Effects of Molecular Hydrogen on Mild Cognitive Impairment (MCI)

Mild cognitive impairment (**MCI**) is the stage between the expected **cognitive decline** of normal aging and the more serious **decline** of dementia. It can involve problems with memory, language, thinking and judgment that are greater than normal age-related changes. Oxidative stress is one of the causative factors in the pathogenesis of neuro-degenerative diseases including mild cognitive impairment (MCI) and dementia. In physiological conditions, there is a balance between oxidant molecules, reactive oxygen species (ROS), and antioxidants species. Oxidative Stress occurs when this balance shifts towards reactive species generation leading to cellular/tissue oxidative damage. Mitochondrial dysfunction and iron homeostasis dysregulation, are believed to be the major causes of cumulative oxidative damage observed in neurons of late onset Alzheimer's disease (LOAD). Moreover, *postmortem* studies on brain tissues identified ROS by-products in proteins, lipids, and DNA from hippocampus and prefrontal regions in MCI and LOAD patients.

Molecular hydrogen (H_2) has potential as a novel antioxidant, and numerous studies have strongly suggested its potential for preventive and therapeutic applications. There are several methods to administer H_2, including inhaling hydrogen gas (H_2-gas), drinking H_2-dissolved water (H_2-water), and injecting H_2-dissolved saline (hydrogen-rich saline). Drinking H_2-water prevents the chronic stress-induced impairments in learning and memory by reducing oxidative stress. H_2-water could suppress aging-dependent memory impairment induced by oxidative stress. Consumption of H_2-water attenuate the shortened lifespan, although H_2-water do not extend the maximum lifespan. H_2-water suppressed the biochemical, behavioral, and pathological decline in oxidative stress. H_2 acts as an efficient antioxidant inside cells owing to its ability to rapidly diffuse across membranes. Moreover, as a secondary anti-oxidative function, H_2 seems to activate NF-E2-related factor 2 (Nrf2), which reduces oxidative stress by expression a variety of antioxidant enzymes. Moderate exercise enhances energy metabolism and suppresses the expression of pro-inflammatory cytokines, and protects vascular systems. H_2 exhibits multiple functions by a decrease in the levels of pro-inflammatory cytokines and an increase in energy metabolism in addition to anti-oxidative roles. To exert multiple functions, H_2 regulates various signal transduction pathways and the expression of many genes. For examples, H_2 protects neural cells and stimulates energy metabolism by stimulating the hormonal expression of ghrelin and fibroblast growth factor 21, respectively. In contrast, H_2 relieves inflammation by decreasing pro-inflammatory cytokines. Thus, the combination of these functions of H_2 on anti-inflammation and energy metabolism-stimulation might prevent the decline in brain function, both of which are improved by regular and moderate exercise. Thus, it is possible that the multipe functions of H_2, including energy metabolism-stimulation and anti-inflammation, may contribute to the improvement of the dementia and the MCI.