

Molecular Hydrogen and its Potential Application in Therapy of Brain Disorders

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Short Communication

It has long been known that molecular hydrogen is a physiologically inert gas. Recent evidence indicates that molecular hydrogen acts as a novel antioxidant which could selectively reduce $\cdot\text{OH}$ and ONOO^- but does not affect physiological reactive oxygen species (ROS) [1]. Subsequent studies have confirmed that consumption of hydrogen reduces oxidative stress in a diverse range of disorders and organ systems including the digestive, cardiovascular and respiratory systems [2]. These studies strongly suggest the potential of molecular hydrogen as an effective therapeutic and preventive antioxidant.

Because of its low molecular weight, hydrogen can easily diffuse across the blood-brain barrier, which allows it to protect cells against degeneration and improve brain function. Chen et al. [3] found that the protective effect of hydrogen in the brain is accompanied by reducing the oxidative stress and blood glucose levels after dextrose injection in rats. It has also been reported that drinking hydrogen-rich pure water prevents superoxide formation in brain slices of vitamin C-depleted SMP30/GNL-knockout mice during hypoxia-re-oxygenation [4]. Molecular hydrogen has also been shown to prevent cognitive decline. Consumption of hydrogen water suppressed the increase in oxidative stress and prevented stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice [5]. In addition, molecular hydrogen likely retards the development and progression of Parkinson's disease. Half-saturated hydrogen water protected against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease (Fu et al., 2009). In another Parkinson's disease mouse model induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), drinking hydrogen-rich water reduced oxidative stress and dopaminergic neuronal loss [6]. In a rat model of Alzheimer's disease, hydrogen-rich saline prevented β -amyloid-induced neuroinflammation and oxidative stress and improved memory dysfunction [7]. Additionally, it has been reported that drinking hydrogen water ameliorated the cognitive impairment in senescence-accelerated mice [8]. Recently, we reported that intake of hydrogen-rich water (HRW) can attenuate Organophosphate (OP) compounds-induced oxidative stress and protect Wistar rats from OPs-induced neurotoxicity [9]. All this evidence indicated the potential of molecular hydrogen for preventive and therapeutic applications in brain disorders.

Molecular hydrogen can be ingested or consumed by several methods. Inhalation of hydrogen gas was used as a straightforward therapeutic method in earlier studies. Although hydrogen gas poses no risk of flammability or explosion at a concentration of less than 4.7% in air, safety is still a concern and inhalation of hydrogen gas may be unsuitable as continuous hydrogen consumption for preventive use. In contrast, drinking hydrogen-rich water may be beneficial since it is a portable, easily administered and safe means of delivering hydrogen.

Hydrogen can be dissolved in water up to 0.8 mM under atmospheric pressure at room temperature. Even though oral administration is safe and convenient, hydrogen in water tends to evaporate and is difficult to control concentration and absorption. Administration of hydrogen via an injectable hydrogen-dissolved saline vehicle is superior to hydrogen gas or hydrogen-rich water, which may allow the delivery of higher and more accurate concentrations of hydrogen [10].

As a potential antioxidant agent, molecular hydrogen has a number of advantages. First, it selectively reduces $\cdot\text{OH}$ and ONOO^- but does not affect physiological reactive oxygen species (ROS) which function as signaling molecules and regulate apoptosis, cell proliferation, and differentiation. Second, hydrogen has not been reported to be toxic at effective dosages, and overdosing is unlikely because excess hydrogen is expired via the lungs. Thirdly, hydrogen can diffuse extremely rapidly into tissue and is likely to reach important target subcellular compartments. Finally, the production of hydrogen is not expensive compared with most other drugs.

Although the protective effects of molecular hydrogen have been reported in many kinds of brain disorders, the mechanism to explain the neuroprotective effects of hydrogen is limited to its antioxidant property [6,8,10]. A possible cause for the neuroprotective effect of hydrogen may be related to its high diffusibility. Hydrogen molecules can readily cross the blood-brain barrier and penetrate biomembranes smoothly to diffuse into the cytosol, nucleus and mitochondria. This is particularly important, as mitochondria is the major source of ROS and notoriously difficult to target. The protective effect of molecular hydrogen on the mitochondria has also been found in our study. However, the detailed mechanism underlying the protective effect of molecular hydrogen on the mitochondria remains unknown. Several reports have demonstrated an effect on the regulation of gene expression and protein-phosphorylation, however, the transcriptional factors and kinases involved in the effects of molecular hydrogen have not been identified. Recently, our study defines a novel mechanism of biological activity of hydrogen by directly increasing the AChE activity, which indicates the possibility of the direct interaction between hydrogen and other enzyme molecules [9]. We believe that once more targets interacting directly with molecular hydrogen are found, the mechanisms underlying the marked effects of the molecular hydrogen will be elucidated.

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