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Peptide therapeutics for the treatment of gastrointestinal disorders

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1. Introduction

Gastrointestinal (GI) disorders have provided a research area eliciting a lot of interest for the development of peptides as potential therapeutic treatment options. For example, the endogenous gut hormones supporting digestion and the signaling along the gut-brain axis have provided interesting starting points for peptide therapeutics[1], a subset of which are covered in this review, and have led to a much-improved understanding of the underlying mechanisms of action. Important discoveries have been made for new peptide structures and their pharmacology.[2,3] However, while providing interesting targets for the treatment of gastrointestinal disorders, the intestinal tract is also unforgiving for peptides, which are typically highly susceptible to degradation at gastrointestinal pH in the presence of local proteases.[4] This mini-review outlines how innovative drug hunters have learned to create analogues of natural hormones or de novo peptides that can withstand the harsh gut environment, at times taking advantage of the therapeutic potential of local receptors in the gut lumen, without the requirement for systemic peptide exposure and the safety concerns that could be associated with it.

Rather than providing a systematic discussion for each peptide along a common template, this review focuses on aspects of several peptide development programs, that are particularly noteworthy or intriguing. What all the peptides described in this article have in common is their unique pharmacology, often acting as closely related, improved analogues of endogenous hormones with an important role in gastrointestinal health. For each of the peptides described in this chapter, interesting medicinal chemistry or pharmaceutical development challenges were solved. These are outlined here in addition to the peptides' pharmacology, some insight into the gastrointestinal disorders these peptide therapeutics are designed to treat and some of their clinical success stories.

2. Teduglutide for the treatment of short bowel syndrome

Teduglutide is a GLP-2 analogue that when administered subcutaneously increases intestinal absorption in patients with short bowel syndrome.[5] It was designed to improve the pharmacokinetic stability of the parent GLP-2 peptide and, interestingly, is the only peptide in this review that is manufactured using recombinant DNA technology.[6] The endogenous 33-amino acid trophic hormone GLP-2 is located at the carboxyterminal of proglucagon and secreted by intestinal enteroendocrine L-cells in the small and large intestines.

GLP-2 itself is quickly degraded by dipeptidyl peptidase IV (DPP-IV) and possesses a very short half-life of only 7.2 ± 2.0 min.[7] The recombinant GLP-2 analogue teduglutide (Fig. 1) was specifically designed to be resistant to DPP-IV degradation by replacing alanine in position 2 of the *N*-terminus with glycine (highlighted in blue in the peptide sequence provided in Fig. 1). In healthy subjects, this modification greatly improved the half-life of teduglutide compared to GLP-2, ranging between 2 h[8] and 6 h[9] when teduglutide is administered subcutaneously in single or multiple doses.

While the complete mechanism of action for GLP-2 and the recombinant teduglutide is not completely resolved, it is suggested that GLP-2 in the gastrointestinal tract acts by activating receptors on the sub-epithelial myofibroblasts, causing the release of growth factors, which in turn stimulate intestinal growth.[10] GLP-2 rapidly decreases gut permeability and increases intestinal barrier function in rodents and in preclinical models of gut injury.[11] Furthermore, GLP-2 decreases gastrointestinal motility and gastric acid secretion. It increases intestinal and portal blood flow, and exogenous GLP-2 also reduces the severity of intestinal inflammation in the small and large bowel. Some of the innate pharmacology to achieve these broad effects could be indirect through vasoactive neurotransmitters, anti-inflammatory mediators or through maintenance of gut barrier integrity.[6]

Short Bowel Syndrome (SBS) is a rare and potentially life threatening malabsorption condition that results from the loss of a significant amount of functional bowel mass due to congenital defects, disease associated loss of absorption or extensive surgical resection.[8] GLP-2, as an intestinotrophic factor, is an important component of intestinal adaptation. During this adaptation, the remaining intestinal tissue undergoes functional and structural changes to compensate for a loss of adsorptive and digestive capacity. When a patient suffers from SBS and gut absorptive function is reduced to below the minimum necessary to absorb nutrients, electrolytes and water, intravenous supplementation or parenteral support (PS) is required. Teduglutide entered Phase 3 clinical development for the treatment of adults with SBS who are dependent on PS. Improvement in intestinal nutrient and fluid absorption, which potentially occurs by promoting intestinal mucosal growth, had been demonstrated during

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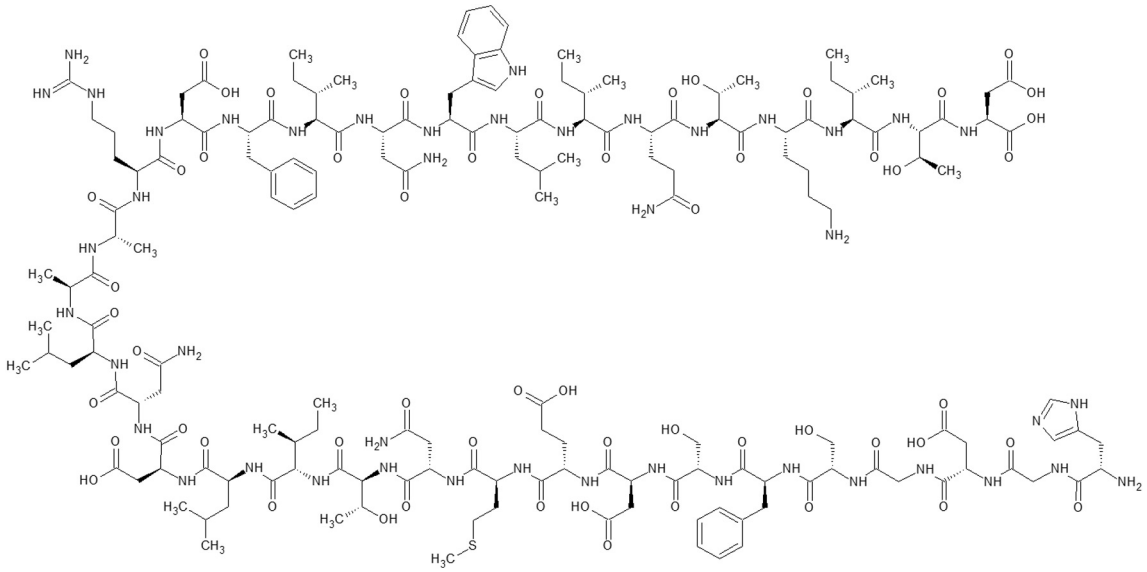

Fig. 1. Structure of the GLP-2 analogue teduglutide (the underlined Gly in position 2 denotes the one amino acid change relative to GLP-2).

a pilot clinical study using biopsy and plasma citrulline as biomarkers.[12] A large 24-week randomized, double blind, placebo controlled Phase 3 clinical study was conducted, in which teduglutide was investigated for its effects in patients with SBS with intestinal failure.[13] The objective of this study was to determine whether the GLP-2 analogue teduglutide could reduce the burden of parenteral nutrition and intravenous fluid requirements. Secondary endpoints included the ability to gain additional days off parenteral support (or to entirely eliminate the need for it). Teduglutide was overall safe and well tolerated and demonstrated restoration of structural and functional integrity of the remaining intestinal tract in patients with SBS with intestinal failure. Biopsies obtained from a subset of patients showed that treatment with teduglutide increased villus height and crypt depth, indicating structural improvements in bowel morphology in the 0.10 mg/kg/day treatment group. A graded response score (GRS) was used to account for intensity and duration of response with higher scores indicating greater parenteral volume reductions at both earlier (weeks 16–20) and later (weeks 20–24) time points. An exploratory analysis showed that the lower dose of teduglutide increased the GRS with statistical significance relative to placebo. The higher dose did not show statistically significant improvement of the GRS score relative to placebo at the end of the treatment period. Notably, three subjects in the study, two patients in the lower 0.05 mg/kg/day treatment group and one patient in the 0.10 mg/kg/day group, were completely weaned from parenteral support. In the confirmatory Phase 3 study, the primary endpoint was a responder rate, defined as percentage of patients who had a $\geq$20% reduction in weekly parenteral support volume from baseline to week 20 and who maintained that response through week 24. At the end of the treatment period, the responder rate endpoint was met for the 0.05 mg/kg/day dose when compared to placebo.[14] The 24-month open label extension study STEPS-2 confirmed prolonged safety and efficacy results.[15]

Based on these and other clinical study results[16,17] (beyond the scope of this short review), teduglutide was approved in 2012 for the treatment of adults with SBS who need additional nutrition from intravenous feeding.[18] The impact of this recombinant structural analogue of the natural hormone GLP-2 on patients with SBS can hardly be overstated when considering the burden and risks associated with regular parenteral administration of nutrients.

3. The guanylate cyclase c agonists linaclotide and plecanatide

Linaclotide and plecanatide, two FDA approved drugs for the treatment of the prevalent gastrointestinal disorders chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C), belong to the guanylin hormone family. Members of this hormone family are potent agonists of the guanylate cyclase C (GC-C) receptor. Fig. 2 outlines the amino acid sequences and disulfide bond patterns for these hormones and their analogues.[19,20]

The natriuretic peptides guanylin and uroguanylin were isolated within a year[21,22], with their biologically active forms showing striking similarities in their structures. Both have emerged as key players in regulating intestinal fluid homeostasis and maintenance of gut physiology.[23] The structural analogue heat-stable enterotoxin (*E. coli* ST-1a or hSTa[20]) was found to be 10 to 100 fold more potent and thus represents an interesting form of molecular mimicry developed by *E. coli* to exploit gut pharmacology in the

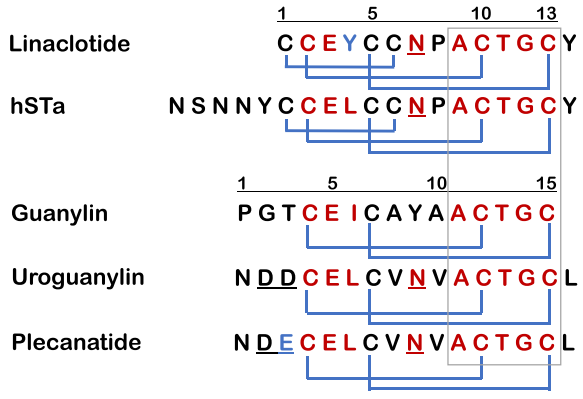

Fig. 2. Amino acid sequences and disulfide patterns for the guanylin hormone family and analogues. (Disulfide bonds are depicted as blue connecting lines, red color is provided to facilitate sequence alignment for conserved peptide sequence elements; key amino acid substitutions for the natural peptide hormone analogues and therapeutics linaclotide and plecanatide are depicted in blue. Disulfide bonds and the boxed amino acids are the most conserved and required structures for binding to the GC-C receptor domain and activating the GC system.[20] A few critical amino acids are underlined and discussed below in the context of plecanatide).