International Journal of Alzheimers & Neurological Disorders

Shigeo Ohta, et al. Int. J Alzheimers & Neuro Disorder 2018, 1: 1
1: 003

Mini Review

Molecular Hydrogen as an Emerging Candidate for Preventing Alzheimer's Disease

Shigeo Ohta[1*], and Takashi Asada[2]

[1]Department of Neurology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan,

[2]Ochanomizu Memory Clinic, The medical reunion of Tokyo Medical and Dental University, 1-5-34 Yushima, Bunkyou-ku, Tokyo 113-0034 Japan

Background

We recently published a paper describing that drinking hydrogen water (water infused with hydrogen gas) improved Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores in subjects with mild cognitive impairment (MCI) in apolipoprotein E4 (APOE4) genotype-carriers by a randomized, double-blind, placebo-controlled clinical trial [1]. In the present mini-review, we introduce molecular hydrogen (H_2) as an emerging candidate for preventing Alzheimer's disease (AD).

AD is a progressive multi-factorial neurodegenerative disorder, in which oxidative stress is widely accepted as one of the causative factors [2-4]. Currently, no effective treatment is available likely because complicated multiple factors are involved in the pathophysiology of AD. Single modality of a specific target strategy for treating AD may not be successful, and future therapies based on a multiple-target strategy are needed to address the multiple aspects of AD and block its progression [5,6].

For a long time, H_2 was believed to be a biologically inert and non-functional molecule in the body; however, we overturned this concept by demonstrating that H_2 protected cultured cells and the brain against excess oxidative stress and proposed its potential for preventive and therapeutic applications [7]. Subsequently, there have been about 1,000 papers published on 170 kinds of animal disease models and more than 30 clinical studies on the use of H_2. These studies have revealed that H_2 acts as a therapeutic and preventive antioxidant with multiple functions, including anti-inflammation, anti-allergy, anti-cell death, and stimulation of energy metabolism, all of which contribute to its marked efficacy in a variety of diseases [8-10]. Figure 1 summarizes publications reporting the clinical efficacies by H_2 on various kinds of human diseases. As a molecular mechanism by which H_2 exerts the multiple functions, H_2 might regulate various gene expression levels in indirect manners under transcription factors such as including NFAT and Nrf2 [11,12].

H_2 seems to differ from conventional pharmaceutical drugs because unlike H_2 most drugs have specificity for and to act on their exact targets. Owing to its multiple functions and great efficacy coupled with its lack of adverse effects, H_2 has great potential for preventing AD.

There are several methods to ingest or consume H_2; inhaling H_2 gas, drinking H_2-dissolved in water (H_2-water), injecting H_2-dissolved in saline (H_2-saline), taking an H_2 bath, or dropping H_2-saline into the eyes.

Introduction

First, to examine the effect of drinking H_2-water on impaired learning and memory abilities, mice were strongly stressed by chronic physical restraint to enhance oxidative stress in the brain. Consumption of H_2-water *ad libitum* suppressed the increase in oxidative stress and prevented cognitive impairment [13].

To explore effective dietary antioxidants to mitigate age-dependent neurodegeneration, it is essential to construct model mice in which AD phenotypes would progress in an age-dependent manner in response to oxidative stress. We constructed transgenic DAL101 mice expressing a polymorphism of the mitochondrial aldehyde dehydrogenase 2 gene (ALDH2*2) [14]. ALDH2*2 is responsible for a deficiency in ALDH2 activity and is specific to North-East Asians [15]. We reported that

***Corresponding Author:** Shigeo Ohta, Department of Neurology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan, E-mail: ohta@nms.ac.jp

Sub Date: June 26th, 2018, **Acc Date:** July 9th, 2018, **Pub Date**: July 10th, 2018.

Citation: Shigeo Ohta and Takashi Asada (2018) Molecular Hydrogen as an Emerging Candidate for Preventing Alzheimer's Disease. Int. J Alzheimers & Neuro Disorder 1: 003.

ALDH2 deficiency is a risk factor for late-onset AD in the Japanese population [16], which was reproduced by Chinese and Korean studies in their respective populations [17,18]. DAL101 mice exhibited a decreased ability to detoxify 4-hydroxy-2-nonenal (4-HNE) in cortical neurons, and consequently an age-dependent neurodegeneration, cognitive decline, and a shortened lifespan ensued [14].

Oxidative stress enhances lipid peroxidation, leading to the formation and accumulation of highly reactive α, β-unsaturated aldehydes, such as 4-HNE [19]. The decline in ALDH2*2 ability failed to detoxify cytotoxic aldehydes, and consequently increased oxidative stress [20].

Moreover, double-transgenic mice were constructed by crossing DAL101 mice with Tg2576 mice, which express a mutant form of human amyloid precursor protein (APP). They showed accelerated amyloid deposition, tau phosphorylation, and gliosis, as well as impaired learning and memory abilities. The lifespan of APP/DAL mice was significantly shorter than that of APP and DAL101 mice [21]. Thus, these model animals are helpful to examine the role of H_2 in the prevention of age-dependent dementia.

As the result, drinking H_2-water reduced oxidative stress in DAL101 mice, suppressed a decline in learning and memory impairment, and suppressed neurodegeneration [1]. Moreover, H_2-water extended the average lifespan of DAL mice [1].

Next, based on these animal experiments, we examined the efficacy of drinking H_2-water in subjects with MCI in a randomized, placebo-controlled, double-blind clinical trial. Seventy-three subjects were enrolled and drank 300 mL on average of H_2-water (0.6 mM) or placebo water for 1 year. After 1 year, there was no observable adverse effect, and the subjects in the H_2-group non-significantly tented to improve more than those in the control groups [1].

One of the most potent risk factors for AD is carrier status of the APOE4 genotype. APOE4 also increases the number of atherogenic lipoproteins and accelerates atherogenesis [22]. The increased oxidative stress in APOE4 carriers is considered to contribute to the risk of developing AD [23]. A combination of antioxidants improved the cognitive function of aged subjects after 3 years, especially in APOE4 carriers [24].

When we evaluated the score-changes in carriers of the APOE4 genotype, the total ADAS-cog and word recall task scores (one of the sub-scores) significantly improved, as assessed by the distribution of the score change in each subject (Figure 2). In the 7 APOE4 carriers, six subjects improved on the total ADAS-cog and 5 subjects on the word recall task score, in the H_2-group [1].

Conclusion

The present mini-review introduced a possibility for slowing the progress of dementia by drinking H_2-water by means of animal experiments and a clinical intervention study for APOE4 carriers. The increased risk from APOE4 in developing AD has been reported to be 3.5-fold, and about half of AD patients are APOE4 carriers [25]. Data from clinical trials suggest that medium-chain triglycerides improve cognition in patients with mild to moderate AD in only APOE4-negative patients [26]. Thus, if we could overcome the risk in patients with the APOE4 genotype, the number of patients that develop AD is expected to decrease markedly. Additionally, H_2 reduced oxidative stress and inflammation in an amyloid-β-induced Alzheimer rat model [27].

These improvements associated with drinking H_2-water are significant when the effect is compared with that of donepezil, one of the approved medicines; Donepezil improved ADAS-cog score by 3 points after 6 weeks; however, after 6 months, the scores had returned to the initial level [28]. In contrast, drinking H_2-water improved the average score at about 3 better than the baseline stages after 1 year in APOE4 carriers.

Moreover, H_2 has strong advantages with its lack of adverse effects. Indeed, virtually all clinical studies indicated that H_2 treatment was safe and effective in patients, as shown in patients with acute cerebral infarction [29]. These results suggested a potential for widespread and general application of H_2 without undue caution.

Longer and larger-scale trial will be necessary to clarify the effect of H_2-water on MCI.

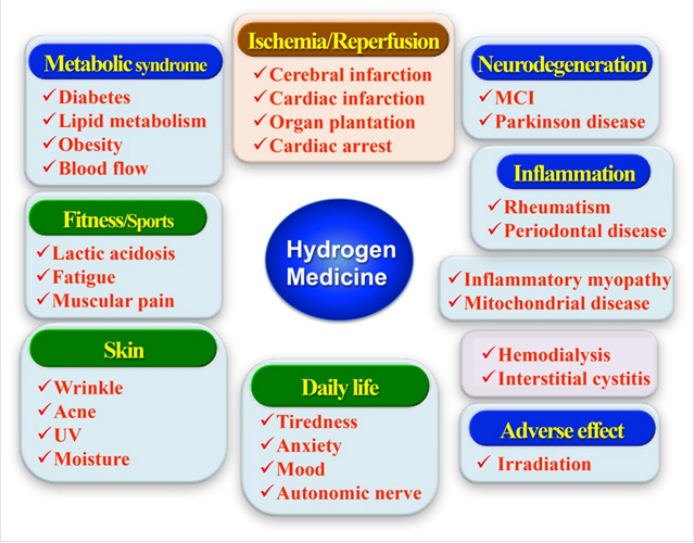

Figure 1: Molecular hydrogen exerts multiple functions on various kinds of diseases. Publications on patients or subjects are shown as examples of the efficacy of molecular hydrogen.

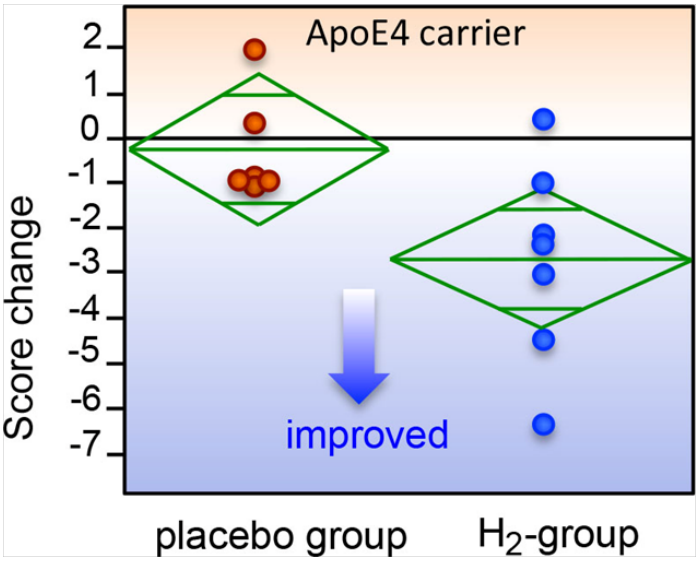

Figure 2: Subjects with MCI and the APOE4 genotype showed improvement in ADAS-cog by drinking H_2-water for 1 year, as assessed in a randomized, double-blind, placebo-controlled clinical trial.

References

1. Nishimaki K, Asada T, Ohsawa I, Nakajima E, Ikejima C et al. (2018) Effects of Molecular Hydrogen Assessed by an Animal Model and a Randomized Clinical Study on Mild Cognitive Impairment. Curr Alzheimer Res 15(5): 482-492.

2. Vergallo A, Giampietri L, Baldacci F, Volpi L, Chico L et al. (2018) Oxidative Stress Assessment in Alzheimer's Disease: A Clinic Setting Study. Am J Alzheimers Dis Other Demen 33(1): 35-41.

3. Mecocci P, Boccardi V, Cecchetti R, Bastiani P, Scamosci M et al. (2018) A Long Journey into Aging, Brain Aging, and Alzheimer's Disease Following the Oxidative Stress Tracks. J Alzheimers Dis 62(3): 1319-1335.

4. Butterfield DA (2018) Perspectives on Oxidative Stress in Alzheimer's Disease and Predictions of Future Research Emphases. J Alzheimers Dis 64(s1): S469-S479.

5. Umar T, Hoda N (2017) Alzheimer's Disease: A Systemic Review of Substantial Therapeutic Targets and the Leading Multi-functional Molecules. Curr Top Med Chem 17(31): 3370-3389.

6. de Freitas Silva M, Dias KST, Gontijo VS, Ortiz CJC, Viega C (2018) Multi-Target Directed Drugs as a Modern Approach for Drug Design Towards Alzheimer's Disease: an update. Curr Med Chem 25(17): 2045-2067.

7. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K et al. (2007) Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 13(6): 688-694.

8. Ohta S (2014) Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. Pharmacol Ther 144(1): 1-11.

9. Ohta S (2015) Molecular hydrogen as a novel antioxidant: overview of the advantages of hydrogen for medical applications. Methods Enzymol 555: 289-317.

10. Iketani M, Ohsawa I (2017) Molecular Hydrogen as a Neuroprotective Agent. Curr Neuropharmacol 15(2): 324-331.

11. Iuchi K, Imoto A, Kamimura N, Nishimaki K, Ichimiya H et al. (2016) Molecular hydrogen regulates gene expression by modifying the free radical chain reaction-dependent generation of oxidized phospholipid mediators. Sci Rep. 6: 18971.

12. Kawamura T, Wakabayashi N, Shigemura N, Huang CS, Masutani K et al. (2013) Hydrogen gas reduces hyperoxic lung injury via the Nrf2 pathway in vivo. Am J Physiol Lung Cell Mol Physiol 304(10): L646-656.

13. Nagata K, Nakashima-Kamimura N, Mikami T, Ohsawa I, Ohta S (2009) Consumption of molecular hydrogen prevents the stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice. Neuropsychopharmacology 34(2): 501-508.

14. Ohsawa I, Nishimaki K, Murakami Y, Suzuki Y, Ishikawa M et al. (2008) Age-dependent neurodegeneration accompanying memory loss in transgenic mice defective in mitochondrial aldehyde dehydrogenase 2 activity. J Neurosci 28(24): 6239-6249.

15. Chen CH, Ferreira JC, Gross ER, Mochly-Rosen D (2014) Targeting aldehyde dehydrogenase 2: new therapeutic opportunities. Physiol Rev 94(1): 1-34.

16. Kamino K, Nagasaka K, Imagawa M, Yamamoto H, Yoneda H et al. (2000) Deficiency in mitochondrial aldehyde dehydrogenase increases the risk for late-onset Alzheimer's disease in the Japanese population. Biochem Biophys Res Commun 273(1): 192-196.

17. Jo SA, Kim EK, Park MH, Han C, Park HY et al. (2007) A Glu487Lys polymorphism in the gene for mitochondrial aldehyde dehydrogenase 2 is associated with myocardial infarction in elderly Korean men. Clin Chim Acta 382(1-2): 43-47.

18. Wang B, Wang J, Zhou S, Tan S, He X et al. (2008) The association of mitochondrial aldehyde dehydrogenase gene (ALDH2) polymorphism with susceptibility to late-onset Alzheimer's disease in Chinese. J Neurol Sci 268(1-2): 172-175.

19. Schneider C, Tallman KA, Porter NA, Brash AR (2001) Two distinct pathways of formation of 4-hydroxynonenal. Mechanisms

of nonenzymatic transformation of the 9- and 13-hydroperoxides of linoleic acid to 4-hydroxyalkenals. J Biol Chem 276(24): 20831-20838.

20. Endo J, Sano M, Katayama T, Hishiki T, Shinmura K et al. (2009) Metabolic remodeling induced by mitochondrial aldehyde stress stimulates tolerance to oxidative stress in the heart. Circ Res 105(11): 1118-1127.

21. Kanamaru T, Kamimura N, Yokota T, Iuchi K, Nishimaki K et al. (2015) Oxidative stress accelerates amyloid deposition and memory impairment in a double-transgenic mouse model of Alzheimer's disease. Neurosci Lett 587: 126-131.

22. Hanson AJ, Craft S, Banks WA (2015) The APOE genotype: modification of therapeutic responses in Alzheimer's disease. Curr Pharm Des 21(1): 114-120.

23. Jofre-Monseny L, Minihane AM, Rimbach G (2008) Impact of apoE genotype on oxidative stress, inflammation and disease risk. Mol Nutr Food Res 52(1): 131-145.

24. Bun S, Ikejima C, Kida J, Yoshimura A, Lebowitz AJ et al. (2015) A combination of supplements may reduce the risk of Alzheimer's disease in elderly Japanese with normal cognition. J Alzheimer's dis 45(1): 15-25.

25. Yasuno F, Asada T (2013) Effect of plasma lipids and APOE genotype on cognitive decline. Dialogues Clin Neurosci 15(1): 120-126.

26. Sharma A, Bemis M, Desilets AR (2014) Role of Medium Chain Triglycerides (Axona(R)) in the Treatment of Mild to Moderate Alzheimer's Disease. Am J Alzheimers Dis Other Demen 29(5): 409-414.

27. Wang C, Li J, Liu Q, Yang R, Zhang JH et al. (2011) Hydrogen-rich saline reduces oxidative stress and inflammation by inhibit of JNK and NF-κB activation in a rat model of amyloid-beta-induced Alzheimer's disease. Neurosci Lett 491(2): 127-132.

28. Krishnan KR, Charles HC, Doraiswamy PM, Mintzer J, Weisler R et al. (2003) Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. Am J Psychiatry 160(11): 2003-2011.

29. Ono H, Nishijima Y, Ohta S, Sakamoto M, Kinone K et al. (2017) Hydrogen Gas Inhalation Treatment in Acute Cerebral Infarction: A Randomized Controlled Clinical Study on Safety and Neuroprotection. J Stroke Cerebrovasc Dis 26(11): 2587-2594.