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REVIEW

Emerging treatment options for short bowel syndrome: potential role of teduglutide

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Introduction: Current medical management of short bowel syndrome (SBS) involves the use of lifelong parenteral nutrition (PN). Glucagon-like peptide-2 (GLP-2), an important intestinotrophic growth factor has been shown to increase intestinal absorption in SBS through augmentation of post-resection intestinal adaptation. This may lead to the reduction of PN dependence in patients with SBS.

Areas covered in review: Advancing research of GLP-2 physiology has spurred the growing understanding of the diverse effects of GLP-2. The development of the degradation resistant GLP-2 analog, teduglutide (Gattex™, NPS Pharmaceuticals, Bedminster, NJ), has allowed its exploration as a therapeutic agent in a variety of clinical settings. Recent multicenter, placebo-controlled studies of GLP-2 in SBS patients demonstrate meaningful reductions in PN requirements with good safety profiles. The reparative and immunomodulatory effects of teduglutide may also be beneficial in patients with inflammatory bowel disease (IBD). Safety concerns about possible carcinogenic properties during long-term use require ongoing evaluation.

Summary: GLP-2 appears to offer a novel adjuvant treatment modality for SBS. Promise for its use in other clinical settings like IBD has been shown in small pilot studies.

Keywords: glucagon-like peptide-2, intestinal failure, intestinal adaptation, parenteral nutrition

Introduction

Short bowel syndrome (SBS) is defined by a combination of symptoms and signs that occur after extensive surgical resection of the intestine. This highly disabling condition is characterized by malabsorption of both fluid and nutrients and, left untreated, can lead to dehydration, malnutrition, and weight loss. The term intestinal failure (IF) applies when an adequate balance of nutrients and water cannot be maintained without dietary support. IF often remains a short-term problem in the postoperative period. However, a small number of patients will require long-term parenteral nutrition (PN) or, in selected cases, intestinal transplantation. Such patients will typically have less than 100 cm of small bowel leading to an end-stoma or less than 50 cm connected to a functioning colon. Although PN has revolutionized IF treatment, it has a significant impact on quality of life and carries considerable risks, mainly hepatic failure, central vein thrombosis, and recurrent sepsis, all of which will reduce life expectancy. Survival following intestinal transplantation is still inferior to that of long-term PN due to the high incidence of graft rejection and other postoperative complications.[1]

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Introduction

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Soon after surgical resection with resulting loss of surface area, the intestine physiologically attempts to increase absorption to maintain homeostasis. This process

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of intestinal adaptation occurs through structural (villous cell hyperplasia, increased crypt depth, and intestinal dilatation) and functional (increased mucosal enzyme activity and reduction of intestinal transit) mechanisms leading to a gradual increase in absorptive capacity. This period of adaptation is thought to last up to 24 months. Nutritional (eg, glutamine) and non-nutritional (eg, growth factors) substances have been implicated in promoting this adaptive response. In the last decade, most IF research has been focused on exploring the potential of these substances as supportive IF treatment. However, clinical trials so far have not demonstrated reproducible or meaningful clinical benefits with the use of glutamine or growth hormone.[2–5]

Current supportive medical management includes the use of agents that reduce secretion (H2 receptor blockers, proton pump inhibitors, and octreotide) and motility (codeine, opium, lomotil, and loperamide).[6] The goal is to reduce the total stool output to <2 L per day. Dietary advice to maximize intestinal absorption is highly beneficial but needs to be tailored to the anatomy of the residual bowel.

The naturally occurring gut hormone, glucagon-like peptide-2 (GLP-2), is a pleiotropic intestinotrophic hormone that enhances digestive and absorptive capacity.[7] Recent advances in our understanding of the basic science of GLP-2 have led to its exploration as a potential 'first in class' therapeutic drug for SBS.

Glucagon-like peptide-2 and teduglutide

Glucagon-like peptide-2 is a 33-amino acid peptide with an estimated molecular mass of 3765.8.[8] GLP-2 is derived from the post-translational processing of pro-glucagon, a large prohormone that is mainly expressed in the pancreas, intestine, and brain (Figure 1). In the intestine, biologically active GLP-2$^{1–33}$ is secreted from enteroendocrine L-cells of the ileum and colon in response to nutritional, hormonal, and neural stimulation. Human and animal studies have revealed that dietary fiber and short-chain fatty acids, carbohydrates, and fats are potent stimulators of GLP-2 secretion.[9]

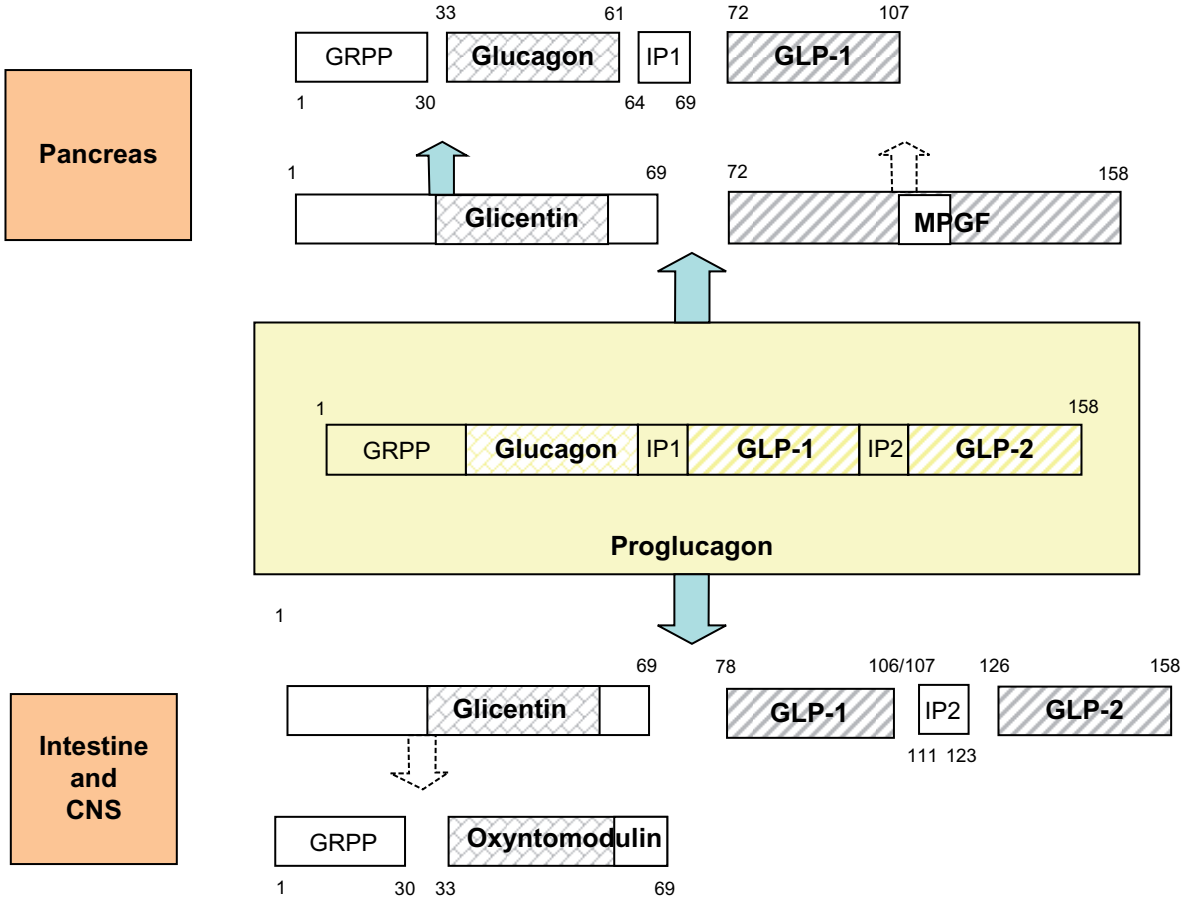

Figure 1 Proglucagon contains three homologous hormonal sequences, glucagon/GLP-1/GLP-2, and is separated by intervening peptides IP1/IP2. Proglucagon is processed differentially in pancreas, intestine, and CNS.
Abbreviations: CNS, central nervous system; GLP, glucagon-like peptide; GRPP, glicentin-related polypeptide; IP, intervening peptide; MPGF, major proglucagon fragment.

GLP-2 exerts a wide variety of effects on the gastrointestinal tract and is a key mediator of intestinal adaptation.[10] In animal studies, GLP-2 treatment induces mucosal growth in the small and large intestine through an increase in crypt cell proliferation and a reduction of villous cell apoptosis (Figure 2).[11,12] This increase in mucosal mass is accompanied by enhanced functional absorptive capacity.[13] Other GLP-2-mediated effects include inhibition of gastric emptying and acid secretion,[14,15] reduction of intestinal permeability,[16,17] anti-inflammatory actions,[18] and stimulation of mesenteric blood flow.[19]

Specific G-protein coupled GLP-2 receptors (GLP-2Rs) are found in abundance in the proximal small intestine and have been demonstrated on enteroendocrine cells,[20] enteric neurons,[19] and subepithelial myofibroblasts.[21] The apparent lack of GLP-2Rs on the proliferative crypt cells suggests that the effects of GLP-2 are mediated through a variety of downstream effectors (Figure 3).[22] Insulin-like growth factor-1 appears to be essential for GLP-2-induced intestinal epithelial proliferation,[23] and nitric oxide might be a key mediator in GLP-2-induced upregulation of intestinal blood flow.[19] Vascular endothelial growth factor and transforming growth factor-β have been linked to GLP-2-induced wound repair.[24] The release of vasoactive intestinal peptide (VIP) from enteric neurons appears to mediate some of the anti-inflammatory effects of GLP-2.[25] For further, in-depth discussion into the complex interplay of GLP-2 and its downstream mediators the authors of this paper recommend a recent review by Rowland and Brubaker.[26]

GLP-2 has a short half-life of approximately 7 minutes in humans and undergoes N-terminal truncation by the proteolytic enzyme dipeptidyl peptidase IV (DPPIV) to the biologically inactive form GLP-2.[3–33] Blocking of DPPIV degradation, either through glycine substitution in position 2, as in teduglutide, or through adjuvant use of DPPIV inhibitors extends the use of GLP-2 half-life and confers greater biological potency. DPPIV inhibition enhances the intestinotrophic effect of GLP-2 in rats and mice.[28]

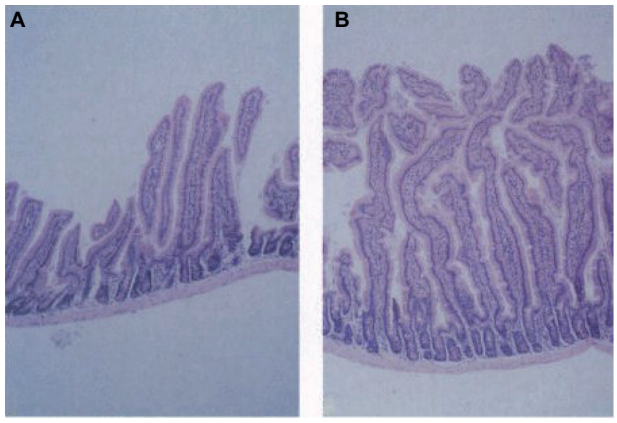

Figure 2 Effect of GLP-2 on murine small intestine. Histological appearance of small intestine epithelium from control (**A**) and GLP-2-injected (10 days) (**B**) mice.
Reproduced with permission from Drucker et al.[11]

Abbreviation: GLP, glucagon-like peptide.

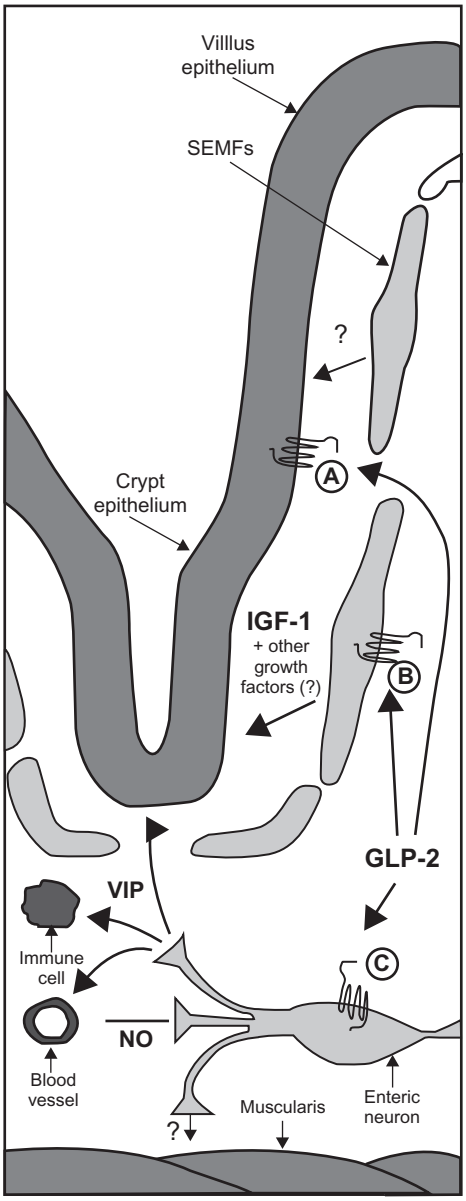

Figure 3 Proposed model for the indirect mechanisms of GLP-2 action in the intestine. Expression of the GLP-2R in intestinal endocrine cells (**A**), intestinal SEMFs (**B**), and enteric neurons (**C**) suggests that GLP-2 acts indirectly to produce its diverse actions in the intestine. IGF-I is critical for the ability of GLP-2 to induce intestinal growth and activate crypt cell proliferation. GLP-2-mediated enteric neuronal signaling enhances intestinal blood flow through a mechanism involving NO production and has anti-inflammatory actions through VIP.
Used with permission from Dubé et al, American Journal of Physiology – Endocrinology and Metabolism, Vol 293; E460–E465, 2007.[22]
Abbreviations: GLP-2, glucagon-like peptide-2; GLP-2R, glucagon-like peptide-2 receptor; IGF, insulin-like growth factor; NO, nitric oxide; SEMF, subepithelial myofibroblast; VIP, vasoactive intestinal polypeptide.

Teduglutide [Gly] GLP-2 (Gattex™, NPS Pharmaceuticals, Bedminster, NJ), a DPPIV-resistant analog of GLP-2 lacking the N-terminal DPPIV cleavage site, has received orphan drug designation for the treatment of SBS from the United States Food and Drug Administration (FDA) and the European Medicines Agency. In 2007, NPS Pharmaceuticals granted Nycomed the rights to teduglutide outside of North America.

Clinical trials of glucagon-like peptide-2 in SBS

The production of GLP-2 occurs in both the small and large bowel via the proglucagon-expressing enteroendocrine L-cells but is most abundant in the distal ileum. This may explain why functional adaptation appears more effective when the residual intestine is ileum rather than jejunum. Those with end jejunostomy and no colon, who have the poorest intestinal adaptation, have a markedly impaired postprandial GLP-2 response, presumably caused by a lack of functioning L-cells.[29] In contrast, SBS patients with preserved colon exhibit increased fasting GLP-2 levels with a postprandial profile comparable to that of healthy controls.[30] These findings, combined with strong evidence of a correlation between GLP-2 and intestinal adaptation in animal models,[13] have raised hopes that GLP-2 therapy might be able to produce clinically meaningful enhancement of intestinal mass and function in patients with SBS.

Results of clinical trials so far have been encouraging. In initial uncontrolled open label studies of SBS patients, native GLP-2 and the long-acting analog teduglutide significantly improved intestinal wet-weight absorption by up to 1 L per day. This occurred in patients with end jejunostomy as well as in patients with a preserved colon, despite the latter group having near normal endogenous GLP-2 levels.[31,32] The effects have been shown to be maintained for up to 2 years of treatment but will quickly wear off following treatment termination. The effect on energy absorption appears to be minor.

A recently published large multinational, randomized, placebo-controlled clinical trial of teduglutide in 83 post-resection SBS patients requiring PN at least three times per week for a minimum of 12 months, has also reported a positive outcome. Following a maximum 8-week optimization of PN with a 4–8-week stabilization period, patients were randomized into a 24-week treatment protocol with placebo (n = 16), 0.05 mg/kg/day teduglutide (n = 35) or 0.10 mg/kg/day teduglutide (n = 32). The main measure of treatment response was a reduction in parenteral nutrition requirements from baseline of more than 20%. The PN reductions were made in standardized fashion when the urine volume increased to a certain threshold. The increased urine production was considered as a surrogate marker for increased intestinal wet-weight absorption. The reported primary efficacy endpoint of the study, was based on a graded response score (GRS) that accounted for both intensity (reduction from baseline of 20%–100%) and duration of response (response at weeks 16, 20, and 24). Although no statistical significance could be shown for the 0.10 mg/kg/day dose group, the GRS in the lower 0.05 mg/kg/day dose group were significantly better than in the placebo group ($P = 0.007$). Also, a >20% reduction of PN was achieved in significantly more patients treated with the 0.05 mg/kg/day teduglutide compared with placebo (46% (16/35) vs 6% (1/16), $P = 0.005$).[33] The difference between 0.10 mg/kg/day teduglutide and placebo was not significant (25% vs 6.3% responders: $P = 0.161$). Three patients were weaned off PN completely (two in the low- and one in the high-dose treatment group).

The apparent lack of significant treatment response using 0.10 mg/kg/day teduglutide is thought to be related to protocol restrictions that could not take into account decreased oral fluid intake, which occurred significantly more often in the high dose patient group, as well as a trend towards higher baseline PN requirements and shorter remnant short bowel. Post hoc evaluation of the net effect of teduglutide estimates a similar efficacy of both treatment doses resulting in increased liquid absorption of approximately 700 mL (4.9 L per week), which is very much in keeping with the results of the open-label trials. The investigators also argue that the therapeutic benefit of teduglutide might have been underestimated by considering PN reduction as isolated endpoints, rather than taking into account additional positive effects on hydration and renal function. Teduglutide led to a significant increase in urine excretion in the low-dose group, and despite a reduced oral intake, urine output was maintained in the high-dose group. Although energy absorption was not quantified in this study, there was a small increase in body weight and lean body mass in both treatment groups, despite reduction in PN calorie provision.[34] Plasma citrulline, a sensitive marker for enterocyte mass and function, increased with low- and high-dose treatment but not with placebo, indicating a teduglutide-related intestinotrophic effect. Accordingly, increased villous height was documented in both treatment groups.

The aforementioned study was followed up with a 28-week extension study that enrolled 65 patients that had completed the initial trial. The aim was to investigate

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