Gut Hormones and Appetite Control

Stephen R. Bloom, MD

A. M. WREN and S. R. BLOOM

Department of Metabolic Medicine, Imperial College London, London, England

Many peptides are synthesized and released from the gastrointestinal tract. Although their roles in the regulation of gastrointestinal function have been known for some time, it is now evident that they also physiologically influence eating behavior. Our understanding of how neurohormonal gut–brain signaling regulates energy homeostasis has advanced significantly in recent years. Ghrelin is an orexigenic peptide produced by the stomach, which appears to act as a meal initiator. Satiety signals derived from the intestine and pancreas include peptide YY, pancreatic polypeptide, glucagon-like peptide 1, oxyntomodulin, and cholecystokinin. Recent research suggests that gut hormones can be manipulated to regulate energy balance in humans, and that obese subjects retain sensitivity to the actions of gut hormones. Gut hormone-based therapies may thus provide an effective and well-tolerated treatment for obesity.

The gut is the most exciting endocrine organ in the body. This remark from an endocrinologist may once have been contentious in a gastroenterology journal. Currently, the neuroendocrine role of the gut in energy homeostasis is a dynamic and rapidly expanding field of scientific investigation that has united researchers across many fields, as testified to by this special issue. The concept of the gut as an endocrine organ is hardly new. The gut peptide secretin was the first substance to be termed a hormone, while the appetite inhibitory actions of cholecystokinin (CCK) were first reported over 30 years ago. However, in recent years, intensification of scientific endeavor in this field has been motivated by the need to develop new strategies to tackle the global pandemic of obesity.

The prevalence of obesity in adults has increased by over 75% worldwide since 1980.[1] Given that obesity is causally associated with cardiovascular disease, type 2 diabetes, hypertension, stroke, obstructive sleep apnoea, and certain cancers, this has translated into healthcare costs of over half a billion pounds every year in the United Kingdom alone.[2] Obesity is not only a problem in the developed world, but is set to overtake infectious diseases as the most significant contributor to ill health worldwide, and has been classified as an epidemic by the World Health Organization.[3] The increasing prevalence of obesity in younger generations suggests that this epidemic will continue to worsen.

Public health initiatives have failed to reverse the rising incidence of obesity. Medical and behavioral interventions, with the exception of bariatric surgery, have limited success, in general promoting no more than 5%–10% reduction in body weight. Furthermore, weight regain, even after this modest weight loss, is almost universal.[4] There are good reasons for this, which can be understood by examining the homeostatic mechanisms that defend body weight. In attempting to lose weight by dieting, the body faces compensatory "starvation" signals from the gut and adipose tissue, all with a single aim of promoting hunger and storage of calories as fat. The notion that energy balance is tightly regulated to defend a "set-point" body weight may seem contradictory to our common experience that food intake varies widely day to day. Such marked diurnal variation may have led to the popular belief, particularly among lean individuals, that regulation of body weight is largely a matter of willpower. It is hard to imagine such a view of the regulation of any similarly important aspect of physiology, for example blood pressure, persisting for so long. In fact, when examined over the longer term, energy balance is extremely finely regulated.

During the evolution of the homeostatic mechanisms regulating body weight, food shortage has been the

Abbreviations used in the paper: AgRP, agouti-related peptide; CCK, cholecystokinin; CNS, central nervous system; GH, growth hormone; GLP-1, glucagon-like peptide 1; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PWS, Prader-Willi syndrome; PYY, peptide YY.

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norm. The mechanisms that have allowed the human race to survive famine may not be so well suited to the current situation. The increasing incidence of obesity coincides with widespread availability of highly palatable food of high energy density that can be obtained without having to expend energy. This review will focus on the peptide hormone signals from the gut that communicate the status of body energy stores to the brain and the brain centers on which they act. These regulatory systems are not only of academic interest, but are likely to underpin any future strategy to tackle obesity, by providing drug targets for the holy grail of a safe sustainable weight loss.

Currently available drug therapies have limited efficacy and considerable side effects. Two agents are currently licensed for weight loss. Orlistat inhibits dietary fat absorption, resulting in an additional loss of 3% to 4% of body weight over diet alone in a 2-year period.[5] It also results in deficiency of fat-soluble vitamins and fairly dramatic gastrointestinal side effects, which make it unacceptable for many patients. Sibutramine is a serotonin and norepinephrine reuptake inhibitor that acts in the central nervous system (CNS) to reduce energy intake and increase energy expenditure. It has similar efficacy to orlistat but also increases incidence of tachycardia and hypertension. Both of these drugs only have data supporting treatment for up to 2 years. In the United Kingdom, national prescribing guidelines generally recommend withdrawal after 1 year, after which significant weight regain is common.[6]

Several newer antiobesity therapies targeting CNS receptors are in development or have recently been marketed. Among these is rimonabant, a cannabinoid CB1 receptor antagonist. This appears to be an effective weight-loss agent but is associated with high levels of drop-out due to anxiety and depression.[7] The CB1 receptor has a very wide distribution, both in the CNS and the periphery, suggesting a wide range of physiologic functions.[8] There is evidence that cannabinoids have neuroprotective, anti-inflammatory and antiatherosclerotic actions, and concerns have been raised that rimonabant may promote diseases including multiple sclerosis and ischemic heart disease.[9,10] Clearly, the search for the ideal antiobesity agent is not at an end.

At the other end of the appetite regulation spectrum, there is a pressing need for more effective, better-tolerated appetite-stimulatory treatments. Loss of appetite and weight are major causes of morbidity and mortality in patients, including those with cancer, kidney failure, human immunodificiency virus, cardiac failure, inflammatory conditions, and postoperatively. Weight loss has an important impact on health economics. Undernutrition is estimated to increase the duration of 10% of hospital admissions by an average of 5 days, costing approximately £266 million annually in the United Kingdom.[11] Although a comprehensive overview of anorexia and cachexia is beyond the scope of this review, which will focus mainly on obesity, the potential role of gut hormones in this area will be briefly discussed.

Long-Term and Short-Term Energy Balance Signals

Peripheral signals involved in regulation of body weight and ingestive behavior are often categorized as long-acting adiposity signals, such as insulin leptin and other adipokines and short-acting gastrointestinal factors. Long-acting signals characteristically reflect the levels of energy stores and regulate body weight and the amount of energy stored as fat over the long term. Short-acting gastrointestinal signals are typified by gut hormones such as CCK and mechanical factors, such as gastric distension, which characteristically relay a sense of "fullness" resulting in postprandial satiation and meal termination. More recently identified appetite regulating hormones from the gut, including the appetite inhibiting hormone peptide YY (PYY) and the appetite-stimulating hormone ghrelin, appear to blur the boundaries between long- and short-term appetite signals, with evidence emerging that they are involved in both regulation of appetite on a meal-by-meal basis and also in longer term energy balance. In addition, the incretin glucagon-like peptide 1 (GLP-1), has been shown to inhibit appetite. This is reviewed in detail elsewhere in this issue and will not be covered here in depth. This review will focus on the evidence for a role of the gut hormones ghrelin, PYY, oxyntomodulin, and pancreatic polypeptide (PP) in the short- and long-term regulation of energy balance.

Central Integration of Peripheral Signals

Clearly, peripheral hunger and satiety signals require central integration to allow efficient energy homeostasis. Neurohormonal signals from the gut and adipose tissue converge on the hypothalamus where they are integrated, and in turn regulate energy intake and energy expenditure. The reader is referred to a number of excellent reviews of the hypothalamic neurocircuits regulating energy balance.[12–15] In brief, a vital component of the hypothalamic regulatory circuits is the arcuate nucleus. Two key neuronal populations have been identified within the arcuate nucleus with opposing effects on energy balance. A group of neurons in the medial arcuate nucleus coexpress neuropeptide Y (NPY) and agouti-related peptide (AgRP) and act to stimulate food intake and weight gain. In contrast, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript coexpressing neurons in the lateral arcuate nucleus inhibit feeding and promote weight loss. The balance between activity of these neuronal circuits is critical to body weight regulation.

Satiety is also regulated by the hindbrain. The nucleus of the solitary tract (NTS) and the area postrema, com-