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# Gut hormones and the regulation of energy homeostasis

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**Food intake, energy expenditure and body adiposity are homeostatically regulated. Central and peripheral signals communicate information about the current state of energy balance to key brain regions, including the hypothalamus and brainstem. Hunger and satiety represent coordinated responses to these signals, which include neural and hormonal messages from the gut. In recent years our understanding of how neural and hormonal brain–gut signalling regulates energy homeostasis has advanced considerably. Gut hormones have various physiological functions that include specifically targeting the brain to regulate appetite. New research suggests that gut hormones can be used to specifically regulate energy homeostasis in humans, and offer a target for anti-obesity drugs.**

Energy balance is a homeostatic system. Although malfunctions of this system can cause obesity[1], the relatively recent increase in the incidence of obesity is not thought to be the result of specific defects, but of a regulatory system unable to cope with the current context of cheap, high-energy foodstuffs, mechanized transport and non-manual labour. Commandeering elements of this regulatory system might provide the best opportunity for us to combat obesity.

The main brain regions responsible for the regulation of energy homeostasis are the hypothalamus and the brainstem. A number of current obesity therapies target central neurotransmitters in order to reduce body weight, as did several past treatments. Sibutramine reduces appetite by potentiating noradrenaline and serotonin signalling, and rimonabant achieves the same goal by antagonizing central type-1 cannabinoid receptors. Sibutramine and rimonabant both produced a modest reduction in body weight in clinical trials[2]. However, the neurotransmitter systems affected by such drugs do not exclusively regulate appetite, so there is a high likelihood of side effects. For example, sibutramine can cause hypertension[3], and there are concerns that rimonabant might cause psychological and reproductive problems[4,5].

The hypothalamus and brainstem receive neural and hormonal signals from the periphery that encode information about acute nutritional state and adiposity. The adipose hormone leptin signals to the brain the size of adipose stores but does not show great promise as an anti-obesity agent. Most obese humans already have high circulating levels of leptin and are resistant to its metabolic effects[6]. So far, no means of preventing this resistance has been validated.

However, shorter-term signals can influence food intake. Postprandial satiety and the hunger felt before a meal are not thought to be primarily mediated by leptin. Neural and endocrine signalling from the gut are believed to have important roles in this short-term regulation of appetite. Mechanoreceptors and chemoreceptors in the gastrointestinal tract signal through the vagal nerve to the brainstem. These neural signals are centrally integrated with those transmitted by a number of hormones released from the gastrointestinal tract and its associated structures. These gut hormones then stimulate ascending vagal pathways from the gut to the brainstem or act directly on neurons in the brain.

This review examines the role of specific gut hormones in the regulation of energy homeostasis. We conclude that gut hormones have physiological and pathophysiological roles in appetite regulation, and might represent useful targets for future obesity therapies.

## Gut hormones

The gastrointestinal tract is the body's largest endocrine organ and releases more than 20 different regulatory peptide hormones that influence a number of physiological processes and act on tissues including exocrine glands, smooth muscle and the peripheral nervous system. Most of these hormones are sensitive to gut nutrient content, and short-term feelings of hunger and satiety are believed to be mediated, in part, by coordinated changes in circulating gut hormone levels[7].

### Ghrelin

Ghrelin is a peptide hormone released into circulation from the stomach that was first discovered as an endogenous ligand for the growth-hormone-secretagogue receptor (GHS-R). Ghrelin is composed of 28 amino acids and is uniquely modified by the addition of an octanoyl group to the serine residue at position three. This acylation is necessary for ghrelin to bind to the GHS-R and to cross the blood–brain barrier[8]. Great excitement heralded reports that ghrelin increased appetite. Although a number of circulating factors, including the adipose hormone leptin and several gut hormones, have been reported to reduce food intake, ghrelin is the only known factor to increase appetite through the circulation. The pattern of ghrelin release suggests that it governs feelings of hunger. Circulating ghrelin levels are increased by fasting, and fall after a meal. Central or peripheral administration of acylated ghrelin to rats acutely stimulates food intake and growth hormone release, and chronic administration causes weight gain. Intravenous infusion or subcutaneous injection of ghrelin to humans increases both feelings of hunger and food intake. Ghrelin is often referred to as the 'hunger hormone'[8].

It has been reported that peripheral ghrelin administration reduces fat use[9] and that chronic central ghrelin infusion increases the expression of enzymes that promote fat storage in adipose tissue[10]. The metabolic effects of ghrelin might not, therefore, be entirely dependent on increased food intake.

Initial reports suggested that *Ghs-r*-knockout and ghrelin-knockout mice lacked important alterations in feeding behaviours and adiposity. However, it has since been discovered that models of disrupted ghrelin

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signalling can show complex energy homeostasis-related phenotypes. *Ghs-r*-knockout mice and male ghrelin-deficient mice show resistance to diet-induced obesity when supplied with a high-fat diet early in life. Ghrelin-deficient mice also show altered metabolic fuel preference, favouring fat as a source of energy to a greater extent than wild-type controls when fed a high fat diet[11]. Other studies have found that diabetic ghrelin-knockout mice show attenuated hyperphagia[12], and that loss of ghrelin attenuates diabetes in the *ob/ob* obese mouse[13].

The idea of blocking ghrelin signalling with GHS-R antagonists is of interest as a means of preventing obesity. A GHS-R antagonist has been reported to reduce food intake in fasted mice and an RNA Spiegelmer (an L-oligonucleotide designed to bind specifically to a particular molecule) to inhibit ghrelin action *in vitro* and *in vivo*[11]. Recently, it has been demonstrated that vaccinating rats against ghrelin can reduce weight gain[14]. However, it may be unwise to use a similarly irreversible technology in humans, and it remains to be shown whether blocking ghrelin signalling is a viable long-term obesity therapy for humans.

Ghrelin agonists might be useful in the treatment of specific patient groups with anorexia. Acute ghrelin administration can stimulate appetite in cancer patients with appetite loss[15] and in dialysis patients with malnutrition[16], and has also been shown to increase gastric emptying in diabetic patients with gastroparesis[17]. Thus anorexic patients might benefit from the orexigenic effects of chronic ghrelin administration, but this remains to be demonstrated. The question of possible side effects would also need to be addressed before ghrelin could be used as a therapy[18]. Interestingly, it has recently been reported that peripheral ghrelin administration can also modify hypothalamic plasticity[19] and hippocampal neuron formation[20].

The gene that encodes ghrelin has also been found to encode another peptide known as obestatin. Obestatin was originally reported to reduce food intake when administered peripherally or intracerebroventricularly, and to reduce body weight gain when administered peripherally[21]. These effects were proposed to be mediated by the orphan G-protein-coupled receptor, GPR39. Much speculation followed as to why the same gene would produce an orexigenic and an anorectic signal. However, subsequent reports have not supported the initial findings and suggest that obestatin might not signal through GPR39 or have a role in the regulation of food intake[22–24].

## Peptide YY

Peptide YY (PYY) is a gut hormone that is related to neuropeptide Y (NPY). Both peptides have the PP fold structural motif and exert their effects through the Y family of receptors. Full-length PYY binds with similar affinity to all of the Y receptors. However, most circulating PYY-immunoreactivity is in the amino-terminally truncated form, $PYY_{3–36}$, which preferentially binds to the Y2 receptor (Y2R).

PYY is found in L cells throughout the length of the gut, although it is present at higher concentrations in more distal sections. PYY is released into the circulation after a meal and is reduced by fasting. Acute peripheral administration of $PYY_{3–36}$ reduces food intake in rodents and humans[25]. These findings were initially contentious, with a number of independent laboratories being unable to repeat aspects of the study[26]. Stress can reduce baseline food intake, making it difficult for anorectic agents to further suppress appetite. Peripheral $PYY_{3–36}$ administration does not reduce food intake in rodents not acclimatized to experimental procedures, or in rats presented with a new environment[27,28]. The susceptibility of the anorectic effects of $PYY_{3–36}$ to these mild stressors might explain the difficulties others initially had in replicating the original $PYY_{3–36}$ results. Subsequent studies have confirmed that $PYY_{3–36}$ acutely inhibits feeding in rodents and primates[29–34]. The anorectic effects of $PYY_{3–36}$ are thought to be mediated by Y2R, because they are attenuated by Y2R antagonists[35] and abolished in *Y2r*-knockout mice[25]. *Pyy*-knockout mice have disrupted energy homeostasis, suggesting that the PYY system does have a physiological role in its regulation[36,37].

Obese humans show normal sensitivity to the anorectic effects of $PYY_{3–36}$, and circulating levels of PYY are not raised in the obese, in contrast to leptin levels[38]. Some studies have reported that obese individuals have lower fasting and postprandial levels of circulating PYY[38–40] but others have found no significant differences between PYY levels in the lean and the obese[41,42], suggesting that a reduction in PYY release is unlikely to be involved in the aetiology of obesity.

High doses of $PYY_{3–36}$ have been reported to cause conditioned taste aversion in animals[43,44] and nausea in humans[45]. This effect is worsened by rapid administration. Steady low-dose intravenous infusion of $PYY_{3–36}$ can reduce food intake without aversive effects in rats[44] or nausea in humans[25,38,40].

The efficacy of chronically administered $PYY_{3–36}$ in reducing food intake is vital to its use as a possible obesity drug. Different chronic administration protocols have drawn different conclusions[25,26]. Intravenous $PYY_{3–36}$ administration has more consistently supported its anorectic effects, suggesting that administrative route is an issue[31,46]. It has recently been shown that intermittent intravenous administration of $PYY_{3–36}$ can cause long-term reductions in food intake, body weight and adiposity in rats. However, dosage pattern seems to be crucial in producing sustained reductions in food intake and body weight[47].

## Cholecystokinin

The role of cholecystokinin in the exocrine pancreas and gallbladder was long established when, in 1973, it became the first gut hormone to be shown to influence food intake. Subsequent studies confirmed these findings in rodents and humans. Cholecystokinin is released postprandially from the small intestine, and seems to reduce food intake through cholecystokinin 1 (CCK1) receptors on the vagal nerve. CCK1 receptor antagonists have been reported to increase food intake in rodents and humans, and the Otsuka Long-Evans Tokushima Fatty rat, which lacks the CCK1 receptor, is hyperphagic and obese, suggesting that cholecystokinin has a physiological role in the regulation of food intake[48]. However, continuous infusion of cholecystokinin fails to influence food intake after 24 hours, and although intermittent administration does reduce food intake acutely, this effect is compensated for by increased food intake between injections[49–51]. It may be that a stringent administration regimen is required to reduce body weight. It has been reported that cholecystokinin cannot activate the appropriate vagal circuits at endogenous circulating concentrations, suggesting that the actions of cholecystokinin on food intake might be paracrine or neurocrine rather than endocrine[52]. High doses of cholecystokinin cause nausea, but lower doses, which do not, can still reduce food intake. Hunger, satiety and nausea have been suggested to represent points on the same physiological spectrum[53]. Nausea is associated with high-dose administration of all of the anorectic gut hormones and analogues, including $PYY_{3–36}$ (ref. 45), glucagon-like peptide-1, exendin-4 (ref. 54) and oxyntomodulin[55].

## Pancreatic polypeptide

Pancreatic polypeptide is a member of the PP fold peptide family that is synthesized and released from the endocrine pancreas. Pancreatic polypeptide shows preferential binding to the Y4 and Y5 receptors. Similarly to $PYY_{3–36}$, it is released after a meal and reduces appetite. Acute peripheral administration to mice and humans reduces food intake[56,57], and chronic administration reduces body weight in *ob/ob* obese mice[58]. No nausea or gastrointestinal distress was reported in the intravenous study investigating feeding effects in humans. The anorectic effects of pancreatic polypeptide might occur partly as a result of delayed gastric emptying[57,59]. The food intake and fat mass of transgenic mice overexpressing pancreatic polypeptide are reduced, but such mice also show reduced gastric emptying[56]. However, at present the physiological role of pancreatic polypeptide in energy homeostasis is unknown.

## Amylin

Amylin, which is also known as islet amyloid polypeptide, is a 37-residue member of the calcitonin peptide family that is released together with insulin from pancreatic β-cells in response to food ingestion. Although its main function is thought to be in glucose homeostasis,

given peripherally at supraphysiological levels amylin can reduce food intake. Administration of the amylin agonist pramlintide reduces body weight in type 1 and 2 diabetics by between 0.5 and 1.4 kg for up to 1 year[60,61].

### Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP) is a 42-residue peptide released from K cells in the duodenum after food ingestion. GIP has not been reported to have an acute influence on food intake. However, GIP-receptor-knockout mice are resistant to obesity when fed a high-fat diet. The reason for this resistance is unclear and there has been speculation that it might reflect a direct effect on adipocytes rather than on central appetite-regulating circuits[62,63].

### Glucagon-like peptide-1

The same gut endocrine cell type that synthesizes PYY also synthesizes a large precursor protein known as preproglucagon. This is processed further to produce a number of biologically active peptides, including glucagon, glucagon-like peptide-1, glucagon-like peptide-2 (GLP-2) and oxyntomodulin.

Glucagon-like peptide-1 exists in several forms, but the most common circulating form is glucagon-like peptide-$1_{7-36amide}$ (GLP-1). GLP-1 is released into the circulation after a meal and is a potent incretin — central or peripheral administration strongly stimulates insulin release. Intracerebroventricular administration of GLP-1 potently reduces food intake in rodents, and peripheral administration of GLP-1 inhibits appetite in animals and humans[54].

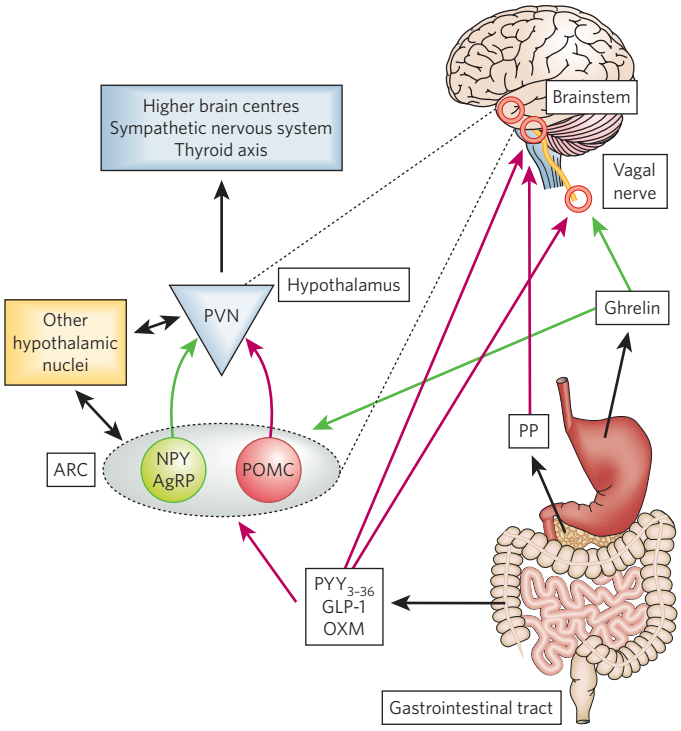


**Figure 1 | The pathways by which gut hormones regulate energy homeostasis.** $PYY_{3-36}$, GLP-1 and oxyntomodulin (OXM) are released from gut L cells after a meal. They can directly stimulate anorectic pathways in the hypothalamus and brainstem, and may also act through the vagus nerve. Pancreatic polypeptide (PP) is released from the pancreas after a meal and is thought to reduce appetite by directly signalling to neurons in the brainstem. Ghrelin is released from the stomach with fasting and might signal directly to the hypothalamus or through the vagus nerve to stimulate food intake. The ARC is important in integrating gut hormone energy homeostasis signals. NPY/AgRP neurons and POMC neurons signal to the PVN and other hypothalamic nuclei to increase or decrease appetite, respectively. Green arrows indicate orexigenic signals and red arrows indicate anorectic signals.

The saliva of the Gila monster lizard, *Heloderma suspectum*, contains a peptide known as exendin-4, which is a potent GLP-1 receptor agonist. A truncated form of this peptide, exendin 9–39, acts as a competitive antagonist at the same receptor. Acute intracerebroventricular administration of exendin 9–39 increases food intake, and chronic administration increases body weight. It seems, therefore, that endogenous peripheral GLP-1 might form part of the physiological mechanism to reduce appetite and food intake after a meal. However, the food intake and body weight of GLP-1-receptor-knockout mice are normal[54].

Clinical trials have shown that exendin-4 (also known as exenatide, and marketed as Byetta) is useful in the regulation of glucose homeostasis in people with type 2 diabetes mellitus. Interestingly, in phase III 30-week clinical trials, exenatide significantly reduced body weight in treated diabetics[64–66]. Although nausea is a relatively common side effect of the treatment, as with $PYY_{3-36}$, it does not seem to be intrinsically linked to the effects on appetite [54]. These results also suggest that even if peripheral GLP-1 does not physiologically regulate appetite, the GLP-1 system might be used to reduce body weight using a peripherally administered drug.

### Glucagon-like peptide-2

GLP-2 is found in the brain and inhibits food intake when administered centrally. Peripheral circulating GLP-2, however, is primarily involved in stimulating gastrointestinal motility, absorption and growth, and does not influence appetite physiologically[67].

### Oxyntomodulin

Oxyntomodulin is also a product of the preproglucagon precursor molecule and, like GLP-1, is released after a meal. Also like GLP-1, it reduces food intake when centrally administered to rats and peripherally administered to rodents and humans[68,69]. This is not surprising — oxyntomodulin seems to signal through the GLP-1 receptor: its anorectic effects are blocked by exendin 9–39 (ref. 68) and abolished in GLP-1-receptor-knockout mice[70]. It also causes a similar pattern of neuronal activation to GLP-1 after peripheral administration[70].

However, there is evidence that oxyntomodulin does not merely mirror the activities of GLP-1. Oxyntomodulin has a roughly 50-fold lower affinity for the GLP-1 receptor than GLP-1, but seems to reduce food intake with similar potency[71]. Although the administration of exendin 9-39 directly into the hypothalamic arcuate nucleus (ARC) has been reported to block the anorectic effects of oxyntomodulin, it does not block those of GLP-1 (ref. 68). Oxyntomodulin and GLP-1 might therefore have different roles in energy homeostasis, perhaps mediated by their different pharmacological properties or by tissue-specific signalling factors.

Chronic central or peripheral oxyntomodulin administration reduces weight gain in rats[68,72]. In addition, chronic oxyntomodulin treatment causes rats to lose more weight than pair-fed controls, suggesting that oxyntomodulin increases energy expenditure[72]. Chronic administration of oxyntomodulin can also cause weight loss in humans. In a 4-week study in which oxyntomodulin or saline were self-administered by overweight and obese volunteers, the oxyntomodulin-treated group demonstrated an average weight loss of 0.45 kg per week more than the saline-treated group[55]. As in rats, oxyntomodulin might increase energy expenditure in humans. Self-administration of oxyntomodulin by overweight and obese volunteers for 4 days significantly increased activity-related energy expenditure, as assessed by continuous electronic movement monitoring[73]. Further work is required to investigate whether oxyntomodulin is effective over long administration periods.

## Gut hormones signal to central appetite circuits

Gut hormones can activate circuits in the hypothalamus and brainstem, the main central nervous system centres responsible for the regulation of energy homeostasis. For many gut hormones, the precise mechanisms of central action are unknown or contentious. A number of gut hormones also act as neurotransmitters in the brain, where they do not necessarily serve the same functions as in the periphery, making it difficult to tease out their endocrine effects.

The ARC is believed to be important in integrating peripheral circulating energy homeostasis signals. ARC neurons expressing NPY and agouti-related peptide (AgRP) signal to increase appetite, and pro-opiomelanocortin (POMC)-expressing melanocortin neurons signal to reduce appetite. The hypothalamic paraventricular nucleus (PVN) is thought to be a critical target of these ARC neurons. The PVN signals to higher brain centres and the sympathetic nervous system, and regulates the thyroid axis. ARC neurons also project to other hypothalamic nuclei that signal, in turn, to the ARC and the PVN to modulate their activity[6] (Fig. 1).

Ghrelin activates NPY neurons in the ARC, and blocking NPY or agouti-related protein (AgRP) signalling abolishes ghrelin's orexigenic actions[8]. Early evidence suggested that $PYY_{3–36}$ reduced food intake through ARC melanocortin neurons[25,27,30]. However, $PYY_{3–36}$ still reduces food intake in mice with disrupted melanocortin signalling, and has been reported to inhibit melanocortin neurons in further experiments, suggesting that $PYY_{3–36}$ reduces food intake by another, as yet unknown, mechanism[27,30,74,75].

There are extensive reciprocal connections between the hypothalamus and the brainstem, and energy intake is coordinated on the basis of information received by both regions[6,54,76]. In the brainstem, the nucleus of the solitary tract (NTS), area postrema and dorsal motor nucleus of the vagus have all been implicated in the regulation of energy homeostasis. Peripheral GLP-1 administration activates neurons in the brainstem and in the hypothalamus[54,70,77]. Peripheral $PYY_{3–36}$ administration has been reported to increase c-Fos immunoreactivity in the area postrema and the NTS. Y2R agonists can inhibit excitatory postsynaptic currents in NTS neurons *in vitro*[78], and in dorsal motor nucleus neurons *in vivo* and *in vitro*[79]. In addition, transecting brainstem–hypothalamic pathways in rodents blocks $PYY_{3–36}$-induced anorexia[80]. The brainstem is therefore likely to have some role in $PYY_{3–36}$ signalling. Pancreatic polypeptide has been suggested to act by directly activating Y4-receptor-expressing neurons in the area postrema[56].

Gut hormones can signal to the brainstem through the vagal nerve. There is strong evidence that this is how cholecystokinin mediates its effects on food intake[52]. The physiological relevance of vagal signalling to other gut hormone systems is less certain. Vagotomy has been reported to block or attenuate the orexigenic effects of ghrelin[81,82] and the anorectic effects of $PYY_{3–36}$ (refs 77, 80), GLP-1 (ref. 77) and pancreatic polypeptide[58]. However, blocking vagal signalling alters the regulation of energy homeostasis and gastrointestinal function considerably, so it is difficult to prove that the effects of vagotomy are specific.

Hypothalamic, brainstem and vagal signalling all have a role in appetite control, but further research is required to determine how each of these signals is weighted and integrated.

## The role of gut hormones in energy homeostasis

Gut hormones have a number of functions, including the regulation of blood glucose levels, gastrointestinal motility and growth, exocrine secretion and adipocyte function (Fig. 2). These functions are often integrated with their actions in the central regulation of appetite circuits, and the gut hormones themselves interact to stimulate or suppress the release of other hormones. For example, cholecystokinin stimulates PYY release[83], whereas oxyntomodulin, $PYY_{3–36}$ and insulin suppress ghrelin levels[25,68,69,84]. Interestingly, there is evidence that insulin and glucagon can suppress ghrelin through central mechanisms[85,86]. Although the system is complex, by examining the wide-ranging effects of gut hormones on appetite it is possible to discern simple themes.

There seem to be three major roles for gut hormones in appetite regulation. First, the release of gut hormones can modulate normal hunger and satiety. Circulating ghrelin levels increase before a meal and correspond to hunger pangs. A number of anorectic gut hormones are released postprandially as satiety signals. However, these increases in circulating concentrations are often small, and it seems likely that satiety might represent the cumulative effects of a number of submaximal gut hormone responses. Gut hormones might thus have additive effects on appetite[87,88].

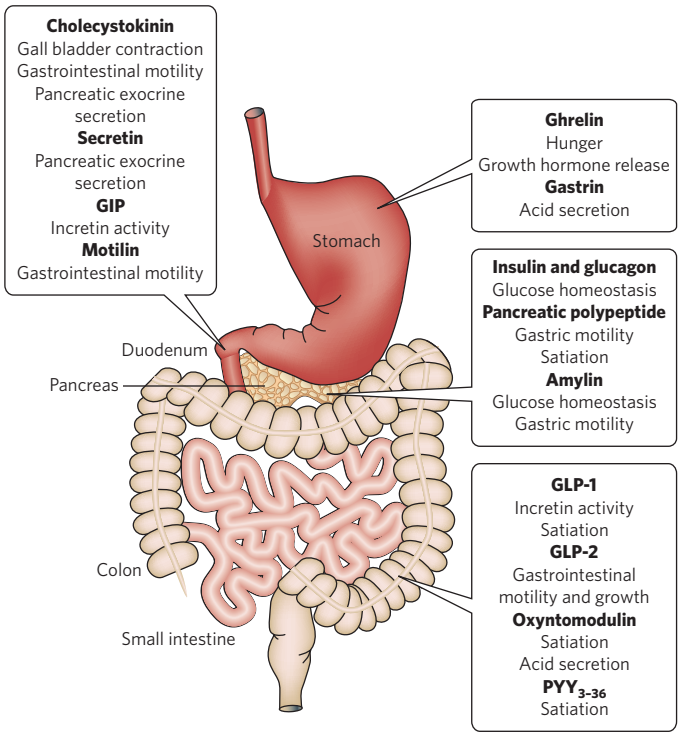


**Figure 2 | A schematic diagram of the gastrointestinal tract illustrating where particular gut hormones are concentrated and their major putative functions.** The gastrointestinal tract releases a number of hormones, including ghrelin and gastrin from the stomach, insulin, glucagon, pancreatic polypeptide and amylin from the pancreas, cholecystokinin, secretin, GIP and motilin from the small intestine, and GLP-1, GLP-2, oxyntomodulin and $PYY_{3–36}$ from the large intestine. These hormones signal to the periphery and to the central nervous system to regulate a number of biological processes.

Second, gut hormones may reduce food intake in patients with specific gut diseases, perhaps as an adaptation to reduce further stress on the gut. A number of anorectic gut hormones are elevated in gut disease[89–91]. This might be a specific function of gut hormones in the distal gastrointestinal tract. Enteroendocrine cells might, for example, release gut hormones at high level in response to undigested foodstuffs, the presence of which would suggest that the function of the upper gastrointestinal tract is compromised. Consistent with this hypothesis, gut bypass surgery is associated with elevated anorectic gut hormone concentrations, which are believed to be at least partly responsible for the reduction in appetite in gut bypass patients[39,92–95].

Third, very high levels of gut hormones may be released to generate conditioned taste aversion and nausea in response to the ingestion of harmful substances. The seeming profligacy of the L cell, which releases three distinct anorectic hormones ($PYY_{3–36}$, GLP-1 and oxyntomodulin), makes more sense if we consider the complex information these hormones might encode about short-term energy balance and the state of the gastrointestinal tract.

## The future of gut hormones in appetite control

Current drugs are insufficiently efficacious to cope with the obesity epidemic sweeping the developed world. At present, the most effective treatment for obesity is bariatric surgery. However, its cost and associated mortality make it impractical to treat rising numbers of obese patients, and it is increasingly reserved for only the morbidly obese. Gut hormones are molecules designed by evolution to be 'administered' peripherally to specifically target appetite circuits in the central nervous system. Although the physiological role of a particular gut hormone in energy homeostasis can be difficult to prove conclusively, administration of exogenous gut hormones can certainly influence food intake in

humans. Hijacking such systems to tackle obesity might prove effective, even if gut hormones do not significantly regulate appetite on a day-to-day basis.

The physiological and pathophysiological roles of gut hormones in energy balance therefore remain to be defined. However, as the obesity epidemic rumbles on, so do the efforts to sate hunger. Gut hormones may yet prove that the way to a man's brain is through his stomach. ■


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