Gut Hormones Fulfill Their Destiny: From Basic Physiology to the Clinic

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The gastrointestinal tract not only is responsible for the digestion and absorption of ingested macromolecules but also plays an essential role in regulating the integrated whole-body response to food intake. Hence, additional functions of the gut include (but are not limited to) the coordination of pancreatic hormone secretion, protection of the body from ingested noxious substances and luminal microbes, aboral transit of the chyme, and expulsion of undigested food products. Another function involves providing feedback to the central nervous system to regulate both gastric emptying and nutrient intake. Many of these biological imperatives are regulated by the release of peptides by the gastrointestinal tract, which serve roles largely as endocrine hormones.

In 1902, Bayliss & Starling (1) discovered the first enteroendocrine peptide: secretin. Since this seminal observation, several dozen gut hormones have been identified by using a large variety of approaches ranging from biochemical to genomic (2). However, in contrast to other peptide hormones that were also discovered in the early part of the twentieth century, such as insulin (3), most gut hormones were not identified until after ~1970, and so the field of gastrointestinal endocrinology has been rather slow to develop. The reasons for this are not entirely clear but may involve the diffuse distribution of enteroendocrine cells in the gut, making purification difficult, and/or a relative lack of identified diseases associated with their deficiency or excess (e.g., compared with type 1 diabetes due to insulin deficiency, or acromegaly/gigantism consequent to growth hormone excess) (2). Another reason may be a prudish objection on the part of investigators to devote their lives to the study of the bowels: "*Life's dirty. Life's unclean, you know. . . . it's the intestinal tract. One big squishy unsanitary mess*" (Andrew Schneider, Emmy award–winning screenwriter and television producer). As a consequence, the translation of findings in gastrointestinal endocrinology to the clinic has also been remarkably slow compared with the case for many other endocrine hormones, including not only insulin, but also glucagon, somatostatin, and parathyroid hormone (3–9). However, the landscape has been profoundly altered over the past decade, with the approval of one gut hormone, glucagon-like peptide-1, in 2005 for the treatment of patients with type 2 diabetes and the approval of a related intestinal hormone, glucagon-like peptide-2, in 2012 for patients with short-bowel syndrome (10, 11). A number of additional enteroendocrine peptides, including the orexigenic hormone ghrelin and the anorexigenic hormone peptide YY, are also under consideration for therapeutic use in the treatment of body weight disorders (12, 13). Furthermore, changes in the levels of all four of these gut hormones have been implicated to a greater or lesser extent in the adaptive intestinal responses, body weight reduction, and/or remarkable "cure" of associated type 2 diabetes in patients undergoing bariatric surgery for the treatment of obesity (14–16).

In this volume of the *Annual Review of Physiology*, leaders in the fields of ghrelin, glucagon-like peptide-1, glucagon-like peptide-2, and peptide YY biology offer their unique perspectives on recent advances in their areas of study. From the basic physiology of enteroendocrine hormone secretion to the mechanism of action and existing or potential clinical relevance of these hormones, these reviews clearly demonstrate that the health benefits of gastrointestinal endocrinology have finally begun to be realized.

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