Gut Hormones and Metabolism

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The gut is the largest endocrine organ in the body. More than 30 hormones are produced by the gastrointestinal tract, pancreas, and fat, with many other related peptides produced in the brain. Many gut hormones are released by the direct action of ingested nutrients onto enteroendocrine cells found within the intestine. These hormones act to control food intake and energy expenditure.

Gut-Brain Axis

The hypothalamus is the co-ordination center for energy homeostasis, and the arcuate nucleus (ARC) in the hypothalamus is the epicenter for integration of signals about the energy status and requirements of an individual. The ARC then relays messages to other brain regions, including the lateral hypothalamic area. There is subsequent output to the sympathetic nervous system, between the brain stem and the hypothalamus. The ARC receives inputs from many different sources. It lies close to the median eminence, which lacks a blood brain barrier, allowing direct access to hormones from the periphery. The hypothalamic-pituitary-adrenal (HPA) axis is another major source of hormones that has an impact on brain function. The vagus nerve connects the gastrointestinal tract to the hypothalamus, relaying messages about gut hormones and gastrointestinal distension. Reciprocal connections also exist between the brain stem and the hypothalamus. The ARC then relays messages to other hypothalamic nuclei, such as the ventromedial nucleus, the dorsomedial nucleus, and the lateral hypothalamic area. There is subsequent output to the sympathetic nervous system, the thyroid axis, the limbic system, and back to the vagus, which then control food intake and energy expenditure.

**Gut Hormones and Obesity**

In normal circumstances, the gut-brain axis ensures that an individual maintains their weight within a narrow range. However, persistent excessive food consumption can overwhelm the normal homeostatic mechanisms and lead to the development of obesity. Furthermore, once a person has become obese, their physiological changes to make weight loss even harder. In obese patients, there is a relative reduction in levels and efficacy of the satiety hormones PPY, POMC/CART, and CCK. There is also a resistance to the effects of leptin, and an increased sensitivity to ghrelin. These changes stop people feeling full and increase food consumption. Unfortunately, when people diet, the body fights against losing weight. The satiety hormones (such as PPY, CCK, leptin and melanocortin) work in an anorexic environment.

**Gut Hormones Drug Therapies and Bariatric Surgery**

Gut hormones can be used as a pharmacological therapy for obesity. Naturally-occurring gut hormones have very short half-lives in the body, which limit their use. However, long-lasting versions are being developed. Exenatide is a GLP-1 analog first discovered in the saliva of the Gila monster. It is resistant to the enzyme dipeptidyl peptidase IV, which breaks down GLP-1, and therefore has a prolonged half-life. The synthetic version, exenatide, is a common treatment for diabetes. Another long-acting GLP-1 analog, liraglutide, is available as a treatment for both diabetes and obesity. Stabilized analogs of both PPY and GLP-1 have been developed and have entered clinical trials as treatments for obesity. There is increasing evidence for targeting obesity with combinations of gut hormones. Chronic infusions of oxyntomodulin, which activates both GLP-1 and glucagon receptors, reduce body weight in obese patients, and a number of oxyntomodulin analogs are in development as a treatment for obesity. Additionally, several drugs targeting both the GLP-1 and GIP pathways, and triple-agonists at the GLP-1, GIP and glucagon receptors, are being developed. Bariatric surgery is now recognized as the most effective, lasting treatment for obesity. The gastric bypass surgery, and after this the post-prandial response is altered so that GLP-1, oxyntomodulin, glucagon and CCK all increase, while ghrelin and GIP levels fall. Gastrin levels also fall but are elevated by PPI treatment. There is no significant change in PPY levels. The changes in gut hormones, particularly GLP-1, may be responsible for the improvement in diabetes seen after bariatric surgery independent of weight loss.

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**References**