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CLINICAL VIEWPOINT

Hydrogen May Be Used as a Treatment for Stress-Induced Gastric Ulceration

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Abstract. Recently, it has been shown that hydrogen, a potent hydroxyl radical (•OH) scavenger, can effectively protect animals against reactive oxygen species-induced tissue damage. Stress-associated ulceration is a type of diffuse lesions of the mucosal layer of the stomach and sometimes also of the duodenum, and it frequently occurs as a result of major stressful events. Direct evidence has been presented to show that •OH is one of the major causative factors of stress-induced gastric ulceration. Treatment with a potent antioxidant or •OH scavenger can decrease stress-induced gastric mucosal damage. In a similar manner, it is suggested here that that hydrogen may be used as an effective means to counteract stress-induced •OH and thus provide protection against stress-induced gastric ulceration.

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1. Introduction

Hydrogen is the most abundant chemical element, constituting approximately 75% of the universe's elemental mass and recent attention has focused on hydrogen as an energy storage medium that burns in a less-polluting way than fossil fuels. Hydrogen has always been considered as a physiological inert gas, which is often used in deep-sea diving over a long period of time. Recently, it has been proved that hydrogen, a potent free radical scavenger, selectively reduce the hydroxyl radical (•OH), one of the most cytotoxic of reactive oxygen species (ROS), and effectively protected organs against ROS-induced damage [1,2].

It has been proved that ROS system such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and •OH, at a relative low concentration, mediate many biological effects. For example, it functions as necessary signaling molecules and critically modulates the activation of the immune system and thus participates in antibacterial defense. However, they become extremely detrimental when they are overproduced and overcome the antioxidant capacity of the host. •OH, one of the most cytotoxic of ROS, can trigger the oxidation of lipids, amino acids and saccharides leading to formation of various secondary free radicals. These toxic products chemically oxidized DNA, proteins, and lipids, causing cellular damage.

In 2007, Ohsawa et al. proved that hydrogen inhalation could protect the brain against I/R injury and stroke by selectively reducing •OH and $ONOO^-$. This study indicated a unique function of hydrogen as a therapeutic gas by specifically targeting •OH and $ONOO^-$ at the first time [1]. Hydrogen rapidly becomes a medical research focus and has been proved to be an effective treatment against many animal disease models including hepatic I/R injury, transplantation-induced intestinal graft injury, acute pancreatitis, myocardial, neonatal hypoxia-ischemia, Parkinson's disease, oxidative stress induced cognitive decline, etc. [3-11]. Although the protective effect of hydrogen as a therapeutic gas for ROS-induced damage has been extensively investigated, its gastroprotective effect has not been reported until now.

2. Stress-Induced Gastric Ulceration

Stress ulceration is diffuse lesions of the mucosal layer of the stomach and sometimes the duodenum, and it frequently occurs as a result of many major stressful events, such as extensive burns, shock, sepsis, major surgery, and severe trauma. Bleeding from stress ulcer in critical ill patients can result in substantial morbidity and mortality [12,13]. A growing body of experimental and clinical evidence suggests that gastric mucosal damage by stress, ethanol, nonsteroidal antiinflammatory drugs, and by Helicobacter pylori is mediated through the ROS.

During the stress process, ROS were rapidly and continuously produced and the resulting oxidative stress was responsible for propagation of gastric damage [14, 15]. A burst of ROS during stress-induced gastric ulceration have consistently demonstrated by numerous of studies [16-18]. The production of ROS is via the xanthine-xanthine oxidase system and neutrophils. Lipid peroxidation initiated by the ROS, accompanied by impairment of antioxidative enzyme activity of cells, has been proved to involve in the formation of acute gastric lesion [19,20]. There are also several ROS -dependent cell signaling contributed to the pathophysiology of stress-induced gastric lesion. In 2007, our group had proved that ROS-mediated p38 and NF-κB activation played an essential role in the pathogenesis of stress-induced gastric inflammatory damage [16, 17].

Early in 1997, Indian scientists had found that •OH, produced from endogenous O_2^- and H_2O_2, was indeed generated in the gastric mucosa during the process of stress to induce gastric ulceration and proved that •OH was one of the major causative factors in stress-induced gastric ulceration. The severity of the mucosal

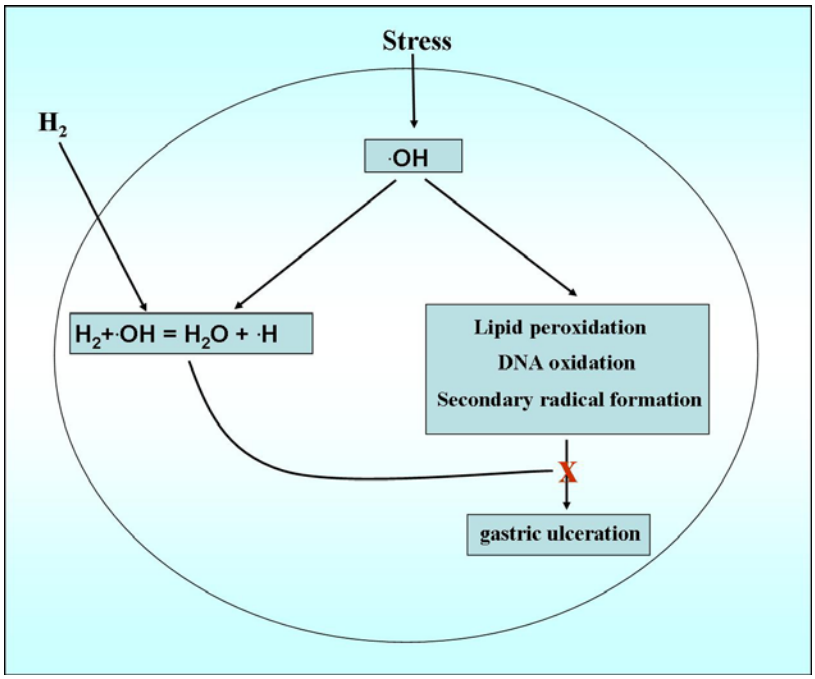

Figure 1. Hypothesis on the mechanism of the protective effect of hydrogen's protection against stress-induced gastric ulceration. Hydrogen can scavenge stress-induced •OH formation, thereby preventing the gastric ulceration formation.

damage (ulcer index) correlates well with the activation of the superoxide dismutase (SOD) and inactivation of the gastric peroxidase during the progress of stress, thus creating a favorable condition for the accumulation of H_2O_2 and the generation of highly reactive •OH. •OH is one of the most cytotoxic of ROS and there only needs one millisecond for it to cause DNA damage and a significant generation of •OH can cause DNA damage, lipid peroxidation, critical cellular proteins oxidation [18], therefore, result in the gastric mucosa damage. There is no known endogenous detoxification system available for •OH. Therefore, scavenging •OH has a tremendous potential to control stress-induced gastric ulceration.

Over the past several decades, several types of gastroprotectant have been proposed including antioxidants to alleviate stress-induced gastric ulceration. It has been found that systemic administration of glutathione or SOD prevented water-immersion stress-induced ulceration. Dengiz et al. have investigated the amiodarone's protective effects on oxidative gastric mucosal damage by its intrinsic antioxidant properties [21]. Dekanski et al. also found Olive leaf extract, a natural antioxidant, had protective effect on stress-induced gastric mucosal damage [22].

Although much effort has been made to find compounds for the prevention and treatment of stress-induced gastric ulceration, at present there is not a single agent that satisfies the comprehensive criteria as an optimal gastroprotectant. Some antioxidants seem to be promising in animal models but they fail in human clinical trials [23]. Needless to say, there has been long-standing interest in finding low-toxicity, high-efficacy, and inexpensive compounds as preventive agents that can be used to reduce the development of stress-induced gastric damages.

3. A Clinical Viewpoint

Based on the hypothesis that hydrogen can selectively counteract •OH, which is one of the major causative factors in stress-induced gastric ulceration, it is suggested that hydrogen may be used to exert a protective effect against stress-induced gastric ulceration (**FIG 1**).

Over the past years, studies have revealed that among many of the available therapeutic strategies, the use of antioxidant strategy is considered one of the most popular approaches. Currently, there is a large body of data indicating that hydrogen, a new antioxidant, can effectively protect tissues against oxidative damage by selectively reducing •OH. Compared with other types of antioxidants, hydrogen may have following advantages: (**i**) Hydrogen is contained in human body and can react with •OH to produce water. Thus, it has a low toxicity. (**ii**) Hydrogen is chemically mild enough not to disturb metabolic oxidation-reduction reactions or to disrupt ROS involved in cell signaling. (**iii**) The low molecule weight of hydrogen makes it easy to penetrate the biomembranes and diffuse into the cell, mitochondria and nucleus; therefore, it can be highly effective for reducing cytotoxic radicals. (**iv**) Dissolving hydrogen gas in physiological saline is easy to apply and safe to use. Inhaling hydrogen gas at a relatively low concentration (below 4.7%) is safe and clinically available. Because of these unique advantages, it is believed that hydrogen may be superior to other antioxidants in the treatment of stress-induced gastric damage.

4. Conclusion

As •OH is one of the major causative factors in stress-induced gastric ulceration, it is suggested here that hydrogen, a selective •OH scavenger, may be effective for the treatment of stress-induced gastric ulceration. Compared to other antioxidants, hydrogen has several unique advantages, such as low toxicity, high efficacy, and ease of use. This clinical suggestion merits further experimental testing to determine its effectiveness and potential adverse effects.

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