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ACARBOSE: A NEW OPTION IN THE TREATMENT OF ULCERATIVE COLITIS BY INCREASING HYDROGEN PRODUCTION

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Abstract

Acarbose，which is clinically widely used to treat Type 2 Diabetes，is thought to act at the small intestine by competitively inhibiting enzymes that delay the release of glucose from complex carbohydrates, thereby specifically reducing post prandial glucose excursion. The major side-effect of treatment with acarbose, flatulence, occurs when undigested carbohydrates are fermented by colonic bacteria, resulting in considerable amount of hydrogen. We propose that enteric benefits of acarbose is partly attributable to be their ability to neutralise oxidative stress via increased production of H_2 in the gastrointestinal tract. Therefore, symptoms of ulcerative colitis in human beings can be ameliorated by acarbose.

Key words: acarbose, ulcerative colitis, hydrogen

Introduction

Ulcerative colitis (UC), with its causes still not fully understood, is a chronic inflammatory disease affecting the rectum and the colon to a variable extent and exerts a substantially negative impact on the quality of life of affected patients who suffer a 10% increased risk in developing colon carcinoma. Although some progress has been made in the treatment of UC in the last decades and many conventional medical treatments such as sulfaslazine,corticosteroids and immunosuppression are introduced into UC treatments from different aspects of UC etiologic process (Hawthorne et al.,2008; Carty,et al.,2003). Unfortunately, all these medicines have side-effects. People have to suffer from the sever adverse effects and the course of UC is still characterized by periods of remission interspersed with exacerbations (Solberg et al.,2008).

The expression of UC is generally believed to associate with the interplay of environmental, genetic and immunological factors (Fries et al.,2011). However, there is still not an integrated concept which explains the initiating event(s) and/or fundamental abnormalities in UC related to the pathophysiological changes. It does seem certain that UC is amplified and propagated by an uncontrolled and sustained host immune response, as the disease is paralleled by an extensive inflammatory infiltrate in the lamina propria, consisting of polymer phonuclear neutrophils, eosinophils and plasma cells. Whereas, the final steps resulting from such an excessive and enduring mucosal immune activation to tissue injury are still not fully confirmed. Ultimately, only a limited number of effector mechanisms, including reactive oxygen metabolites (ROM), might be responsible for the excessive cellular/tissue damage, chronic inflammation and destruction of normal tissue is observed in UC (Karp et al.,2006). Impaired antioxidant mechanism is implicated as one of pathogenic causes of UC. Inflamed tissues generate hydroxyl radicals, the most cytotoxic reactive oxygen species (ROS), which up-regulate TNF-α expression through NF-kB signaling pathway and activate NADPH-Oxygenase (NOX) expression, increasing ROS production as a vicious circle (Gloire et al.,2006; Moe,et al.,2006).

In principle, excessive generation of ROM may lead to the attack and damage of all cellular and extracellular components (Roessner et al.,2008). However, it is important to realize that the overall high reactivity and short half-life of ROM implies that the inflicted tissue damage is generally close to the site of ROM generation. In UC, activated macrophages

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and neutrophils which produce excessive ROS aggregate in the inflaming gut and severe oxidative stress will occur subsequently. When exceeding the antioxidative ability of the intestinal antioxidant defense system, ROS will cause substantial damages in membrane lipid ,protein, and DNA, making the oxidative stress injuries in patients with UC worse and worse (Grisham et al.,1998). Since both inflammation and oxidation processes are reciprocally connected, antioxidants are viewed as a promising therapy for UC that can significantly alleviate the symptoms, i.e. body weight loss, visible fecal blood and diarrhea (HS et al.,2005). Therefore, the world has focused on finding new antioxidants in UC treatment .

Molecular hydrogen (H_2):a novel hotspot of antioxidant and inflammation suppressor

In recent years, experimental evidences have proved that molecular hydrogen (H_2) acts as a novel antioxidant and inflammation suppressor with the following interesting properties(Ohsawa et al.,2007): (1) H_2 can permeates cell membranes and target the cellular organelles, including the mitochondria and nuclei (Li et al.,2012); (2) H_2 specifically quenches detrimental ROS, such as $^{\cdot}OH$ and peroxynitrite (ONOO-), while maintaining the metabolic oxidation-reduction reaction and their less-potent ROS, such as $O_2^{\cdot-}$, H_2O_2 and nitric oxide ($NO^{\cdot}$) (Chen et al., 2011). It could be very important in clinics in the future that H_2 could selectively react with exclusively detrimental ROS, such as hydroxyl radical and peroxynitrite, exerting protective effects. H_2 did not react with other physiological ROS, such as superoxide anion and H_2O_2, which possess physiological roles. Therefore, unlike the other antioxidant supplements with strong reductive reactivity, H_2 is mild enough without disturbing metabolic oxidation-reduction reactions or disrupting Oxidative Stress (OS) involved in cell signaling (Yoshida et al.,2012). Additionally, as H_2 is electrically neutral and much smaller than the oxygen molecule, it easily penetrates membranes and enters cells and organelles such as nucleus and mitochondria (Kawai et al.,2012). This is particularly important, as the latter is the primary site of ROS generation and notoriously difficult to target, and hydrogen could diffuse freely within the body, without any side effects (Ohta.,2011). H_2 can be administered orally in the form of H_2-dissolved saline. Mikihito Kajiya reported that the administration of saturated hydrogen water for 7days reduced the levels of several biomarkers of proinflammatory cytokine, such as IL-12 ,TNF-α and IL-1β (Kajiya et al., 2009). In other experiments, hydrogen gas treatment has significant protective effects on schistosomiasis associated chronic liver inflammation and H_2-rich saline treatment significantly attenuates the severity of L-Arg-induced acute pancreatitis by ameliorating the increased serum amylase activity, inhibiting neutrophils infiltration and lipid oxidation (Chen et al.,2010). Therapeutic effects of H_2 have been confirmed in the cell damage after stroke, ischemia-reperfusion injuries，transplantation injuries and other injuries related to oxidative stress (Hayashida et al.,2008; Fukuda,et al.,2007). Thus, H_2 can protect cells from oxidative stress injuries. In inflammation process, H_2 mediates suppression of proinflammatory cytolcines, especially IL-1β , TNF-α , IL-6 in inflammatory tissues. These research results suggest that persistent intake of H_2 has the potential to reduce oxidative stress and may treat UC.

Acarbose : facilitate H_2 generated in gastrointestinal tract and ameliorates symptoms of UC

Acarbose is an α-glucosidase inhibitor acting specifically at the level of postprandial glucose excursion. This compound lowers HbA_{1c} by 0.5-1% in patients with Type 2 diabetes, either drug naive or in combination with other antidiabetic drugs. In those with impaired glucose tolerance (IGT), it reduces the incidence of newly diagnosed diabetes by 36.4% (Chiasson et al., 2003). Furthermore, it has beneficial effects on overweight, reduces blood pressure and triglycerides, and downregulates biomarkers of low-grade inflammation (Hanefeld et al.,2004). The major side-effect of treatment with α-glucosidase inhibitors, flatulence, occurs when undigested carbohydrates are fermented by colonic bacteria, resulting in gas formation. The reason of flatulence is thought to act at the small intestine by competitively inhibiting enzymes that delay the release of glucose from complex carbohydrates, thereby specifically reducing post prandial glucose excursion. Then spontaneous production of H_2 gas in the human body occurs via the fermentation of undigested carbohydrates by the resident enterobacterial flora (Yoshihiko et al., 2009).

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H_2 is not produced endogenously in mammalian cells, since the hydrogenase activity responsible for the formation of H_2 gas may not be present (Stephen et al., 2012). Instead, spontaneous production of H_2 gas in the human body occurs via the fermentation of undigested carbohydrates by the resident enterobacterial flora. H_2 is transferred to the portal circulation and excreted through the breath in significant amounts (Michael et al.,1969). Flatulence is regarded as the major side-effect of treatment with acarbose (Ladas et al., 1992). Yoshihiko Suzuki reported that acarbose treatment significantly increased the amount of exhaled H_2 by detecting in eleven healthy volunteers (10 males and 1 female) who were administered acarbose at a dosage of 300 mg/day (100 mg three times a day) for 4 days under free-feeding conditions. Kajiyama treated patients with type 2 diabetes or impaired glucose tolerance with 900ml/day (300ml three times a day) H_2-dissolved water. After drinking 300 ml of H_2-dissolved water, the exhaled H_2 gas concentration reached a maximum of 56±27.8 ppm at 15 min, and returned to the baseline level at 150 min (Kajiyama et al.,2008). This peals level of H_2 gas reduced the levels of oxidative stress biomarkers and improved glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. Considering that gastrointestinal tract derived H_2 , which is closely related to reduced cardiovascular events, could reduce general oxidative stress injuries, we assume that the induced H_2 by acarbose might be the key to the symptoms alleviation in UC by cutting Myeloperoxidase (MPO) level.

According to the published data in 2009, mice UC induced by dextran sodium sulfate (DSS) was treated with saturated hydrogen water for 7 days. The study demonstrated that H_2 could attenuate DSS-induced colitis by down-regulating the expression of proinflammatory cytokines, as well as suppressing the infiltration of macrophages in the colon lesion. The administration of H_2 remarkably reduced the clinical symptoms of DSS-induced colitis, i.e., body weight loss, visible fecal blood and diarrhea, colitis score, and shortening of colon length. Histopathological evaluation further supported the effects of H_2 on the prevention of DSS-mediated destruction of epithelium crypt structure. These observations clearly indicate that the amounts of H_2 gas generated by acarbose are sufficient to reduce systemic oxidative stress. Oral administration of acarbose may be superior to drinking H_2-rich water in terms of maintenance of the appropriate H_2 gas levels in the body.

Conclusion

Based on these observations and experimental results, H_2 has been proved effective in DSS-induced mice colitis and acarbose was thought to generate H_2 in gastrointestinal tract .Therefore, we hypothesize that acarbose may be a novel and promising therapeutic option for UC as an indirect antioxidant. It may significantly restrict inflammation and alleviate clinical UC symptoms, improving the life quality of patients,and that these benefits can be attributed at least in part to the abilities of acarbose to neutralise oxidative stress by increasing the production of H_2 in the gastrointestinal tract. Although acarbose probably has many other beneficial antioxidant effects on other diseases such as transplantation induced organs injury, cardiovascular diseases, cerebrovascular accidents etc., we still need to further study the biological mechanism.

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