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Original research article

Hydrogen-rich water partially alleviate inflammation, oxidative stress and intestinal flora dysbiosis in DSS-induced chronic ulcerative colitis mice

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Abstract

Purpose

Oxidative damage and intestinal flora dysbiosis play important roles in the progression of chronic ulcerative colitis (UC). This study explored the effect and mechanism of molecular hydrogen in chronic UC.

Materials and methods

Male C57BL/6 mice (19.6 ± 0.4 g, 7 weeks) were randomly divided into 3 groups: normal control (NC) group, UC (Dextran Sulfate Sodium, DSS) group, and hydrogen-rich water (HRW, 0.8 ppm)-treated UC (DSS + HRW) group. Mice in the DSS treatment group were treated with DSS for the following 3 cycles to establish chronic UC model: the first 2 cycles consisted of 2.5% DSS for 5 days, followed by drinking water for 16 days, and a third cycle consisted of 2% DSS for 4 days, followed by drinking water for 10 days. The mice in the DSS + HRW group were administered HRW daily throughout the experiment.

Results

The mice in the DSS groups developed typical clinical signs of colitis. HRW treatment partially ameliorated colitis symptoms, improved histopathological changes, significantly increased glutathione (GSH) concentration and decreased TNF-α level. Notably, HRW treatment significantly inhibited the growth of Enterococcus faecalis, Clostridium perfringens and Bacteroides fragilis (P < 0.05 vs. DSS group), with the relative abundance that was close to the levels in the NC group. Microarray analysis revealed that 252 genes were significantly modified after HRW treatment compared with those in the DSS-treatment alone group, and 17 genes were related to inflammation, including 9 interferon-stimulated genes (ISGs).

Conclusions

Hydrogen-rich water partially alleviates inflammation, oxidative stress and intestinal flora dysbiosis in DSS-induced chronic UC mice.

Introduction

Ulcerative colitis (UC) is a complex, chronic, immune-mediated inflammatory disorder of the colon. Epidemiological and experimental studies have suggested that diet is one of the environmental factors that contributes to the onset and pathophysiology of UC [1]. Studies have shown that higher consumption of total fats, oleic acid, saturated fatty acids (SAFAs), total polyunsaturated fatty acids (PUFAs), trans fat, monounsaturated fatty acids (MUFAs), and linoleic acid is significantly associated with an increased risk for UC [2]. A diet high in protein, particularly animal protein, may also be associated with an increased risk of inflammatory bowel disease and relapse [3]. In recent years, UC incidence has increased in many countries because of unhealthy diet styles in many regions [4,5].

UC has a significant impact on the quality of life of patients since it causes digestive disorders and inflammation in the gastrointestinal tract, leading to diarrhea, abdominal pain, rectal bleeding, weight loss and susceptibility to infection, in addition to the side effects of therapeutic drugs. Notably, patients with longstanding UC have an increased risk of colorectal cancer (CRC) [6]. As the global UC incidence and prevalence continue to increase, the development of an effective strategy to prevent this disease and improve patients' quality of life are urgently needed.

It is widely believed that the disease pathology of UC is caused by various factors, such as heredity, inflammation, oxidative stress, and intestinal flora imbalance [7]. Among them, oxidation and inflammation are reciprocally related. Activated macrophages and neutrophils aggregate in the inflamed gut and produce an excessive amount of reactive oxygen species (ROS). The increase in the level of ROS results in severe oxidative stress and substantial damage to DNA, proteins and lipids, thus exacerbating oxidative stress injuries in UC patients [8]. Thus, an impaired antioxidant mechanism has been implicated as a pathogenic cause of colitis, and the use of antioxidants has been proposed as a novel therapeutic strategy for UC [9]. In addition, studies have shown that the intestinal microbiota is also one of the key players in the etiology of UC since gut microbiome dysbiosis usually leads to a dysregulated immune response [10]. Therefore, manipulation of microflora with probiotics and/or prebiotics is also an attractive strategy for the management of UC [11].

In recent years, the antioxidant and anti-inflammatory activities of hydrogen (H_2) in certain diseases have attracted much attention [12]. Previous studies have shown that H_2 acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals (e.g., ONOO⁻, ·OH) and protecting cells from oxidative stress injuries. Moreover, H_2 molecules also exhibit marked anti-inflammatory characteristics during the course of the inflammatory response [13], [14], [15]. In particular, Shen et al. [16] demonstrated the significant therapeutic potential of hydrogen-rich water (HRW) in dextran sulfate sodium (DSS)-induced acute colitis via inhibition of oxidative stress, partial inflammatory factors, endoplasmic reticulum (ER) stress and upregulation of the expression of heme oxygenase-1 (HO-1). Other studies have shown the protective effect of H_2against acute UC in animal experiments via the inhibition of DSS-induced pathogenic outcomes, including loss of body weight, increase in colitis score, pathogenic shortening of colon length, elevated levels of IL-12, TNF-α and IL-1β in colon lesions, and colonic tissue destruction [17]. However, a previous study related to the beneficial effects of H_2 have mainly focused on acute animal models [18]. How H_2 will act on chronic UC remains unclear. In the present study, we investigated the effect of HRW on oxidative stress, inflammation and intestinal bacteria in DSS-induced chronic UC mice, and the preliminary mechanism was also explored.

Section snippets

Animals and groups

Male C57BL/6 mice (19.6 ± 0.4 g, 7 weeks) were purchased from Slack Laboratory Animal Co., Ltd. (Shanghai, China). The animals were caged under specific pathogen-free (SPF) conditions under a light cycle at 23 ± 2 °C and 50 ± 10% relative humidity. All mice were housed in solid-bottom cages with wood shavings and fed standard mouse chow and tap water *ad libitum*.

We randomly divided 38 mice into 3 groups as follows: (1) normal control group (NC, n = 10); (2) DSS-treated group (UC, ...

HRW partially ameliorates the manifestations of DSS-induced chronic UC in mice

To investigate the preventive role of HRW in chronic UC, we used a model in which 8-week-old mice were subjected to 3 cycles of DSS administration in drinking water (Fig. 1). The clinical indices usually used in the evaluation of colitis include body weight, diarrhea state, colon length and the histopathological appearance of the colonic tissue. The normal control C57BL/6 mice (NC group) remained healthy throughout the experiment. In contrast, the DSS-treated mice developed typical clinical ...

Discussion

UC is a global disease with increasing incidence and is characterized by superficial mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain, which lead to a decrease in patients' quality of life. Moreover, long-term chronic UC is one of the main factors in the pathogenesis of CRC [6,24]. Therefore, prevention of chronic UC through a convenient and simple method that can be implemented in daily life (e.g., by drinking water) will be meaningful.

Molecular H_2 is recognized as possessing ...

Conclusions

In summary, we preliminarily explored the antioxidative and anti-inflammatory effects of HRW on chronic UC. its improvement efficacy with respect to some common indices of colitis, and its regulatory effect on gut bacteria as well as the expression of ISGs. The present study provides in vivo evidence that HRW can partially improve clinical parameters in a chronic UC mouse model. These data implied its potential applicability in the prevention of chronic UC. However, the efficacy of HRW in ...

Financial disclosure

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The author contribution

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Data Interpretation: Lihua Song, Hongli Yan.

Manuscript Preparation: Y Zhang, XW Ding, L Yang.

Literature Search: XW Ding, L Yang.

Funds Collection: Lihua Song, Hongli Yan. ...

Declaration of competing interest

The authors declare no conflicts of interest. ...

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2024, Free Radical Biology and Medicine

Citation Excerpt :
...Tryptophan metabolites produced by microbes have various physiological roles, including regulating the adaptive and innate immune systems, and affecting asthma by binding to the aryl hydrocarbon receptor (AhR) [27]. Additionally, recent animal studies have found that HRW has significant anti-inflammatory effects in rheumatoid arthritis, neuropathic pain [28], DSS-induced colitis [29], and Alzheimer's disease [30] by regulating gut microbiota. The beneficial effect of HRW on inflammation in asthma may also be partially attributed to the gut microbiota and its metabolites....

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2023, International Immunopharmacology

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...H_2 inhalation-affected intestinal flora may lead to a decrease in intestinal permeability, which decreases the development of metabolic endotoxemia and inflammation. Of course, this does not rule out hydrogen molecules directly acting on gut function, and some studies found that hydrogen-rich water alleviates chronic ulcerative colitis and inflammatory bowel disease [23,24]. Indeed, our results showed that H2 protected against acute alcohol-induced intestinal barrier damage by increasing the expression of TJ proteins, which led to a decrease of LPS in liver....

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