https://doi.org/10.46389/rjd-2022-1181
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 3, pages 376-380

Review

New approaches in modulating the GLP-1/GLP-2 AXIS: link between metabolic diseases and inflammatory bowel disease

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Received: 1 June 2022 / Accepted: 23 July 2022

Abstract

Glucagon-like peptides (GLP)-1 and GLP-2, currently approved as a therapy for diabetes, have gained interest as hormones with roles in maintaining intestinal architecture and homeostasis. The current review is an integrative model of the emerging data, aiming to investigate the impact of GLP-1/GLP-2 in inflammatory bowel diseases (IBD) pathogeny and as effective and safe therapy in patients with IBD and also proposes the following future research directions regarding the role and safety of incretins in IBD, and indicates their scientific relevance: Quantification of GLP-1, GLP-2 and DPP-IV expression on inflamed intestinal mucosa from patients with IBD, allowing the use of GLPs as markers of IBD phenotype;Mapping of GLP-1/GLP-2 receptors in different types of intestinal cells, allowing a better understanding of the intestinal effects mediated by GLPs; Assessment of the impact of GLP-1/GLP-2 receptor agonists, DPP-IV inhibitors and short chain fatty acids on intestinal cell proliferation and inflammation in patients with IBD, allowing the identification of the optimal therapeutic strategy to preserve the quiescent IBD phenotype; Quantifying GLP-1/GLP-2 expression from neoplastic or precancerous intestinal lesions and evaluating the intestinotrophic effects of incretins and their relation to intestinal neoplasia, allowing identification of a potential limitation of incretin therapy in IBD.

Keywords: Glucagon-like peptide-1 (GLP-1), Glucagon-like peptide-2 (GLP-2), inflammatory bowel disease, intestinal neoplasia, preneoplastic intestinal lesions.

Introduction

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), secreted by the enteroendocrine L cells in the gut, play a fundamental role in controlling postprandial blood glucose through stimulating glucose-dependent insulin secretion, inhibiting glucagon secretion and delaying gastric emptying, in promoting pancreatic β-cell growth and also exerts an anorexigenic effect, thus being involved in controlling energy intake and body weight [1–3].

GLP-1 receptor agonists are currently approved for treating patients with type 2 diabetes. Recently, GLPs has gained particular interest as hormones with potent anti-inflammatory effects and a crucial role in maintaining intestinal architecture and homeostasis [1, 2, 4–7].

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with complex and yet unrevealed pathogenesis, associated with proinflammatory cytokines release, alterations of the innate and adaptive immune system, microbiota, and epithelial function, secondary to interactions among genetic, gut microbiome, environmental and immunologic factors [1, 8–10].

Given the potential involvement of GLP1/GLP2 axis in the IBD, the GLP's effects have been investigated in several pre-clinical and very few clinical studies involving models of IBD.

GLP-1 is mainly released in the ileum and the colon under the influence of nutrients and luminal stimuli such as bile acids, dietary-fiber-derived or microbiota-derived short-chain fatty acids, and bacterial

metabolites [11, 12]. GLP-1 ensures the integrity and functionality of the intestinal mucosa and slows gastric emptying, thus ensuring a longer contact of the chyme with a functional intestinal mucosa, thus maintaining an efficient absorption of nutrients [13, 14]. GLP-2 is expressed in the small intestine, mainly in the terminal ileum and the colon, the GLP-2 density increases from proximal to distal part, being maximal in the rectum [1, 15]. GLP-2 is released in response to nutritional, neural, and hormonal stimulation and is involved in epithelial homeostasis, barrier function and repair following injury and also exerts anti-inflammatory functions [11, 16]. GLPS act via G-protein-coupled receptors, which are expressed in many tissues, including pancreatic islets, intestine, thyroid, pituitary, central nervous system, kidney, heart, lung and immune cells [17, 18]. GLPs are rapidly degraded by dipeptidyl peptidase IV (DPP-IV), which results in their short half-lives *in vivo*. The effect of DPP-IV in IBD is not well understood. Studies in animal models of IBD suggest that using DPP-IV inhibitors decreases disease activity.

On the other hand, IBD patients have lower serum levels of DPP-IV than healthy subjects. However, DPP-IV expression on T cells from IBD patients is elevated. Furthermore, lower concentrations of DPP-IV are inversely associated with increased disease activity, although it is not clear whether this is the cause or consequence of the disease. Concurrently, the results of a recent meta-analysis investigating the risk of developing IBD in patients on DPP-IV inhibitor therapy point out the need for further research [19].

The existing data are conflicting regarding the GLP-1/GLP-2 secretion profile and involvement in IBD pathogenesis. Several studies have shown that GLP-1 and GLP-2 release is predominantly increased in the inflamed intestinal mucosa characteristic of active IBD, but not in the quiescent stage of IBD [1, 3, 20]. In contrast, other studies demonstrated no difference in plasma or tissue concentrations of GLP-1 and GLP-2 between patients with IBD and non-IBD controls [1, 21]. There is also evidence that chronic exposure to TNF reduces the secretion of GLP-1 and GLP-2, which could be reversed after anti-TNF treatment [11, 22, 23]. Studies in animal models have shown an increase in GLP-1 secretion from L cells in the early stages of intestinal inflammation as a protective mechanism against intestinal mucosal injury [24]. Thus, GLP-1 could be useful as an early marker of intestinal mucosal injury. On the other hand, in the advanced stages of the disease activity, the secretion of GLP-1 is reduced, the potential explanation being the decrease in the number of L cells [25]. These data need to be verified and confirmed in humans, as it is known to be difficult to assess GLP-1 in mice [26].

Considering the role of GLPs and DPP-IV in IBD pathogenesis, the GLPs analogs/receptor agonists and DPP-IV inhibitors have recently gained attention in IBD research [1, 27, 28]. Several investigations showed that treatment with GLPs may lead to reduction of histopathological inflammation, improvement in crypt cell proliferation and histological morphology, and reduction of the intestinal epithelium apoptosis, which enhances the absorptive capacity of the intestine [1–3, 7, 11].

These findings have directed research toward the therapeutic benefits of GLPs in treating IBD, but the findings have also raised concerns regarding the GLPs potential association with intestinal neoplasia. It is conceivable that increased GLP-2/GLP-2 receptor expression may play a role in promoting intestinal cancers in humans, as GLP-2 is associated with mucosal growth and development of adenomas in the murine intestine [29–31]. In summary, a large proportion of studies showed significant growth and tumor-promoting effects in rodent models, especially in the case of long-term exposure to GLP-2 [29–31]. The potential molecular mechanisms involved in cellular growth and tumor-promoting effects of GLP-2 in the intestine are represented mainly by activating the PI3K-dependent Akt-mTOR signaling pathway and activating the IGF-1 signaling pathway, and subsequent activation of the beta-catenin signaling pathway [29, 32–34]. Because DPP-IV inhibitors prolong the duration of action of endogenous GLPs, multiple studies have investigated the potential for tumor cell proliferation associated with treatment with DPP-IV inhibitors, especially in patients with undiagnosed colon adenomas. Several studies performed on different types of human colon cell lines and also animal studies indicated an enhancement in the intestinotrophic effects of GLPs when DPP-IV inhibitors were added, suggesting that DPP-4 inhibitors might increase the risk of tumor growth enhancement [29, 35, 36]. In contrast, another study found no signs of the influence of long-term administration of DPP-IV inhibitors on intestinal neoplasia in mice [31].

Future perspectives and scientific relevance

The current review is an integrative model of the emerging data, aiming to summarize the hypothesis of

the incretins' involvement in the pathogenesis of IBD, the beneficial effects of incretins in IBD, but also the potential risk of promoting tumor cell proliferation associated with the administration of incretins.

In order to better understand the involvement of incretins in IBD, the following research directions are proposed in this review:

- Quantification of GLP-1, GLP-2, GLP-1 receptors, GLP-2 receptors and DPP-IV expression on biopsies from areas with inflammation collected from patients with IBD and comparison with their level in biopsies collected from areas with normal mucosa;
- Exploring the relationship of GLP-1 and GLP-2 expression with the degree of intestinal L cell biology (based on inflammatory activity and mucosal injury);
- Mapping GLP-1 and GLP-2 receptors in different types of intestinal cells (Brunner's glands, neurons, lymphocytes, enterocytes, myofibroblasts, crypt cells) will allow a better understanding of the intestinal effects mediated by GLPs and how to optimize the therapeutic interventions;
- Assessment of the impact of GLP-1/GLP-2 receptor agonists, DPP-IV inhibitors and short-chain fatty acids on promoting cell proliferation and modulation of the intestinal immune response and inflammation in patients with IBD;
- Quantifying GLP-1, GLP-2, GLP-1 receptors and GLP-2 receptors' expression on biopsies from areas with an intestinal neoplasm or precancerous lesions and comparing them with their level in biopsies collected from areas with normal mucosa;
- Evaluation of the intestinotrophic effects of GLPs analogs/receptor agonists and DPP-IV inhibitors and their relation to intestinal neoplasia, thus allowing the identification of a potential limitation of GLPs receptor agonist therapy in patients with IBD.

The correlation between GLPs and IBD phenotype has great importance because GLPs can represent new markers of the IBD phenotype and can be used as an early marker of intestinal mucosal injury. We will thus be able to prevent the transition from the quiescent phenotype to the active, symptomatic phenotype of IBD, reducing in this way considerably the costs.

Mapping GLP-1 and GLP-2 receptors in different types of intestinal cells will allow a better understanding of the intestinal effects mediated by GLPs and how to optimize the therapeutic interventions.

Identifying the GLPs involvement in the modulation of the anti-inflammatory and intestinotrophic effects will allow the therapeutic intervention to promote the improvement of intestinal mucosa architecture and function and to preserve the quiescent IBD phenotype.

Assessing whether the levels of GLPs depend on the degree of inflammation and mucosal injury extension and also assessing the effect of acute *versus* longer-term administration of GLPs and the effect of individual *versus* simultaneous GLP-1/GLP-2 administration will allow individualizing the doses, the optimal GLP-1/GLP-2 ratio but also the opportune timing for the initiation of the therapy with GLP-1/GLP-2 receptor agonists.

The association of GLP-1/GLP-2 with neoplastic and precancerous intestinal lesions should be evaluated, in order to identify the potential limitation of GLPs receptor agonist therapy in patients with IBD.

The importance of this proposed future research direction derives from the fact that we haven't found any previous studies which investigate human samples, in an integrative manner, the involvement of GLPs in the pathogenesis of IBD, the beneficial effects of incretins in IBD, but also the potential risk of promoting tumor cell proliferation associated with the administration of incretins in IBD.

Conclusions

Emerging data indicating the role of incretins in promoting the inactive phenotype of IBD and the integrity of the intestinal mucosa and in modulating the anti-inflammatory response suggest that modulation of the GLP-1/GLP-2 axis may be an important therapeutic tool in the treatment of IBD patients.

In the context in which incretins do not exert an immunosuppressive effect, and the safety profile of incretins is confirmed in terms of promoting cell tumor proliferation, incretins may become first-line therapy in the management of patients with IBD. Nevertheless, future fundamental research and a randomized clinical trial are warranted to determine the effectiveness and safety of incretins in IBD.

Conflict of interest

The author declares no conflict of interest.

https://doi.org/10.46389/rjd-2022-1181

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