Nitric oxide donor, S-nitrosoglutathione, to maintain intestinal barrier integrity: Potential therapeutic candidate for prevention of inflammation recurrences

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Abstract

Intestinal barrier integrity is malleable and multiple mechanisms have been shown to be capable of modulating intestinal permeability (a measure ofintestinal barrier function). Modulating factors include cytokines, immune cells, and exogenous factors.Nitric oxide (NO) is known to play a pivotal role to maintain the intestinal barrier integrity, such as regulation of oxidative stress, healing, mucus secretion, immune system regulation, etc. S-nitrosoglutathione (GSNO), a nitric oxide donor is naturally secreted by enteric glial cells after stimulation of the vagus nerve. GSNO is known to prevent inflammatory events and to preserve intestinal barrier integrity. We have highlight in a Using chamber model that there is a concentration-dependant effect of NO on rat ileon intestinal permeability.

Disruption of normal barrier function is a fundamental factor in the pathogenesis of inflammatory bowel disease, which includes increased epithelial cell death, modified mucus configuration, altered expression and distribution of tight junction proteins, along with a decreased expression of antimicrobial peptides. Inflammatory bowel disease is associated with life-long morbidity for affected patients, and both the incidence and prevalence is increasing globally, resulting in substantial economic strain for society. Mucosal healing and re-establishment of barrier integrity are associated with clinical remission, as well as with an improved patient outcome. Hence, these factors are vital treatment goals, which conventionally are achieved by a range of medical treatments, although none are effective in all patients, resulting in several patients still requiring surgery at some point. Therefore, novel treatment strategies to accomplish mucosal healing and to re-establish normal barrier integrity in inflammatory bowel disease are warranted, and luminal stem cell-based approaches might have an intriguing potential. Transplantation of in vitro expanded intestinal epithelial stem cells derived either directly from mucosal biopsies or from directed differentiation of human pluripotent stem cells may constitute complementary treatment options for patients with mucosal damage, as intestinal epithelial stem cells are multipotent and may give rise to all epithelial cell types of the intestine. This review provides the reader with a comprehensive state-of-the-art overview of the intestinal barrier's role in healthy and diseased states, discussing the clinical application of stem cell-based approaches to accomplish mucosal healing in inflammatory bowel disease. This effect is not observed in the presence of glutathion equivalent concentrations. Moreover, GSNO degradation and absorption on isolated rat intestine were studied and we found that an enzymatic activity of gamma-glutamyl-transpeptidase expressed on intestinal epithelioma (and also by microbiota), is involved in GSNO intestinal permeability. Also, the inhibition of endogenous secretion of NO by using N-nitro-L-arginine methyl ester (NO synthases inhibitor) showed us that NO observed effect in intestinal permeability comes from exogenous supply with GSNO. From these results, GSNO could be proposed as an innovative prophylactic agent, in order to prevent relapses of inflammation for inflammatory bowel diseases patient in clinical remission.

The human gastrointestinal tract is equipped with physical and biological barriers whose function is not only to isolate the internal host's milieu from the external environment but also to regulate the immune system, absorption of nutrients, and to limit the access of microorganisms, both commensal, and pathogens. Hence, the intestinal mucosa operates in a dynamic manner in order to maintain intestinal integrity and immune homeostasis. Alterations of gut barrier integrity have been associated not only to inflammatory bowel diseases (IBD) but also to autoimmune disorders occurring outside the gut, such as Multiple Sclerosis (MS) both in experimental models and humans. These alterations are associated with dysbiosis, i.e., modification of microbiota composition, along with a persistent activation of the immune system within the gut mucosa. The mechanisms through which gut dysbiosis, breakage of gut barriers, and brain autoimmunity are linked are still unknown, but it has been proposed that a condition of dysbiosis can promote inflammation and morphological and functional changes of intestinal mucosa thus favoring uncontrolled passage of macromolecules, microorganisms or their derivates from the intestine to the systemic circulation where they activate myelin-reactive T cells

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