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Molecular Hydrogen: New Antioxidant and Anti-inflammatory Therapy for Rheumatoid Arthritis and Related Diseases

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease in which the progressive destruction of joint causes morbidity. It is also associated with an increased risk of atherosclerosis, which can result in cardiovascular disease and mortality. The therapeutic goal is to control the systemic inflammation to obtain not only the remission of symptoms, but also improve general state of health. Although recent biologic immunosuppressive therapies targeting pro-inflammatory cytokines have spawned a paradigm shift regarding the prognosis of RA, these therapies possess inherent side effects. Also, early diagnosis of the disease remains confounded by uncertainty. While the mechanisms responsible for the onset of RA remain unclear, reactive oxygen species (ROS) play a significant role in the pathogenesis of RA. ROS play a central role both upstream and downstream of NF-κB and TNFα pathways, which are located at the center of the inflammatory response. Among the ROS, the hydroxyl radical is the most harmful, and molecular hydrogen (H_2) is a selective scavenger for this species. Recently, it has been shown that H_2 is useful when administered along with the conventional therapy in RA as it acts to reduce oxidative stress in the patients. Especially in the early stage, H_2 showed significant therapeutic potential, which also seemed to assist diagnosis and treatment decisions of RA. The possible expectations regarding the potential benefits of H_2 by reducing the oxidative stress, resulting from inflammatory factors, are raised and discussed here. They include prevention of RA and related atherosclerosis, as well as therapeutic validity for RA.

Keywords: Rheumatoid, atherosclerosis, prevention, Oxidative Stress, 5 ppm, Molecular Hydrogen, 8-hydroxylguanine, Hydroxyl Radical.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the population. It is characterized by irreversible joint disorder accompanied by destruction of bone and cartilage, which causes serious morbidity. In addition, the chronic inflammation associated with RA can increase one's risk of atherosclerosis, which is a significant cause of mortality with the cardiovascular failure [1, 2]. Atherosclerosis associated with RA progresses rapidly, even in the absence of the conventional risk factors, such as hypertension, diabetes mellitus, or obesity. Consequently, the aim of RA therapy includes not only improving the disease activity, which is commonly estimated by the joint disorder and inflammatory markers, but also controlling the systemic and unremarkable inflammation of endothelial cells. Recent progress of anti-cytokine therapies is improving the risk for cardiovascular disease (CVD) [3].

Although the etiology is unknown, RA is certainly associated with autoimmune disorders, and its pathogenesis has been well investigated [2]. Auto-reactive T cells that infiltrate the synovial tissue promote the immune response, resulting in an overproduction of pro-inflammatory cytokines such as tissue necrosis factor alpha (TNFα), interleukin 1 (IL-1) and interleukin 6 (IL-6). Accordingly, early therapy was based on aggressive biological modification of the disease by controlling the synovial T cells and/or reducing the levels of the cytokines. Unfortunately, this approach has met limited therapeutic success, raising the issue that important regulatory factors were missing in the existing mechanistic model of RA. Reactive oxygen species (ROS) could be one of the unidentified regulatory factors. The synovial fluid and peripheral blood of RA patients have high levels of ROS and ROS-generated molecules, including superoxide, peroxide, hydroxyl radicals and reactive nitrogen species like peroxynitrite [4-6]. They oxidize various cellular and extracellular components, including nucleotides, DNA, proteins, polysaccharides, and lipids, by means of their unpaired free radicals. Of these, 8-hydroxyguanine (8-OHdG), which is produced by the oxidation of guanine bases in DNA and also in the nucleotide pools, is considered important [7-9]. 8-OHdG is a standard biomarker for oxidative stress. Numerous studies have reported that 8-OHdG accumulates in diseases related to oxidative stress, such as cancer, diabetes mellitus, Alzheimer's disease, hypertension, cardiovascular disease, metabolic syndrome, and autoimmune disease [10-16]. Elevated levels of 8-OHdG have been reported in RA [17, 18]and atherosclerosis [19].

In the past decade, it has been shown that molecular hydrogen (H_2) selectively eliminates highly reactive hydroxyl radical in cultured cells and living organisms [20, 21]. H_2 targets hydroxyl radicals, but not super oxide, peroxide, or nitric oxide, which are important molecules for organisms [22]. Recently, it was demonstrated that consumption of water with a high concentration of molecular hydrogen (4-5 ppm in the water) significantly improves the disease activity and reduces the oxidative stress in RA [23]. H_2 seemed to complement or provide a substitute for conventional therapy by reducing oxidative stress and improving damage associated with RA, especially in the early stages of the disease and in the case of Antibodies against cyclic citrullinated peptide (ACPA)-negative RA.

In this review article, prospective applications of new H_2 therapies, for both the diagnosis and treatment of RA, are discussed. Also the possible expectation for the prevention of RA and related atherosclerosis by the daily consumption of high H_2 water are mentioned.

GENERATION OF ROS IN CHRONIC INFLAMMATION

ROS are produced as an inevitable byproduct of electron transfer in oxidative phosphorylation during aerobic metabolism [24]. On the other hand, during inflammatory stages of RA, infiltration or proliferation of immune activated cells in the synovium actively generate ROS via the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase system (Nox) [25-27]. Among the actively generated ROS, superoxide anion is the primary product and liberated into extracellular matrix as well as sequestered in lysosomes. Su-

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