Short-Term H₂ Inhalation Improves Cognitive Function in Older Women: A Pilot Study

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1. Introduction

A decline in cognitive function accompanies aging as one of the most distinctive and hard-to-manage features of the process of growing old. Many different pharmacological and non-pharmacological procedures have been used to tackle age-related cognitive impairment in clinical environment with mixed results. Molecular hydrogen (H₂) is a novel biomedical gas with polyvalent therapeutic properties. H₂ has recently been reported to alleviate cognitive impairment in clinical environment with mixed results. 1 Molecular biological procedures have been used to tackle age-related cognitive growing old. Many different pharmacological and non-pharmacological procedures have been used to tackle age-related cognitive impairment in clinical environment with mixed results. 2 H₂ has recently been reported to alleviate cognitive impairment and neurodegeneration in several animal models, 3–5 yet no studies so far evaluated its effectiveness in human trials. In this open-label pilot study, we analyzed the effects of 4-week H₂ inhalation on cognitive performance in women aged 65 and above.

2. Methods

The participants (n = 13) were community-dwelling older women (age 68.0 ± 3.0 years; weight 66.9 ± 10.3 kg; height 161.1 ± 5.8 cm) who volunteered to participate in this open-label pilot trial (registered at ClinicalTrials.gov, NCT02830854). Exclusion criteria included the presence of serious disease or psychiatric comorbidity. The study was conducted according to the guidelines of the Declaration of Helsinki, with local institutional review board approved the study protocol. All participants gave their informed consent, and were asked to maintain their usual lifestyle and dietary intake during the study. The participants received H₂ by inhalation for 15 min once per day for 4 weeks. Gaseous H₂ (4%) was provided by biological gas supplying apparatus (MIZ Company Ltd, Kanagawa, Japan), with day-to-day H₂ inhalation supervised by study investigators throughout the trial. The primary endpoint of treatment efficacy was the change in the Mini Mental State Exam (MMSE) score from baseline to week 4. Additionally, assessment of other cognition markers and side-effects evaluation were performed at baseline and after 4 weeks after study commence. The cognitive function of participants was assessed using the MMSE and Alzheimer disease assessment scale cognitive subscale (ADAS-Cog) at baseline and at follow up. H₂ intervention significantly increased total MMSE scores (for 14.2% on average; p < 0.01), thereby improving cognitive function from mild dementia at baseline (a score of 25.6 out of 30) to normal cognition at follow up (above a cut score of 27). In addition, ADAS-Cog scores were significantly improved by H₂ inhalation, with better performance for word recall test (p < 0.01), and improved word recognition (p = 0.01) at post-administration, respectively. This pilot trial seems to corroborate previous animal studies, suggesting that gaseous H₂ might be considered as a beneficial agent for age-related cognitive health.

3. Results

All participants completed the follow-up measures, with no participants were excluded from the study due to adverse events, or reported any side effect of H₂ intervention. The compliance with the regimen was 95.8%. Changes in cognitive function outcomes during the study (baseline vs. 4-week follow up) are presented in Table. H₂ intervention significantly increased total MMSE scores (for 14.2% on average; p < 0.01), thereby improving cognitive function from mild dementia at baseline (a score of 25.6 out of 30) to normal
cognition at follow up (above a cut score of 27). In addition, ADAS-Cog scores were significantly improved by H2 inhalation, with better performance for word recall test (p < 0.01), and improved word recognition (p = 0.01) at post-administration, respectively. Other nine domains of ADAS-Cog scores (naming task, commands, constructional praxis, ideational praxis, orientation, spoken language ability, remembering test instructions, word-finding difficulty, and comprehension) were performed correctly (e.g. score = 0) at both assessment periods (not presented).

4. Discussion

In this first-in-human, open-label trial of H2 efficacy for cognitive performance in elderly, a daily inhalation of 15 min of gaseous H2 for four weeks improved selected markers of cognition in a cohort of apparently healthy women aged 65 and above. Twelve women (out of 13) displayed higher MMSE scores at post-administration, while enhanced word-sensitive cognition was reported in ADAS-Cog test after H2 intervention. In addition, inhaling H2 appeared to have acceptable safety profiles, with no evidence of subjectively reported side effects. This pilot trial seems to corroborate previous animal studies, suggesting that gaseous H2 might be considered as a beneficial agent for age-related cognitive health. Cognitive impairment appears to be closely related to oxidative stress in elderly.7 Since exogenous H2 acts as a selective antioxidant,8 it might help to maintain or retrieve redox balance within the central nervous system, and promote cognitive longevity. Nagata and co-workers reported that consumption of H2 reduces oxidative stress in the brain, and prevents oxidative-stress-induced decline in hippocampus-dependent learning and memory tasks in mice.3 Besides antioxidant effect, H2 is also reported having an anti-inflammatory and anti-apoptosis effect, an anti-allergic action, a lipid metabolism-improving effect, a neuroprotective effect, and an intracellular signaling regulatory effect.8 These diverse effects would also contribute to the improvement of cognitive impairment, and the accurate mechanism of H2 to affect cognition requires future research. However, several limitations must be considered when study findings are interpreted. The study population included only female participants; it remains unknown whether gaseous H2 affects cognitive performance in older men and if gender-based differences occur in response to H2 inhalation. Other limitations include relatively small sample size and no control or placebo-control group. Finally, a 4-week study is perhaps too short to examine the lasting effect of cognitive benefit and to avoid the possibility of practice effect when repeated during serial cognitive tests. Hence, randomized controlled trials are highly warranted to substantiate this cognition-boosting power of gaseous H2 in humans, with other markers of cognitive function (e.g. functional neuroimaging, cerebrospinal fluid and blood-based biomarkers) monitored during the intervention, as well as further validation in larger samples. If proven effective and safe in well-designed human trials, gaseous H2 might be considered as an innovative therapeutic agent for other cognitive disorders, including amnesia, Alzheimer’s disease or vascular dementia in the future.

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Conflict of interest

The authors declare no conflict of interest.

References