Can Gut Hormones Control Appetite and Prevent Obesity?

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The current obesity epidemic is fuelled by the availability of highly palatable, calorie-dense food, and the low requirement for physical activity in our modern environment. If energy intake exceeds energy use, the excess calories are stored as body fat. Although the body has mechanisms that act to maintain body weight over time, they primarily defend against starvation and are less robust in preventing the development of obesity. Knowledge of this homeostatic system that controls body weight has increased exponentially over the last decade and has revealed new possibilities for the treatment of obesity and its associated comorbidities. One therapeutic target is the development of agents based on the gastrointestinal hormones that control appetite. This review discusses the hormones oxyntomodulin, peptide YY, glucagon-like peptide 1, pancreatic polypeptide, and ghrelin and their emerging potential as anti-obesity treatments.

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The grave personal, societal, and economic consequences presaged by the continued worldwide rise in the prevalence of obesity are well documented (1,2). Currently, licensed nonsurgical interventions are of limited efficacy (3–6). This relative failure of available therapies has imparted impetus to work directed at harnessing the physiological mechanisms of appetite control. The pursuit of the body's own satiety signals as therapeutic targets promises effective reductions in body weight with minimum disruption to other systems, avoiding the side effects that occur as an unwanted consequence of therapies targeting ubiquitous neurotransmitter and receptor complexes.

THE GUT-BRAIN AXIS — The lines of communication between the gastrointestinal (GI) tract and central nervous system (CNS) form a key component in a recently established model of appetite regulation. This gut-brain axis has both neural and humoral components that relay information to important CNS centers, including the hypothalamus and the brainstem (7). These CNS structures have extensive reciprocal connections and both receive neuronal input from the periphery, with the brainstem-vagus nerve complex being of particular significance in the control of feeding (8–10).

Neuronal activity in hypothalamic and brainstem nuclei is susceptible to influence by circulating hormones. In the hypothalamic arcuate nucleus (Arc), signals from the periphery result in changes in the relative activity of two subpopulations of neurons: an orexigenic population co-expressing the neurotransmitters neuropeptide Y and agouti-related peptide and an anorexigenic population co-expressing pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript. Alterations in the release of these neuropeptides affect feeding behavior and energy expenditure, resulting in the maintenance of energy homeostasis.

The mechanisms by which hormones interact with CNS appetite centers are the subject of some contention. The proximity of both the hypothalamus and brainstem to structures with a relative deficiency of blood-brain barrier (the median eminence in the case of the hypothalamus and the area postrema in respect of the brainstem) may allow circulating factors direct access to CNS neurons. There is a growing body of evidence, however, that points to the vagus nerve as a primary site of action of some appetite-modulating hormones (11–15). From a therapeutic perspective, targeting the interaction of appetite signals with their receptors in the vagal nerve offers the potential advantage of being able to manipulate appetite at a site distant from the CNS.

GUT HORMONES — The GI-pancreatic complex is the largest endocrine organ in the body and a source of important regulatory peptides. Cholecystokinin was the first to be implicated in the short-term control of food intake (16), and other appetite-regulating hormones have subsequently been characterized. Of these, ghrelin is the only known orexigenic gut hormone, whereas a number of satiety factors exist, including glucagon-like peptide (GLP)-1, oxyntomodulin (OXM), peptide YY (PYY), and pancreatic polypeptide (PP) (7). Unlike leptin, which is thought to signal longer-term energy status, these gut hormones appear to act as meal initiators and terminators. Alterations in levels of gut hormones after bariatric surgery may contribute to the appetite suppression and sustained weight loss seen in patients undergoing this procedure and supports the development of these hormones as therapeutic targets (17,18).

Ghrelin

This 28–amino acid peptide is synthesized principally in the stomach (19). It acts via the growth hormone secretagogue receptor to increase food intake in rodents (20) and also acts to stimulate food intake in humans (21,22). Clinical studies have thus far concentrated on its use as an orexigenic agent in conditions characterized by anorexia and cachexia (23–26). Antagonists to ghrelin have been used in preclinical studies, however, paving the

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Abbreviations: CNS, central nervous system; DPP-IV, dipetidyl peptidase IV; GI, gastrointestinal; GLP, glucagon-like peptide; OXM, oxyntomodulin; PYY, peptide YY.

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way for possible future evaluation as a therapy for obesity in humans (27).

GLP-1

A product of proglucagon cleavage, GLP-1 is released from the L-cells of the GI tract postprandially in proportion to the calories ingested. GLP-1 and longer-acting GLP-1 receptor agonists, such as exendin-4, reduce food intake in rodents when injected into the CNS (28) or peripherally (12,29). Given the observation of reduced circulating levels of GLP-1 and an attenuated postprandial response in the obese (30), it is not unreasonable to hypothesize that restoration of satiety through the use of exogenous GLP-1 receptor agonists might result in weight loss. To date, clinical development has focused on its strong incretin effect and its resultant use as an anti-diabetic agent: a 6-week subcutaneous infusion of GLP-1 improved blood glucose levels in poorly controlled diabetic subjects (31). However, in contrast to insulin, GLP-1 results in a tendency to reduce body weight (32). The advantages of a hypoglycemic agent that also promotes weight loss are obvious. These results may also be encouraging for the use of GLP-1 as an anti-obesity therapy.

A major hurdle to the therapeutic use of native GLP-1, and one common to many gut hormones, is its short half-life. The principle mediator of GLP-1 inactivation is the enzyme dipetidyl peptidase IV (DPP-IV). A number of DPP-IV–resistant GLP-1 receptor agonists, including liraglutide (Novo Nordisk, Denmark) and exenatide (Byetta, Amylin Pharmaceuticals, San Diego) have therefore been developed. Liraglutide has been synthesized using the GLP-1 sequence with the addition of an acyl side chain that allows for noncovalent binding to albumin and prolongs its half-life in the circulation (33). As an alternative strategy, exenatide (exendin-4) was extracted from the venom of the gila monster (*Heloderma suspectum*). It potently binds to and activates the GLP-1 receptor and is resistant to DPP-IV breakdown in the plasma.

Exenatide was recently licensed by the Food and Drug Administration for use as an adjunctive therapy for suboptimal glucose control in type 2 diabetic patients and is now undergoing further clinical trials to evaluate its utility specifically as a therapy for obesity. Initial data from open-label extension studies in diabetic patients have shown that a weight loss of 4.4 kg can be achieved by 82 weeks (34). However, like GLP-1, dose-limiting side effects of nausea and vomiting define the maximal tolerated dose (35). The use of exenatide is also associated with hypoglycemia, although this occurs predominantly in patients receiving the drug in combination with another hypoglycemic agent (36). It has been reported that up to 30% of patients taking exenatide develop antibodies to this foreign peptide, although the clinical significance of this remains unclear (33).

Oxyntomodulin

Another product of the tissue-specific differential cleavage of proglucagon, OXM, is co-secreted with GLP-1 and $PYY_{3–36}$ into the circulation by intestinal L-cells after nutrient ingestion (37). OXM is a satiety signal and administration reduces energy intake in both rodents and humans (38–42). Indeed, preprandial subcutaneous administration of OXM to overweight and obese humans over a 4-week period resulted in a significant reduction in body weight of 2.3 kg, compared with 0.5 kg for the placebo arm (42). In addition, OXM has been found to have a beneficial effect on energy usage, in that it increased activity levels back toward normal in overweight and obese volunteers (43). Oxyntomodulin administration was well tolerated in these studies. Longer-term trials are now required to determine whether its beneficial combination of properties can be sustained.

Although direct comparisons have not been made, OXM appears to cause less nausea than GLP-1–based treatments and thus may prove a potentially rewarding avenue of investigation. OXM is thought to act via the GLP-1 receptor (29). However, despite this common receptor, there are biological differences between the two hormones. There is evidence that OXM acts through different CNS pathways (40,44) and has a weaker incretin effect than GLP-1 (41,42,45). Its effect on food intake is more potent than that of GLP-1 in humans (41,42). In addition, the increased activity levels observed during oxyntomodulin therapy (43) have not been demonstrated with GLP-1 treatment, whose effect on energy expenditure remains controversial (46–48). The reasons for these dissimilar actions awaits elucidation but may lie in differential penetration of OXM and GLP-1 into different areas of the CNS or modification of ligand binding to the GLP-1 receptor in specific CNS regions by a receptor-associated protein. This latter scenario is intriguing, since it offers another possible point for therapeutic intervention.

Like GLP-1, OXM is inactivated in large part by DPP-IV, and its advancement as a clinically useful treatment will be reliant on the development of a breakdown-resistant analog. Thiakis and Imperial Innovations (London, U.K.) are in the process of developing novel analogs of oxyntomodulin for the treatment of obesity.

Inhibitors of DPP-IV

In the quest for an effective anti-obesity treatment, some researchers have adopted the approach of augmenting the effectiveness of endogenous gut peptides. Multiple DPP-IV inhibitors have been tested in animals, and although they improve glucose levels in rodent models of type 2 diabetes, their effect on weight is more equivocal (49–52). A number of DPP-IV inhibitors are at various stages of development as adjuvant therapy for use in type 2 diabetic subjects with poorly controlled blood glucose levels. Of these, sitagliptin (Januvia, Merck) was granted marketing approval by the Food and Drug Administration in October 2006, and vildagliptin (Glavus, Novartis) is currently undergoing Food and Drug Administration review. The evidence from clinical trials to date suggests that these therapies were well tolerated with few adverse effects, but also have little effect on weight (53). Longer-term safety and outcome data are awaited.

Amylin

Co-secreted with insulin from the β-cells of the pancreas, the peptide amylin forms the basis of pramlintide (Symlin; Amylin Pharmaceuticals), a novel treatment for diabetes that has recently been granted Food and Drug Administration approval. In addition to favorable effects on blood glucose, pramlintide reduces food intake and has been shown to result in a 1.8-kg reduction in body weight over 26 weeks in overweight diabetic subjects (54). Phase 2 clinical trials of pramlintide for the treatment of obesity have shown weight loss of 3.5 kg over 16 weeks in 204 obese subjects (160 without diabetes and 44 with non–insulin-treated type 2 diabetes). Further evaluation of this drug as a therapy specifically for the treatment of obesity is awaited.

Peptide YY

$PYY_{3–36}$, the major circulating form of PYY, is co-secreted from intestinal L-cells with GLP-1 and OXM. Although there was initially some contention regarding the effects of $PYY_{3–36}$ on energy intake in animal models (55), a number of research groups have demonstrated that peripheral $PYY_{3–36}$ inhibits food intake and reduces body weight gain in several species (56–63). The minimization of stress, which can itself result in an inhibition of food intake, is vital to observe the anorectic effect of $PYY_{3–36}$ in rodents (27,64). This has led some to question the utility of $PYY_{3–36}$ as a basis for human therapy (55). However, the evidence from human studies to date is encouraging.

In the first clinical study of the intravenous administration of $PYY_{3–36}$, spontaneous food intake was reduced by 30% at plasma levels similar to those seen physiologically (56). A further recent study observed a dose-dependent reduction in appetite and food intake in response to intravenous $PYY_{3–36}$ administration in normal-weight volunteers, although nausea occurred at higher doses (63).

It has been suggested that obesity is a $PYY_{3–36}$–deficient state, with lower basal levels and a blunted postprandial response (65). $PYY_{3–36}$ "replacement" would therefore seem an apposite therapy for obesity, and there is evidence that obese individuals retain sensitivity to its appetite-suppressant effects (58). However, the therapeutic potential of $PYY_{3–36}$ as an anti-obesity treatment is currently unknown, since there are limited data regarding the effect of repeated doses of $PYY_{3–36}$ on body weight in humans.

Two drug companies are engaged in developing $PYY_{3–36}$ for the treatment of human obesity. Amylin Pharmaceuticals has completed Phase I trials of its investigational compound AC162352, although no data are in the public domain regarding its efficacy. Nastech Pharmaceutical Company (Bothell, WA), in collaboration with Merck (Whitehouse Station, NJ), has recently completed Phase I trials of $PYY_{3–36}$ delivered via the intranasal route. Acutely, $PYY_{3–36}$ caused significant reductions in visual analog appetite scores, and there was a trend toward a dose-dependent reduction in food intake at a test meal (66). The most significant adverse effect noted was nausea, but this was seen in those subjects with the highest plasma levels of $PYY_{3–36}$ after administration. Furthermore, preprandial use of the nasal spray for 6 days in 37 obese volunteers was associated with significant reductions in daily caloric intake that were sustained over the study period. Thrice-daily administration of the peptide yielded a reduction in caloric intake of 2,713 kJ and weight loss of 0.6 kg after 6 days of treatment. The results of more extensive trials are awaited.

Pancreatic polypeptide

Sharing some common structural features with $PYY_{3–36}$, pancreatic polypeptide is principally secreted by a population of cells located at the periphery of pancreatic islets. It is released into the circulation in a biphasic manner in response to nutrient ingestion and is subject to control by the vagus nerve and a number of other factors (67).

The role of pancreatic polypeptide in the regulation of energy balance is unclear. Studies have shown that circulating levels are reduced in the context of obesity, and there is a reduced second phase release after a meal (68), whereas in anorexic patients, levels are elevated (69). However, these findings have not been universally replicated (70,71).

PP reduces food intake when administered to rodents and humans (72–74). It remains to be evaluated whether this effect is preserved in obese humans. Work in individuals with Prader-Willi syndrome, characterized by overeating and morbid obesity, is encouraging (75), but not necessarily applicable to the more general nonsyndromic obese population. However, the observation that a single infusion of pancreatic polypeptide caused a measurable effect on food intake as long as 24 h afterward in normal-weight volunteers (74) suggests that pancreatic polypeptide may have potential as a long-term suppressor of appetite.

CONCLUSIONS

— Even the modest weight loss resulting from the use of currently available therapies, such as sibutramine, rimonabant, and orlistat, can result in improvements in health and life expectancy (4,6). However, projections of future trends in the prevalence of overweight and obesity underline the urgent need for more effective treatments if the attendant socioeconomic consequences are to be lessened.

The mechanisms of postprandial satiety are still being characterized. Satiety factors secreted by the GI tract appear to occupy an important position in meal termination and the limitation of meal size. Their use as a basis for therapy in obesity therefore promises efficacy with minimal adverse effects.

Nevertheless, the therapeutic development of gut peptides is not without its difficulties. As indicated above, the short half-life of many native gut peptides necessitates unwieldy and inconvenient administration regimens (42,76). The use of stable analogs and novel methods of drug delivery, thus avoiding the need for subcutaneous injection or infusion, are two means by which this issue may be circumvented. The former is exemplified by the GLP-1 receptor agonists exenatide and liraglutide and the latter by interest in nasal delivery of $PYY_{3–36}$. Orally stable preparations of gut peptides remain some way off (77,78), although the development of nonpeptide receptor agonists offers a potentially fruitful alternative avenue.

Several gut hormones cause nausea in a proportion of patients receiving therapy, and this has limited the usefulness of GLP-1–based therapies to some extent (35). Satiety and nausea likely lie at different points along a spectrum of reactions to GI stimuli, and gut peptide–regulated pathways may mediate aspects of both responses (79–81). Although problematical, the application of dose-escalation regimes provides one possible solution and would not be dissimilar to the manner in which patients are commenced on other commonly used therapies such as metformin.

Perhaps a greater obstacle to the entry of GI hormone–based therapies lies in considerations of efficacy. The regulation of food intake is complex, and although its role is significant, the gut-brain axis operates alongside other components including CNS reward pathways, input from higher centers, and societal and environmental influences. The homeostatic system has developed with a high degree of in-built redundancy to guard against starvation, and this is signified by the discontinuation of development of the cholecystokinin receptor agonist 181771 by GlaxoSmithKline (Brentford, Middlesex, U.K.) after the results of clinical trials made it commercially nonviable. Similar concerns have been raised over $PYY_{3–36}$ (55).

However, individual gut peptides are not released in isolation in response to nutrient ingestion. Rather, there is a coordinated release of a number of GI hormones, which act additively in orchestrating efficient nutrient absorption and meal termination (22). It therefore

seems not unreasonable to propose that in the therapeutic targeting of appetite regulation, polypharmacy with a number of therapies might maximize clinical effect while minimizing side effects, mirroring trends in the management of other chronic conditions such as hypertension (82). Furthermore, the development of an effective gut hormone–based therapy will not absolve patients from responsibility for their own lifestyle. As with current medical therapies for obesity, the greatest weight loss is likely to be seen within the context of a multidisciplinary approach.

What then of the original question, "Can gut hormones reduce appetite and prevent obesity?" The answer at present seems to be a cautiously optimistic "yes." The etiology of obesity is complex and multifactorial. This coupled with our incomplete understanding of all the nuances and intricacies of appetite regulation will likely mean that no single treatment approach will be a panacea for the public health and economic challenges that are already starting to make themselves felt (83). Investment in a strategy that involves lifestyle, behavioral, public health, medical, and, where appropriate, surgical interventions would appear to be the most practical course to adopt. Within that framework, by exploiting the body's own satiety signals, drugs based on the actions of gut hormones will undoubtedly have a crucial role to play.

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