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Lactulose: An indirect antioxidant ameliorating inflammatory bowel disease by increasing hydrogen production

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SUMMARY

Lactulose, which cannot be digested and absorbed by body, is clinically widely used to treat constipation and hepatic encephalopathy. Fermented by gastrointestinal tract bacteria, lactulose can produce considerable amount of hydrogen, which is protective for DSS-induced colitis as a unique antioxidant. We propose that lactulose is an indirect antioxidant that mobilizes endogenous hydrogen production which in turn can reduce oxidative stress and ameliorate symptoms of inflammatory bowel disease in human beings.

Introduction

Inflammatory bowel disease (IBD) – Crohn's disease and ulcerative colitis, whose causes are still not fully understood, exerts a substantially negative impact on the quality of life of affected individuals, among whom patients with chronic ulcerative colitis bear an 10% increased risk in developing colon carcinoma. Conventional medical treatments, inflammation inhibition, i.e. corticosteroids, aminosalicylates, immunosuppression, i.e. thiopurine, and alternative immunomodulatory medications, i.e. methotrexate, TNF-α monoclonal antibodies, are introduced into IBD treatments from different aspects of IBD etiologic process [1]. Unfortunately, none of the drugs above is universally effective. Meanwhile, these medications could bring sever adverse effects.

A growing number of evidences support the notion that oxidant-mediated injury plays an important role in the pathogenesis of IBD [2]. Inflamed tissues generate hydroxyl radicals, the most cytotoxic reactive oxygen species (ROS), which up-regulate TNF-α expression through NF-κB signaling pathway [3] and activate NADPH-Oxygenase (NOX) expression, increasing ROS production [4] as a vicious circle.

Oxidation and inflammation are reciprocally related. In IBD, activated macrophages and neutrophils, which produce excessive ROS, aggregate in the inflaming gut. Subsequently, severe oxidative stress occurs [5]. When exceeding the antioxidative ability of the intestinal antioxidant defense system, ROS will cause substantial damages in protein, lipid and DNA, thus worsening the oxidative stress injuries in patients with ulcerative colitis [6]. Based on these findings, impaired antioxidant mechanism is implicated as one of the pathogenic causes of DSS-induced colitis [7]. Therefore, antioxidants are suggested as a novel therapy for IBD in recent years, which can significantly alleviate the symptoms, i.e. body weight loss, visible fecal blood and diarrhea [8]. Thus, identifying new antioxidants in IBD treatment has recently attracted great attention worldwide.

Molecular hydrogen (H_2) serves as a novel inflammation suppressor

In recent years, experimental evidences have documented that without influencing other less potent ROS, important in intracellular signaling, molecular hydrogen (H_2) possesses the ability to selectively neutralize $ONOO^-$ and $^{\cdot}OH$, the most cytotoxic ROS, which can damage cellular macromolecules aggressively and indiscriminately. Thus, H_2 can protect cells from oxidative stress injuries [9]. Therapeutic effects of H_2 have been confirmed in the cell damage after stroke, ischemia–reperfusion injuries [10,11], transplantation injuries [12] and other injuries related to oxidative stress. In inflammation process, H_2 mediates suppression of pro-inflammatory cytokines, especially CCL2, IL-1β, TNF-α, IL-6 in inflammatory tissues. In experiments, hydrogen gas treatment has significant protective effects on schistosomiasis-associated chronic liver inflammation [13] 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 [14]. It was reported that H_2 mediated suppression of colon inflammation induced by dextran sodium sulfate (DSS) in 2009 [15].

As a novel antioxidant, H_2 possesses a number of advantages. (1) Due to its high permeability, H_2 can easily penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus.

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(2) It is nontoxic to the organisms, which has been proven by hyperbaric diving for decades. (3) Thanks to its selectivity as an antioxidant, it has less impact on other less active but very important ROS within the cells.

Lactulose mediates H_2 production and ameliorates DSS-induced colitis in mice

Lactulose is a synthetic sugar used in the treatment of constipation [16] and hepatic encephalopathy. It is a disaccharide formed from one molecule each of the simple sugars fructose and galactose and cannot be absorbed by human bodies but can be digested by bacteria colonizing within the gastrointestinal tract, especially in the colon. One of the main byproducts is H_2. Oral administration of lactulose significantly increases H_2 production [17], which can be detected by H_2 breath test, introduced several decades ago as a diagnostic test for small bowel bacterial overgrowth [18].

In 2004, in an animal experiment, it was observed that lactulose had some protective effects on DSS-induced colitis. The authors attributed it possibly to alterations of colonic microflora [19], namely, increased number of beneficial microflora and decreased number of pathogenic microflora. According to the already known pathogenesis of IBD, host–microbiome interactions are quite complicated, which can be mutually beneficial or can be deleterious. Bacteria that can adhere to and invade the intestinal mucosa may be particularly important, as in the case of *Escherichia coli,* one of the main bacteria colonizing in the colon [20]. Based on recent findings, we put forward some concerning questions. 1. New mechanisms of DSS-induced colitis were found by recent researches that the colon had an inner attached mucus layer devoid of bacteria [21]. DSS could cause alterations in the inner colon mucus layer and made it permeable to bacteria. Direct contact stimulates persistent immune response, causing inflammatory damage. Thus, the colitis occurred [22]. Under such circumstances, it is difficult to distinguish between beneficial and harmful microflora. This explained why most mouse models of colitis require intestinal bacteria for inflammation to occur [23]. Besides, antibiotics are effective in some patients with inflammatory bowel disease. Antibiotic therapy attenuates colitis in IL-10 gene-deficient mice [24] and long term treatment with nitroimidazoles or clofazimine are proved to be effective in patients with Crohn's disease [25]. 2. In the experiment, interestingly enough, the authors also observed that lactulose reduced the severity of colonic lesions induced by DSS treatment in a dose-dependent manner, the effect at 100 mg/kg being more potent than that of 5-ASA. Lactulose treatment also prevented the colon shortening and ameliorated the histological inflammation, together with significant attenuation of the increase in MPO activity as well as lipid peroxidation following DSS treatment. The lowered oxidative stress state could not be simply explained by alterations of colonic microflora.

Considering that gastrointestinal tract derived H_2, which is closely related to reduced cardiovascular events, could reduce general oxidative stress injuries [26], we assume that the induced H_2 by lactulose might be the key to the symptoms alleviation and lowered MPO level in DSS-induced colitis, which seems to be a more reasonable explanation.

According to the published data, patients with type 2 diabetes or impaired glucose tolerance were treated with 900 ml/day (300 ml three times a day) H_2-dissolved water. Drinking 300 ml of H_2-dissolved water lead to exhaled H_2 gas concentration reaching a maximum of 56 ± 27.8 ppm at 15 min, and returning to the baseline level at 150 min. This peak level of H_2 gas down-regulated oxidative stress biomarkers and improved glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance [27]. In previous study, it has been proven that 20 g lactulose administration could increase the exhaled H_2 nearly to the same level of exhaled H_2 as compared to the consumption of 300 ml H_2 dissolved water and had a longer maintenance time of H_2 concentration [16]. Thus, we consider that oral administration of lactulose may be better than drinking H_2-rich water in terms of maintenance of the appropriate H_2 gas levels in the body.

Hypothesis

Lactulose has been proved effective in DSS-induced mice colitis. Based on these observations and experiments, we hypothesize that lactulose may be a novel and promising therapeutic option for IBD as an indirect antioxidant. By increasing gastrointestinal tract derived H_2, it may significantly restrict inflammation and alleviate clinical IBD symptoms, improving the life quality of patients. What's more, it is noteworthy that lactulose probably has many other beneficial antioxidant effects on a wide range of aspects, such as cardiovascular diseases, cerebrovascular accidents, neurodegenerative diseases et al., which still needs further study.

Conflicts of interest statement

None declared.

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References

[1] Carty E, Rampton DS. Evaluation of new therapies for inflammatory bowel disease. J Clin Pharmacol 2003;56(4):351–61.
[2] Karp SM, Koch TR. Oxidative stress and antioxidants in inflammatory bowel disease. Dis Mon 2006;52(5):199–207.
[3] Gloire G, Legrand-Poels S, Piette J. NF-kappaB activation by reactive oxygen species: fifteen years later. Biochem Pharmacol 2006;72(11):1493–505.
[4] Moe KT, Aulia S, Jiang F, Chua YL, Koh TH, Wong MC, et al. Differential upregulation of Nox homologues of NADPH oxidase by tumor necrosis factor-alpha in human aortic smooth muscle and embryonic kidney cells. J Cell Mol Med 2006;10(1):231–9.
[5] Grisham MB, Granger DN. Neutrophil-mediated mucosal injury: role of reactive oxygen metabolites. Dig Dis Sci 1998;33(3S):6S–15S.
[6] Suematsu M, Suzuki M, Kitahora T, Miura S, Suzuki K, Hibi T, et al. Increased respiratory burst of leukocytes in inflammatory bowel diseases-the analysis of free radical generation by using chemiluminescence probe. J Clin Lab Immunol 1987;24(3):125–8.
[7] Korenaga D, Takesue F, Kido K, Yasuda M, Inutsuka S, Honda M, et al. Impaired antioxidant defense system of colonic tissue and cancer development in dextran sulfate sodium-induced colitis in mice. J Surg Res 2002;102(2):144–9.
[8] Oz HS, Chen TS, McClain CJ, de Villiers WJ. Antioxidants as novel therapy in a murine model of colitis. J Nutr Biochem 2005;16(5):297–304.
[9] Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007;13(6):688–94.
[10] Hayashida K, Sano M, Ohsawa I, Shinmura K, Tamaki K, Kimura K, et al. Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia-reperfusion injury. Biochem Biophys Res Commun 2008;373(1):30–5.
[11] Fukuda K, Asoh S, Ishikawa M, Yamamoto Y, Ohsawa I, Ohta S. Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. Biochem Biophys Res Commun 2007;361(3):670–4.
[12] Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar TR, et al. Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. Am J Transplant 2008;8(10):1–10.
[13] Gharib B, Hanna S, Abdallahi OM, Lepidi H, Gardette B, De Reggi M. Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation. CR Acad Sci III 2001;324(8):719–24.
[14] Chen H, Sun YP, Li Y, Liu WW, Xiang HG, Fan LY, et al. Hydrogen-rich saline ameliorates the severity of L-arginine-induced acute pancreatitis in rats. Biochem Biophys Res Commun 2010;393(2):308–13.
[15] Kajiya M, Silva MJ, Sato K, Ouhara K, Kawai T. Hydrogen mediates suppression of colon inflammation induced by dextran sodium sulfate. Biochem Biophys Res Commun 2009;386(1):11–5.

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[16] Voskuijl W, de Lorijn F, Verwijs W, Hogeman P, Heijmans J, Mäkel W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut 2004;53(11):1590–4.
[17] Florent C, Flourie B, Leblond A, Rautureau M, Bernier JJ, Rambaud JC. Influence of chronic lactulose ingestion on the colonic metabolism of lactulose in man (an in vivo study). J Clin Invest 1985;75(2):608–13.
[18] Rhodes JM, Middleton P, Jewell DP. The lactulose hydrogen breath test as a diagnostic test for small-bowel bacterial overgrowth. Scand J Gastroenterol 1979;14(3):333–6.
[19] Rumi G, Tsubouchi R, Okayama M, Kato S, Mózsik G, Takeuchi K. Protective effect of lactulose on dextran sulfate sodium-induced colonic inflammation in rats. Dig Dis Sci 2004;49(9):1466–72.
[20] Barnich N, Carvalho FA, Glasser AL, Darcha C, Jantscheff P, Allez M, et al. CEACAM6 acts as a receptor for adherent-invasive *E. coli*, supporting ileal mucosa colonization in Crohn disease. J Clin Invest 2007;117(6):1566–74.
[21] Johansson MEV, Phillipson M, Petersson J, Holm L, Velcich A, Hansson GC. The inner of the two Muc2 mucin dependent mucus layers in colon is devoid of bacteria. Proc Natl Acad Sci 2008;105(39):15064–9.
[22] Johansson MEV, Gustafsson JK, Sjöberg KE, Petersson J, Holm L, et al. Bacteria penetrate the inner mucus layer before inflammation in the dextran sulfate colitis model. PLoS ONE 2010;5(8):e12238. doi:10.1371/journal.pone.001223.
[23] Elson CO, Cong Y, McCracken VJ, Dimmitt RA, Lorenz RG, Weaver CT. Experimental models of inflammatory bowel disease reveal innate, adaptive, and regulatory mechanisms of host dialogue with the microbiota. Immunol Rev 2005;206:260–76.
[24] Madsen KL, Doyle JS, Tavernini MM, Jewell LD, Rennie RP, Fedorak RN. Antibiotic therapy attenuates colitis in interleukin 10 gene-deficient mice. Gastroenterology 2000;118(6):1094–105.
[25] Feller M, Huwiler K, Schoepfer A, Shang A, Furrer H, Egger M. Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials. Clin Infect Dis 2010;50(4):473–80.
[26] Suzuki YSano M, Hayashida K, Ohsawa I, Ohta S, Fukuda K. Are the effects of alpha-glucosidase inhibitors on cardiovascular events related to elevated levels of hydrogen gas in the gastrointestinal tract? FEBS Lett 2009;583(13):2157–9.
[27] Kajiyama S, Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, et al. Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. Nutr Res 2008;28(3):137–43.

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