OR memory OR hippocampus OR neuroplasticity OR neuroinflammation OR neurogenesis OR neuroprotection).

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

1. Experimental studies, clinical trials, or reviews investigating the effects of molecular hydrogen on the central nervous system.

2. Publications dated between 2020 and 2025.
3. Articles written in English or Portuguese.
4. Studies presenting outcomes related to neural plasticity, neuronal regeneration, synaptic function, or cognitive performance.
5. Research conducted in humans or animal models evaluating brain structure or function.

Studies were excluded if they:

1. Did not directly investigate the central nervous system.
2. Presented insufficient or inconsistent data.
3. Did not address cognition, neuroprotection, or neural plasticity.
4. Were editorials, commentaries, conference abstracts, or duplicate manuscripts.

Study Selection

The selection process occurred in three stages. In the first stage, titles and abstracts were screened. In the second stage, potentially relevant articles were evaluated in full. In the third stage, the eligibility criteria were applied. Discrepancies were resolved by consensus. At the end of the process, 20 studies fully met the criteria and were included in the integrative synthesis.

Data Extraction and Evaluation

The information extracted from the studies included: authors, year of publication, country, methodological design, type of molecular hydrogen intervention, treatment duration, experimental model, biomarkers assessed, analytical methods, and main outcomes related to neural plasticity and cognition. These data were organized into an analytical matrix containing the essential elements for comparison across studies.

Data Synthesis

Data synthesis was conducted narratively and descriptively, emphasizing convergences and divergences among the findings, as well as the neurobiological mechanisms involved. The studies were grouped into thematic axes reflecting the main effects observed: neuroprotection, synaptogenesis, neurogenesis, improvement in memory and attention, modulation of neuroinflammation, and support for healthy brain aging. This approach made it possible to integrate preclinical and clinical evidence, providing a broader perspective on the therapeutic potential of molecular hydrogen.

RESULTS

Analysis of the 20 included studies revealed consistent evidence regarding the effects of molecular hydrogen on mechanisms that support neural plasticity, neuroprotection, and cognitive performance. The findings were grouped into five thematic axes, allowing for an integrated understanding of the preclinical and clinical contributions available in the recent literature.

Axis 1. Modulation of Oxidative Stress and Neuroinflammation

Most studies highlighted the central role of molecular hydrogen in reducing oxidative stress, which is considered one of the major contributors to neuronal and synaptic damage. Experimental models demonstrated that hydrogen administration significantly decreases reactive oxygen species, reduces lipid peroxidation, and restores mitochondrial function [1,6,17,18]. In addition, a strong anti-inflammatory effect was observed, with reduced microglial and astrocytic activation, decreased pro-inflammatory cytokines, and protection of the blood–brain barrier [4,5,14]. These mechanisms converge to create an environment conducive to neuronal survival and synaptic integrity.

Axis 2. Synaptic Plasticity, Neurogenesis, and Neuronal Integrity

Several studies demonstrated that molecular hydrogen promotes neural plasticity. Increased dendritic spine density, stimulation of neurogenesis, and improvement in electrophysiological markers such as long-term potentiation were observed [7,8,15,18]. In Alzheimer's disease models, hydrogen reduced classical pathological markers, preserved synaptic connections, and resulted in significant improvements in cognitive performance [3,17]. These findings suggest that hydrogen plays an important role in both the maintenance and structural recovery of compromised neural circuits.

Axis 3. Cognitive Performance and Learning

The analyzed studies demonstrated that molecular hydrogen improves different cognitive domains, including spatial memory, short-term memory, executive function, and processing speed. In humans, its administration led to enhanced sustained attention, improved alertness, and better cognitive performance in sleep-deprived young adults and elderly individuals [2,10,11,16]. In clinical settings, such as mild cognitive impairment, continuous use of hydrogen slowed the progression of cognitive decline, suggesting a potential preventive therapeutic action [20].

Axis 4. Structural Protection and Blood–Brain Barrier Integrity

Molecular hydrogen showed the ability to preserve vulnerable neural structures, particularly the blood–brain barrier. This protection included reduced vascular permeability, decreased cerebral edema, and maintenance of microvascular integrity in inflammatory and ischemic models [5,7,14]. Structural preservation enhances neuronal functionality and contributes to improved cognitive outcomes.

Axis 5. Clinical Evidence and Therapeutic Applicability

Although more limited than preclinical evidence, the set of human studies demonstrates important therapeutic potential. Clinical trials indicated cognitive improvement, enhanced performance in neuropsychological tests, and favorable metabolic effects on brain physiology after prolonged hydrogen use [2,10,11]. Studies in vulnerable populations, such as older adults and patients with mild cognitive impairment, reinforce its possible role as a complementary or preventive intervention [20].

Table 1. Included Studies and Main Outcomes

Nº	Authors (Year)	Study Type	Main Outcome
1	Chen W et al., 2020	Review	Neuroprotection mechanisms
2	Todorović N et al., 2021	Clinical	Improved alertness and cognition
3	Lin YT et al., 2022	Experimental	Reduced plaques and improved memory
4	de Deus JL et al., 2023	Experimental	Reduced neuroinflammation
5	Bai Y et al., 2023	Experimental	BBB protection and cognition
6	Jin X et al., 2023	Experimental	Improved cerebral metabolism
7	Xu K et al., 2025	Experimental	Neurogenesis and synaptic integrity
8	Lee D et al., 2025	Experimental	Immune modulation and memory
9	Shinada T et al., 2024	Experimental	Memory improvement
10	Shinada T et al., 2024	Clinical	Cognitive improvement in older adults

11	Zanini D et al., 2021	Clinical	Improved neural metabolism
12	Sim M et al., 2020	Clinical	Reduced inflammation
13	Johnsen HM et al., 2023	Review	Emerging clinical evidence
14	Yu Y et al., 2020	Experimental	BBB protection
15	Meng P et al., 2021	Experimental	Increased BDNF and synaptogenesis
16	Li J et al., 2021	Clinical	Improved reaction time
17	Wang Z et al., 2022	Experimental	Enhanced synaptic and cognitive function
18	Huang L et al., 2023	Experimental	Increased LTP
19	Xie K et al., 2021	Review	Neuroprotective mechanisms
20	Hashimoto M et al., 2020	Clinical	Slowed MCI progression

Closing of the Results

The synthesis of the 20 analyzed studies demonstrates that molecular hydrogen acts at multiple levels of neural physiology, encompassing antioxidant and anti-inflammatory modulation as well as direct effects on synaptic plasticity, neurogenesis, and cognitive performance. The convergence of preclinical and clinical findings indicates that this molecule holds significant therapeutic potential in the context of neural regeneration and the enhancement of cognitive functions. Despite the predominance of experimental research, the available clinical evidence reinforces its applicability and supports the expansion of controlled trials in humans, especially in populations at risk for cognitive decline.

DISCUSSION

The findings of this integrative review demonstrate that molecular hydrogen exhibits a remarkable set of neuroprotective, antioxidant, and neural plasticity-regulating properties, establishing itself as an emerging therapeutic strategy within the field of translational neuroscience. The analysis showed that the observed effects are consistent

across different experimental models and, although still limited in human studies, the available clinical evidence reinforces the possibility of meaningful therapeutic applications.

Preclinical results strengthen the understanding that hydrogen acts broadly on cellular pathways associated with oxidative stress, neuroinflammation, and mitochondrial dysfunction, factors recognized as central to neurological injury and cognitive decline. The reduction in reactive oxygen species, modulation of microglial activation, and restoration of neuronal bioenergetics observed across several studies suggest that hydrogen plays a homeostatic reorganization role in compromised neural tissue. This feature is particularly relevant in neurodegenerative diseases, in which redox imbalance and chronic inflammation drive pathological progression.

Beyond its cytoprotective effects, this review showed that hydrogen directly influences mechanisms that support neural plasticity. Studies involving models of Alzheimer's disease, brain irradiation, and vascular dementia reported increased neurogenesis, greater dendritic spine density, synaptic recovery, and enhanced levels of neurotrophic factors such as BDNF. These findings indicate that hydrogen not only prevents damage but also promotes repair and structural reorganization, representing one of the most important scientific contributions of this research field.

The cognitive improvements observed in animal models further reinforce the link between cellular effects and behavioral outcomes. Enhancements in spatial memory, learning, and short-term memory across various models indicate that the mechanisms modulated by hydrogen result in meaningful functional changes. Although animal models cannot fully replicate the complexity of human cognition, the consistency of results across species and pathological contexts strengthens the reliability of these findings.

The clinical studies analyzed, though fewer in number, presented promising results. Trials involving young adults demonstrated improvements in attention and cognitive processing speed following the consumption of hydrogen-rich water, while studies with older adults showed benefits in neural metabolism and working memory. In vulnerable populations, such as individuals with mild cognitive impairment, the progression of cognitive deterioration appeared to be attenuated after continuous hydrogen administration. These results, although preliminary, suggest that hydrogen may act as a modulator of cognitive functions even in brains without severe structural pathology.

Despite the strength of the preclinical evidence, it is essential to acknowledge certain limitations within the reviewed studies. First, much of the research has been conducted in animal models or under controlled experimental conditions, which limits immediate extrapolation to clinical practice. Furthermore, available clinical trials often feature small sample sizes, short intervention durations, and a lack of standardization in terms of administration routes, hydrogen concentration, and exposure time. These factors restrict comparability and generalizability.

Another important gap concerns the absence of consolidated clinical protocols defining dosage, optimal delivery method (inhalation, hydrogen-enriched water, intravenous solutions), or therapeutic duration. The lack of large-scale, multicenter, randomized trials further highlights the need for broader investigations capable of assessing the long-term impact of molecular hydrogen in diverse populations.

Even so, the collective body of studies presents a highly promising scientific scenario. Molecular hydrogen offers several advantages over other therapeutic approaches, including high safety, ease of administration, rapid tissue diffusion, and minimal adverse effects. Its simultaneous action on multiple pathophysiological pathways suggests that it may serve both as a preventive measure and as a complementary intervention in complex neurological conditions such as brain aging, neurodegenerative diseases, traumatic injuries, and inflammatory encephalopathies.

Given the results, it becomes evident that clinical research must be expanded, particularly studies aimed at evaluating the direct impact of hydrogen on human neural plasticity. Investigations employing functional neuroimaging, specific biomarkers of plasticity, and longitudinal follow-up may provide clearer insights into the therapeutic potential of molecular hydrogen. Similarly, studies exploring individual differences related to genetics, metabolism, and oxidative response may contribute to the development of personalized protocols.

In summary, molecular hydrogen emerges as a highly promising intervention capable of acting on multiple mechanisms associated with neural preservation and regeneration. The evidence suggests that its application may, in the future, integrate innovative therapeutic strategies aimed at strengthening neural plasticity and enhancing cognitive performance, particularly in populations susceptible to cognitive decline. The consolidation of robust clinical trials will be the next essential step toward validating its use in clinical practice.

CONCLUSION

This integrative review demonstrated that molecular hydrogen represents a promising intervention in the fields of neuroprotection and neural plasticity. The analyzed evidence shows that its effects encompass fundamental mechanisms essential for the integrity and functioning of the central nervous system, including the reduction of oxidative stress, modulation of neuroinflammation, structural protection, stimulation of neurogenesis, and enhancement of synaptic plasticity. These mechanisms converge to support the functional recovery of neural circuits and sustain cognitive performance across different contexts.

In animal models, findings consistently show that molecular hydrogen improves memory, learning, and synaptic integrity, in addition to reducing pathological markers associated with neurodegenerative diseases. In clinical studies, although still limited in

number and scope, improvements have been observed in specific cognitive domains, as well as positive effects on cerebral metabolic markers and the progression of mild cognitive impairment. These results reinforce the potential of hydrogen as a complementary therapeutic approach in conditions associated with cognitive dysfunction and brain aging.

Despite the favorable outlook, there remains a need for larger, standardized, and longer-term clinical trials capable of defining usage protocols, optimal concentrations, administration methods, and patient profiles that may derive the most significant benefits. Investigations that integrate neural biomarkers, neuroimaging, and in-depth cognitive assessment will be essential to consolidate its application in clinical practice.

In conclusion, molecular hydrogen exhibits strong potential to contribute to innovative strategies aimed at preserving and promoting neural plasticity, with direct impact on cognitive performance and brain health. Its high safety profile, broad applicability, and multidimensional nature position it as an emerging and increasingly relevant agent within the field of neuroregenerative therapies.

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