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Free Radic Res. 2018 Dec;52(11-12):1311-1322. doi: 10.1080/10715762.2018.1460749.

Epub 2018 Apr 23.

## Hydrogen-rich water improves cognitive impairment gender-dependently in APP/PS1 mice without affecting A $\beta$ clearance

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PMID: 29683360 DOI: [10.1080/10715762.2018.1460749](https://doi.org/10.1080/10715762.2018.1460749)

### Abstract

Alzheimer's disease (AD) is characterised as a provoked inflammatory response and oxidative stress along with amyloid  $\beta$  peptide (A $\beta$ ) deposition and neurofibrillary tangles in the brain, and effective treatment is greatly needed. Molecular hydrogen, which has been proposed to be an antioxidant that selectively reduces reactive oxygen species, was found to exert beneficial effects in A $\beta$  injection-induced cognitive dysfunction. However, whether and how hydrogen affects AD pathogenesis remains uninvestigated. Thus, in the present study, APP<sup>swe</sup>/PS1<sup>dE9</sup> (amyloid precursor protein (APP)/PS1) mice, a transgenic AD mouse model, were administered hydrogen-rich water for 3 months and the effects on cognitive function and molecular pathways were investigated. We found that hydrogen-rich water significantly improved cognitive behaviour in female transgenic AD mice without affecting A $\beta$  clearance, and reversed the brain oestrogen level, ER $\beta$ , and brain-derived neurotrophic factor (BDNF) expressions that were damaged in female transgenic AD mice, but not in males. Furthermore, hydrogen-rich water ameliorated oxidative stress and inflammatory responses more profoundly in the brains of female AD mice than in those of males. Our results demonstrate a novel sex-specific beneficial effect of hydrogen via oestrogen and brain ER $\beta$ -BDNF signalling in AD pathogenesis.

**Keywords:** Alzheimer's disease; Molecular hydrogen; cognitive function; female; oestrogen.

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