Mini Review

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

Shigeo Ohta¹, and Takashi Asada²

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

²Ochanomizu 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 (H₂) 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, H₂ was believed to be a biologically inert and non-functional molecule in the body; however, we overturned this concept by demonstrating that H₂ 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 H₂. These studies have revealed that H₂ 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 H₂ on various kinds of human diseases. As a molecular mechanism by which H₂ exerts the multiple functions, H₂ might regulate various gene expression levels in indirect manners under transcription factors such as including NFAT and Nrf2 [11,12].

Owing to its multiple functions and great efficacy coupled with its lack of adverse effects, H₂ has great potential for preventing AD.

There are several methods to ingest or consume H₂: inhaling H₂ gas, drinking H₂-dissolved in water (H₂-water), injecting H₂-dissolved in saline (H₂-saline), taking an H₂ bath, or dropping H₂-saline into the eyes.

Introduction

First, to examine the effect of drinking H₂-water on impaired learning and memory abilities, mice were strongly stressed by chronic physical restraint to enhance oxidative stress in the brain. Consumption of H₂-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.

Copyright: © 2018 Shigeo Ohta, et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
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 H2 in the prevention of age-related dementia.

As the result, drinking H2-water reduced oxidative stress in DAL101 mice, suppressed a decline in learning and memory impairment, and suppressed neurodegeneration [1]. Moreover, H2-water extended the average lifespan of DAL mice [1].

Next, based on these animal experiments, we examined the efficacy of drinking H2-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 H2-water for 1 year. After 1 year, there was no observable adverse effect, and the subjects in the H2-water group non-significantly tended 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 H2-group [1].

**Conclusion**

The present mini-review introduced a possibility for slowing the progress of dementia by drinking H2-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, H2 reduced oxidative stress and inflammation in an amyloid-β-induced Alzheimer rat model [27].

These improvements associated with drinking H2-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 H2-water improved the average score at about 3 better than the baseline stages after 1 year in APOE4 carriers.

Moreover, H2 has strong advantages with its lack of adverse effects. Indeed, virtually all clinical studies indicated that H2 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 H2 without undue caution.

Longer and larger-scale trial will be necessary to clarify the effect of H2-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 H2-water for 1 year, as assessed in a randomized, double-blind, placebo-controlled clinical trial.

References


