Recent Advances in Clinical Application of Gut Hormones

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Many peptide hormones that are synthesized and secreted from the gastrointestinal (GI) tract have been discovered. Gut hormones play an important role in regulation of food intake, GI motility, energy balance and body weight by working with the complex neural circuits in the brainstem, hypothalamus and higher cortical centers. Recent introduction of bariatric surgery for treatment of type 2 diabetes in overweight patients further highlights the differential effects of gut hormones on the enteroinsular axis and glycemic control. In addition, another promising anti-obesity strategy is to attain a negative energy balance through manipulation of the circulating gut hormones as well as their target receptors. In this article, the basic physiology of several peptide hormones associated with GI motility disorders, obesity and diabetes is reviewed, and advances in the clinical application of gut hormones are discussed (Table).

Ghrelin and GI Motility Disorders

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor, and is secreted mostly by the X/A-like cells in the gastric fundus. Ghrelin is currently the only orexigenic gut hormone to promote food intake and accelerate gastric emptying. Therefore, ghrelin and its analogs have been used in patients with anorexia or malnutrition. For example, Ashby et al showed that malnourished dialysis patients can achieve a sustained positive energy balance by daily ghrelin treatment.1 Circulating ghrelin levels have been reported to be lower in patients with functional dyspepsia which implies a therapeutic role of ghrelin and related compounds. For example, repeated administration of ghrelin can stimulate appetite in patients with functional dyspepsia.2 In addition, ghrelin accelerates gastric emptying in patients with diabetic gastroparesis. A synthetic, selective ghrelin receptor agonist, TZP-101, is well-tolerated and effective for diabetic gastroparesis and postoperative ileus after partial colectomy.3,4 Therefore, analogs of ghrelin could represent a new class of prokinetic agents in the future.

Pancreatic Polypeptide-fold Peptides, Amylin and Obesity

Pancreatic polypeptide-fold peptides consist of two gut hormones: peptide YY (PYY) and pancreatic...
polypeptide (PP). PYY is released from L-cells of the distal gut into the circulation. PP is secreted from F-cells in the pancreas and the colon. Amylin is co-released with insulin from pancreatic β cells and has a similar physiological profile to insulin.

PYY 3-36 (the predominant circulating form of PYY), PP and amylin increase satiety, reduce food intake, delay gastric emptying and regulate energy expenditure. As a result, these hormones could be of benefit to weight control and obesity treatment. In human studies, obese subjects have been found to have low levels of PP and PYY. In addition, chronic PYY treatment in mice enhances insulin sensitivity, and promotes insulin-mediated glucose disposal. Intravenous PP infusion reduces food intake in healthy people and patients with Prader–Willi syndrome, who have a deficiency in basal and meal-stimulated circulating PP levels and present with dramatic hyperphagia and morbid obesity. In obese mice, repeated administration of PP has been shown to decrease body weight gain and ameliorate insulin resistance and hyperlipidemia.5

It has been reported that the combination of amylin and PYY 3-36 has greater anorexigenic and weight-reducing effects than either peptide alone.6 Concurrent administration of amylin and leptin can induce synergistic weight loss in leptin-resistant, diet-induced obese rats. In patients with obesity and type 2 diabetes, administration of pramlintide, a synthetic analog of human amylin, has been shown to improve glycemic control and cause weight loss. Furthermore, in a 24-week randomized, double-blind study, co-administration of pramlintide and recombinant human leptin elicited a mean weight loss of 12.7% in overweight/obese subjects.7

Glucagon-like Peptide 1 (GLP-1) and Diabetes

GLP-1 belongs to a family of incretins that stimulate insulin secretion in a glucose-dependent manner. GLP-1 promotes glucose sensitivity and insulin biosynthesis and inhibits glucagon release.
In addition, GLP-1 delays gastric emptying and decreases appetite and body weight.

Previous studies have indicated that patients with type 2 diabetes have decreased plasma concentrations of GLP-1, and continuous subcutaneous administration of GLP-1 greatly improves glucose profiles and lowers body weight and hemoglobin A1c levels. However, GLP-1 is rapidly inactivated by dipeptidyl-peptidase 4 (DPP-4). Accordingly, several GLP-1 analogs or DPP-4 inhibitors have been developed to treat diabetes. Exenatide (exendin-4), a DPP-4-resistant GLP-1 receptor agonist and sitagliptin, a DPP-4 inhibitor, have been shown to reduce food intake and body weight, and thus improve glycemic control in patients with type 2 diabetes. In metformin-treated type 2 diabetes patients, exenatide has a greater effect than sitagliptin to increase insulin secretion and reduce postprandial glucagon secretion and glucose levels. Another long-acting human GLP-1 analog, liraglutide, also improves glycemic control and is well tolerated.

**Conclusion and Future Perspective**

In summary, gut hormones help to regulate appetite and GI motility and maintain body energy homeostasis. With a marked expansion of knowledge about the structure and pathophysiology of gut hormones, various new drugs have been developed with remarkable efficacy and tolerance on the basis of natural peptides and their agonists or antagonists. Such pharmacological approaches could shed light on the management of obesity, diabetes, and GI motility disorders in the foreseeable future. Further investigations are warranted to optimize the route of administration, dosing and drug combination, and to minimize the adverse effects of these new agents in our clinical practice.

**References**