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Applications of peptide hormone ligands for the treatment of dumping and short bowel syndrome

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Dumping syndrome is a common and debilitating complication of upper gastrointestinal surgery. Accelerated gastric emptying and dysregulated secretion of gastrointestinal (GI) hormones are involved in its pathophysiology. Pasireotide, a novel somatostatin analogue, improved dumping in a phase-2 study. Preliminary data suggest that the glucagon-like peptide-1 (GLP-1) analogue liraglutide can also improve dumping. Short bowel syndrome is the most common cause of intestinal failure and involves not only a loss of mucosal absorptive area but also hypersecretion and accelerated transit. GLP-2 is the best studied hormone involved in intestinal adaptation. An increasing body of evidence demonstrates that the GLP-2 analogue teduglutide reduces parenteral support needs. New GLP-2 analogues and analogues of other GI hormones such as liraglutide are being investigated as promising treatments in short bowel syndrome.

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Introduction

Dumping syndrome is a common and debilitating complication of esophageal and gastric surgery which is characterized by accelerated gastric emptying (GE) following a meal with early and late symptoms [1]. The rapid delivery of undigested nutrients in the small bowel causes a fluid shift from the intravascular to the luminal compartment and secretion of gastrointestinal (GI) peptide hormones with GI and vasomotor symptoms (early dumping) and/or reactive hypoglycemia (late dumping). Although the majority of patients with mild symptoms respond to dietary measures, a significant subset will require medical therapy, mainly somatostatin analogues. The increasing incidence of dumping syndrome, especially after bariatric surgery, has fueled the evaluation of both analogues and antagonists of other GI peptide hormones.

Intestinal failure (IF) has been defined by the European society of clinical nutrition and metabolism (ESPEN) as a reduced absorptive capacity of the GI tract, below the minimum necessary to sustain life and/or growth, necessitating parenteral nutrition and/or intravenous fluids and electrolytes [2]. IF is associated with a reduced quality of life and a 5-year survival of 64% [3]. Short bowel syndrome (SBS) is the most common cause of IF worldwide [4•]. Until recently, medical therapy was limited to supportive treatment, including anti-secretory and anti-motility treatment, to increase absorption and limit fecal losses. However, the advent of GLP-2 analogues has drastically changed the management of SBS.

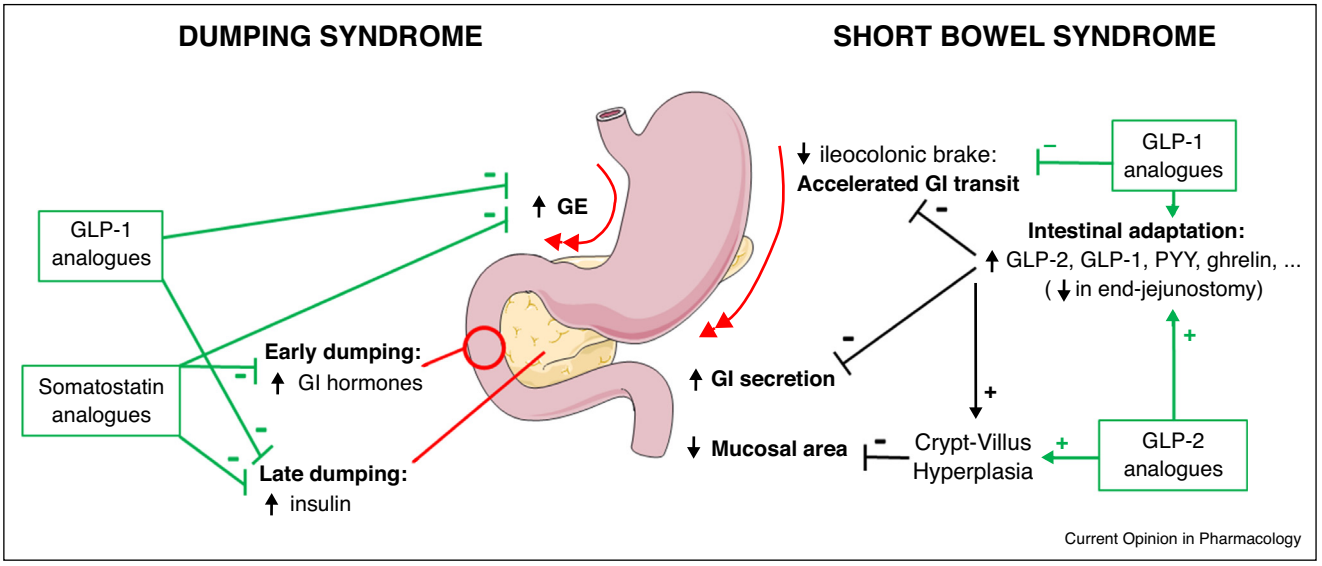
A schematic overview of the disease mechanisms and the effects of treatments targeting GI peptide receptors is represented in Figure 1. Rapid transit and dysregulated release of GI peptide hormones play a role in both conditions.

In the current narrative review, we report on the recent advances in the treatment of dumping and short bowel syndrome using agonists and blockers of GI peptide hormone receptors. An electronic literature search was conducted using Pubmed up to 1st of July 2018. The following keywords were used in various combinations: 'dumping syndrome', 'short bowel syndrome', 'peptide hormones', 'somatostatin analogues', 'octreotide', 'lanreotide', 'pasireotide', 'glucagon-like peptide 1', 'GLP-1', 'glucagon-like peptide 2', 'GLP-2', 'teduglutide', 'glepaglutide'. A manual search was performed of the reference list of the initially selected articles, and the abstract lists of the two major yearly gastroenterology conferences Digestive Disease Week and United European Gastroenterology Week. Only articles in English were reviewed.

Dumping syndrome

Somatostatin analogues (SSA) slow down GE and decrease the meal-induced release of insulin, glucagon and several gastrointestinal peptide hormones implicated in the pathogenesis of dumping, including glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), neurotensin, vasoactive intestinal peptide (VIP) and pancreatic polypeptide (PP) via activation of the somatostatin

Figure 1



Schematic overview of disease mechanisms and potential treatments targeting gastrointestinal peptide hormone receptors in dumping syndrome (left) and short bowel syndrome (right).
+: stimulating effect; -: inhibitory effect; GE: gastric emptying; GI: gastro-intestinal; GLP: glucagon-like peptide; PYY: peptide YY.

receptor [5•]. Both short-acting and long-acting release (LAR) formulations of octreotide, a first-generation SSA, have demonstrated efficacy in improving hypoglycemia and early and late dumping symptoms with higher quality of life (QoL) on LAR therapy [6,7]. However, long-term treatment discontinuation up to 60% has been reported, mainly due to side effects, including pain at the injection site and steatorrhea, and secondary loss of efficacy [8]. Pasireotide is a second-generation multi-receptor targeting SSA with high affinity for 4 of the 5 receptor subtypes and strong inhibition of GLP-1 and insulin secretion due to its 40-fold higher affinity for somatostatin receptor subtype 5 compared to octreotide [9]. In a pilot study 300 μg pasireotide t.i.d. improved signs of early and late dumping in a prolonged oral glucose tolerance test (OGTT) which is the most commonly used diagnostic test for dumping syndrome [10]. Because of the strong effect on glycemia in the pilot study, 4 lower doses (50–200 μg) were selected for a subsequent multi-center phase 2 open-label study in 43 post-operative dumping patients with symptomatic hypoglycemia [11••]. The primary endpoint, that is absence of hypoglycemia during the prolonged OGTT, was achieved in 60% of patients at the end of the 3-month subcutaneous phase. Improvement in symptoms and QoL was also noted and maintained in the intramuscular phase. At the end of the 3-month intramuscular phase, the response rate decreased to 39%. Although these data are encouraging, a placebo-controlled or octreotide-controlled trial is warranted to further assess its effect, especially in terms of symptoms and adverse effects including hyperglycemia.

GLP-1 is an incretin hormone secreted by L cells in the distal small intestine in the presence of nutrients [12]. GLP-1 analogues reduce body weight and hyperglycemia in patients with type 2 diabetes mellitus and have also shown beneficial effects in obesity by slowing GE, decreasing appetite and food intake [13]. Liraglutide 3 mg OD in addition to diet and exercise resulted in reduced body weight and improved glycemic control in obese patients with and without prediabetes and irrespective of baseline BMI [14]. The same dose delayed GE in the first postprandial hour [15] and weight loss was associated with delayed emptying of solids, which may be a predictor of response and help guide treatment choices [16]. Although GLP-1 is likely to be involved in the pathophysiology of early dumping syndrome [17] and the GLP-1 receptor antagonist exendin (9–39) indeed prevented hypoglycemia in patients with dumping after bariatric surgery [18], the pharmacological effects of GLP-1 analogues on GI motility have prompted assessment in the treatment of dumping as well. GLP-1 analogues have indeed shown beneficial effects on postprandial hypoglycemia following Roux-en-Y gastric bypass (RYGB) [19]. Similar effects were reported after fundoplication and other non-resecting gastric surgical interventions which may also accelerate GE resulting in dumping [20]. The accelerated GE triggers a glucose-insulin mismatch due to an earlier and larger increase in plasma glucose and GLP-1 with prolonged and overshooting insulin output leading to reactive hypoglycemia [21]. The glucose-stabilizing mechanisms, possibly via more persistent GLP-1 receptor activation, may contribute to