Gut feeling – the secret of satiety?

Steve Bloom, Katie Wynne and Owais Chaudhri

ABSTRACT – The worsening global epidemic of obesity has increased the urgency of research aimed at understanding the mechanisms of appetite regulation. An important aspect of the complex pathways involved in modulating energy intake is the interaction between hormonal signals of energy status released from the gut in response to a meal, and appetite centres in the brain and brainstem. In particular, the gut peptides cholecystokinin, peptide YY, glucagon-like peptide 1, oxyntomodulin and pancreatic polypeptide have been implicated in signaling satiety post-prandially. The ultimate goal of work in this field is the development of effective treatments for obesity, and manipulation of these gut–brain axes offers potentially useful strategies for the conquest of this significant cause of morbidity and mortality and future burden on healthcare systems worldwide.

KEY WORDS: appetite, cholecystokinin, ghrelin, glucagon-like peptide 1, gut peptides, hypothalamus, oxyntomodulin, pancreatic polypeptide, peptide YY

The World Health Organization estimates that over a billion adults are currently overweight worldwide, and the increasing prevalence of obesity in younger generations points to a worsening of this epidemic in the future, resulting in an inevitable strain on healthcare systems. Obesity is causally associated with cardiovascular disease, non-insulin dependent diabetes mellitus, obstructive pulmonary disease and certain cancers, a disease burden which currently costs the National Health Service over half a billion pounds every year. Although even modest weight loss can reduce the morbidity and mortality associated with diabetes and cardiovascular disease, public health campaigns to improve diet and promote exercise have not prevented the nation's weight from increasing exponentially, and initiatives aimed at prevention are hampered somewhat by charges of excessive 'nannying'.

While drugs such as orlistat and sibutramine are moderately effective in the short-term, with some authors suggesting that 50–80% of patients achieve greater than 5% weight loss,[1] their effects are relatively short-lived and their usefulness is limited by side effects. More durable weight loss has been achieved through gastrointestinal surgery, but resource limitations and complications restrict its use to motivated patients suffering from morbid obesity. The mechanism by which surgery effects its weight loss is thought to involve a permanent loss of appetite,[2] and this appetite loss may be secondary to a change in the signals of energy balance released from the gut. Over the last decade, our understanding of these signals has advanced substantially. The regulation of appetite and food intake is dependent on complex interactions between higher cognitive centres, more primitive areas of the brain and the periphery, and the gut–endocrine system plays an important role in inducing and maintaining the feeling of satiety. Although signals involved in energy homeostasis have, in evolutionary terms, developed to maintain body weight, interactions between the environment and genetic factors can result in obesity. Manipulation of the gut–brain endocrine axis to overcome this failure of homeostasis may provide a new approach in the design of anti-obesity drugs.

The gut and satiety

Gut peptides are released in response to a meal and these hormones optimise the digestive process and signal a change in energy status that influences both physiology and behaviour. Previous work has identified the gut hormones cholecystokinin, peptide YY (PYY), glucagon-like peptide 1 (GLP-1), oxyntomodulin and pancreatic polypeptide as factors which influence post-prandial satiety. The main appetite-related sites of action of these peptides are certain key areas of the hypothalamus (such as the arcuate and the dorso-medial nuclei), the brainstem (and in particular, the nucleus of the solitary tract), and the vagus nerve. The interrelationships between the nervous system, the seat of appetite, and the endocrine intermediaries deployed by the gastrointestinal tract, the site of nutrient absorption, are complex. However, an understanding of these interactions, the main aspects of which are illustrated in Fig 1, is a necessary precursor to the successful development of viable therapies.

Cholecystokinin

Cholecystokinin (CCK) is rapidly released from the gastrointestinal tract post-prandially and plasma

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Key Points

Obesity is a cause of significant morbidity and mortality. Its rising incidence worldwide constitutes a public health crisis

Medical and diet-orientated therapies for obesity have not yielded satisfactory outcomes and although surgical therapy can result in more durable weight loss, it is not a treatment that can be offered to all patients

Our understanding of the influence of the diffuse gastrointestinal endocrine system on energy intake and the control of appetite advanced significantly in the latter decades of the last century

Gut hormones such as peptide YY, glucagon-like peptide-1, oxyntomodulin and ghrelin act at all levels of the brain–gut axis in the maintenance of energy homeostasis and offer potentially fruitful targets for the development of an effective medical therapy for obesity

levels remain elevated for up to 5 hours. Although it is widely distributed within the gastrointestinal tract, the majority is found in cells of the upper small intestine. The stimulatory effect of CCK on gall bladder contraction, pancreatic enzyme release and intestinal motility is well established, as is its inhibitory effect on gastric emptying, but CCK was also the first gut hormone to be implicated in satiety, as it was found to reduce food intake when administered to rodents.[3] Its acute effects in man are similar: an intravenous infusion of the terminal octapeptide reduces both meal size and meal duration.[3]

The usefulness of CCK as a therapeutic agent is, however, likely to be limited by its short half-life; it is ineffective when given more than 30 minutes before a meal and repeated administration does not alter body weight in rats, for although food intake is reduced, meal frequency increases, and so overall intake is unchanged. In fact, when given to rats as a continuous intraperitoneal infusion, the anorectic effect is lost after 24 hours.[4]

Although the therapeutic potential of CCK may seem less than promising, there is evidence that CCK might influence body weight over a more prolonged timescale, perhaps by interacting with long-term signals of adiposity. Studies of specific receptor agonists suggest that the CCK_A receptor mediates the effects of CCK on appetite; chronic administration of CCK_A receptor antagonists or anti-CCK antibodies accelerates weight gain in rodents, though without evidence of significant hyperphagia,[5] whereas the Otsuka Long-Evans Tokushima fatty (OLETF) rat, which lacks CCK_A receptors, is both hyperphagic and obese.[6] These effects of CCK on body weight may be the result of an interaction with leptin, as peripheral administration of CCK potentiates the central effect of leptin on body weight.[4]

The CCK_A receptor is present on the vagus nerve, enteric neurones, the brainstem and the dorso-medial nucleus of the hypothalamus (DMH), and there is evidence that the role of CCK in regulating appetite occurs via both the brainstem and hypothalamus. Peripheral administration of CCK induces localised synthesis of c-fos, a marker of neuronal activation, in brainstem areas, and release of CCK at low concentrations from the gut modulates vagus nerve activity, which then relays satiety signals to the brainstem.[4] CCK may signal nutritional status via the hypothalamus by crossing the blood–brain barrier and acting on receptors expressed in the DMH, where it reduces the level of a potent orexigenic peptide, neuropeptide Y (NPY).[7]

Peptide YY

Gut endocrine cells, particularly those from the distal intestine, release peptide YY $(PYY)_{1–36}$ and a shortened form, $PYY_{3–36}$, post-prandially. PYY levels rise to a plateau 1–2 hours post-ingestion in proportion to the calories ingested, and remain elevated for up to 6 hours. Amongst its actions, PYY increases ileal absorption, slows gastric emptying and delays gall bladder and pancreatic secretions. The truncated form, $PYY_{3–36}$, created by cleavage of the N-terminal residues by dipeptidyl peptidase IV, is thought to be the biologically active species and has been reported to decrease food intake in rodents[8,9] and primates,[10] and reduce food intake and promote satiety in man, an effect which persists even after plasma PYY levels have returned to baseline.[8]

Chronic administration of PYY to rodents results in reduced weight gain[8] and PYY levels are raised in man in conditions associated with weight loss, such as tropical sprue, inflammatory bowel disease, and post-gastrointestinal surgery for obesity. Conversely, fasting PYY levels are suppressed in obese subjects[11] and overweight subjects have a relative deficiency of post-prandial PYY release associated with reduced satiety,[12] although they retain sensitivity to the anorectic effect of exogenous $PYY_{3–36}$;[11] $PYY_{3–36}$ may therefore be a pathogenic factor in their weight gain. With better definition of its effects on body weight in man,

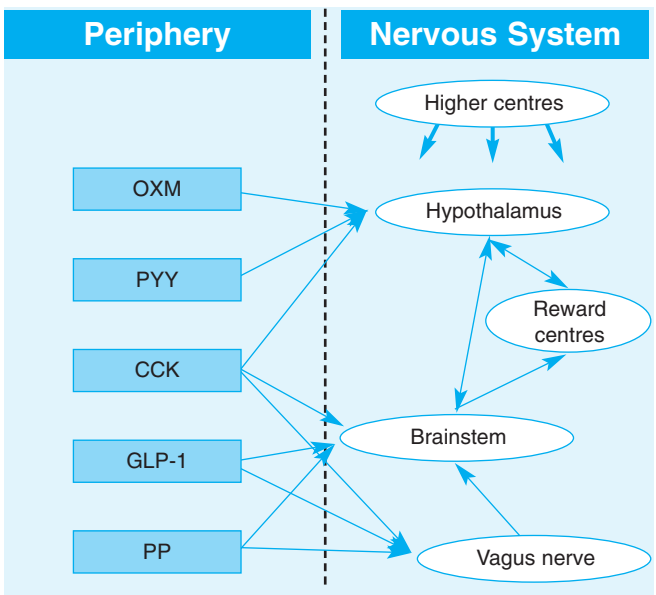

Fig 1. The neuronal sites of action of gut hormones associated with induction and maintenance of a feeling of satiety. CCK = cholecystokinin; GLP-1 = glucagon-like peptide 1; OXM = oxyntomodulin; PP = pancreatic polypeptide; PYY = peptide YY.

$PYY_{3–36}$ might then constitute a good candidate target for an anti-obesity therapy.

$PYY_{3–36}$ crosses the blood–brain barrier freely by non-saturable mechanisms, and the peripheral administration of $PYY_{3–36}$ results in an induction of c-fos in the arcuate nucleus of the hypothalamus in rodents. It has been proposed that here, circulating $PYY_{3–36}$ affects energy homeostasis by acting directly on Y_2 receptors, and in particular, those expressed on NPY neurones.[13] These receptors occur on the pre-synaptic membrane and are thought to inhibit neurotransmitter release. $PYY_{3–36}$ reduces levels of NPY and also increases signalling through anorectic melanocortin neurones.[8] There remains some debate in the literature, however, as to the precise nature of the interaction with these latter neurones and there is some evidence that the melanocortin pathway may not be obligatory for the actions of $PYY_{3–36}$.[9] Despite this, $PYY_{3–36}$ is noted to be ineffective in Y_2 receptor null mice, inferring that NPY signalling is essential.[8] It is also worthy of comment that several investigators have had difficulty in reliably reproducing the anorectic effects of $PYY_{3–36}$ in rodents. This may be secondary to the confounding effects of stress, which can in itself cause a reduction in food intake[9] via actions on the arcuate nucleus.

Glucagon-like peptide

The glucagon-like peptides are products of the pre-proglucagon gene, which is widely expressed in the pancreas, small intestine and nucleus of the solitary tract in the brainstem.[14] Post-translational cleavage of proglucagon by prohormone convertase 1 and 2 results in the generation of glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) and oxyntomodulin in the intestine and brain, whereas glucagon is the primary product in pancreatic tissue (Fig 2).

Gut endocrine cells release GLP-1 after a meal, and GLP-1 then augments post-prandial insulin release, inhibits glucagon release and delays gastric emptying.[4] This integrative role in post-prandial digestion is accompanied by an inhibitory effect of GLP-1 on food intake. Several studies have demonstrated a reduction in food intake and increase in satiety after an intravenous infusion of GLP-1 in healthy subjects, obese subjects, and diabetic patients. Although the effect on food intake seems small when the dosing of GLP-1 mimics post-prandial concentrations of the hormone, a recent meta-analysis of GLP-1 administration has concluded that a dose-dependent reduction in food intake does occur.[15]

Circulating GLP-1 levels and post-prandial GLP-1 release are reduced in obese individuals, and if low GLP-1 contributes to the pathogenesis of obesity, it is not unreasonable to suggest that exogenous GLP-1 might restore satiety and result in weight loss. Injections of subcutaneous GLP-1 administered prior to eating have been found to produce a small, but significant, weight loss in healthy obese subjects over 5 days of treatment. An effect on body weight has also been demonstrated, as a secondary endpoint, in studies of the incretin effect in diabetic patients: a 6-week continuous infusion of GLP-1 resulted in improved glycaemic control and a 2 kg reduction in body weight.[17] The implications for the management of type 2 diabetic patients are obvious. Translating these findings into clinical practice will prove a challenge, but not an insurmountable one. One of the disadvantages of GLP-1 as a potential therapy is its short half-life, as it is rapidly broken down by dipeptidyl peptidase IV. Resistant analogues of the hormone and GLP-1 receptor agonists such as exendin-4, as well as orally active dipeptidyl peptidase IV inhibitors, are currently in various stages of development.

GLP-1 exerts its effects via the GLP-1 receptor, which is present in the nucleus of the solitary tract in the brainstem and the hypothalamus,[3] and GLP-1 may exert its effect on food intake through signalling pathways in both these areas. Indeed, GLP-1 given peripherally to rodents results in c-fos activation in the hypothalamus and brainstem,[18] and GLP-1 administered into the third or fourth ventricle, or into hypothalamic nuclei, reduces calorie intake in rodents. However, transgenic mice lacking the GLP-1 receptor are diabetic, but do not become obese,[18] suggesting that GLP-1, while therapeutically a potentially rewarding target, does not play an indispensable role in energy homeostasis.

Oxyntomodulin

Oxyntomodulin is another product of the preproglucagon gene and is released from the endocrine cells of the small intestine in proportion to nutrient ingestion.[19] One physiological function of oxyntomodulin is to delay gastric emptying and decrease gastric acid secretion, but oxyntomodulin also reduces food intake in rodents when administered peripherally[19,20] or directly into the hypothalamus,[19,21] and exogenous oxyntomodulin induces satiety and reduces food intake in normal-weight human subjects.[22] This effect on appetite may, in part, be explained by the observation that oxyntomodulin administration suppresses the levels of endogenous ghrelin,[20,22] an orexigenic hormone released from the stomach.

As well as these short-term effects on appetite, oxyntomodulin may play a role in the regulation of body weight, and thus be another therapeutic target. Like PYY, oxyntomodulin is raised in conditions associated with weight loss such as tropical sprue, and after jejunoileal bypass surgery. Repeated administration of oxyntomodulin to rodents over seven days reduces body-weight gain and adiposity,[20] and this effect may partly be due to an increase in energy expenditure, as well as a reduction in food intake.[23] It remains to be seen whether oxyntomodulin could represent an effective anti-obesity therapy. However, preliminary results from our laboratory have shown that subcutaneous oxyntomodulin, self-administered pre-prandially three times daily for four weeks by overweight subjects, results in a reduction in food intake and a loss of more than 2% of body weight.

A better understanding of the mechanism of action of oxyntomodulin may shed light on its role as a potential treatment for obesity, but here, again, the current literature raises more questions than it answers. It has been suggested that oxyntomodulin exerts its anorectic effect by signalling through the GLP-1 receptor, as it is ineffective in GLP-1 receptor knockout mice.[24]

Moreover, the administration of a GLP-1 receptor antagonist (exendin$_{9\text{-}39}$) into the cerebral ventricles inhibits the anorectic actions of both centrally administered GLP-1 and oxyntomodulin.[21,25] However, there is some evidence that oxyntomodulin may also signal appetite via an unidentified receptor. The effect of peripherally administered oxyntomodulin is blocked by exendin$_{9\text{-}39}$ administered directly into certain areas of the hypothalamus, but the effect of peripheral GLP-1 is retained despite antagonism of hypothalamic receptors in these areas.[20] Furthermore, human and rodent studies show that GLP-1 and oxyntomodulin both potently reduce food intake, even though the affinity of oxyntomodulin for the GLP-1 receptor is two orders of magnitude lower than that of GLP-1. It is thus possible that oxyntomodulin signals through an alterative pathway that has not been elucidated.

Pancreatic polypeptide

Pancreatic polypeptide (PP) is mainly secreted by cells situated at the periphery of the pancreatic islets, but is also released by the exocrine pancreas and distal gut. Post-prandially, PP is secreted in a biphasic manner in proportion to food intake, and plasma levels remain elevated for up to 6 hours. Peripheral PP administration reduces food intake in lean and genetically obese mice, and also reduces food intake when given as an intravenous infusion in man.[26]

Evidence that PP signalling might have a role in the development of obesity takes the form of demonstrably low endogenous PP levels in obese subjects and a reduced second-phase release after a meal. Reduced basal and blunted post-prandial PP release is also noted in patients with the Prader-Willi syndrome, characterised by hyperphagia and obesity.[26] As expected, circulating PP levels are higher in very lean individuals, such as anorexic subjects. Interestingly, levels of PP are reduced after gastric surgery for obesity, but increased after jejuno-ileal bypass surgery for obesity. Thus, PP might contribute to the loss of appetite and weight that occurs after bypass of the small intestine. However, the relationship between PP and body weight remains controversial and some investigators have shown similar levels in lean and obese patients with stable body weight.[27] A recent prospective study in Pima Indians demonstrated that high fasting baseline levels of PP were positively correlated with weight change, whereas a high post-prandial PP release was negatively correlated with weight change over the subsequent years of follow-up.[28]

There is evidence that artificially increasing PP levels reduces body weight. Mice over-expressing PP to supraphysiological levels are lean and hypophagic with reduced gastric emptying. Repeated administration of PP to genetically obese mice results in reduced insulin resistance and hyperlipidaemia, increased energy expenditure, hypophagia and reduced weight gain.[29] Although PP could represent a possible therapeutic target for the treatment of obesity, the current lack of clarity regarding its effect on appetite and body weight in obese humans diminishes its potential in the absence of more data. Whilst PP administration has resulted in desirable effects on food intake when infused twice daily in subjects with Prader-Willi syndrome,[30] these patients do not provide an ideal model of non-syndromic obesity, and the effectiveness of PP in the vast majority of obese patients remains to be determined.

PP shares significant sequence homology with PYY and both are members of a PP-fold family of peptides which have a 'U-shaped' tertiary structure.[26] This family of peptides bind to a group of G-protein-coupled receptors, classified as Y_1–Y_5.[31] PP has the highest affinity for Y_4 and Y_5 receptors, which are present in both the arcuate nucleus and brainstem. However, evidence suggests several types of Y receptor may be involved in the feeding response to PP. Some of the influence of circulating PP on appetite may be mediated via the vagal pathway to the brainstem.

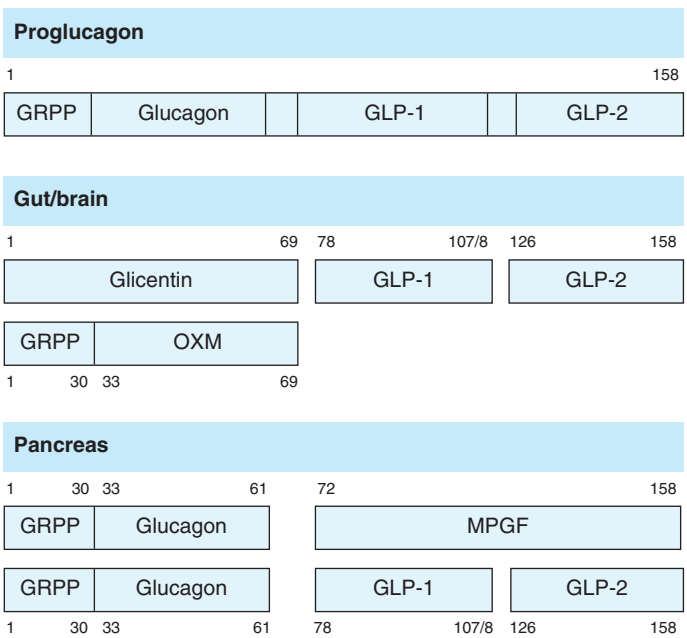

Fig 2. The major cleavage products of proglucagon in the gut and brain, and in the pancreas. GLP-1 = glucagon-like peptide 1; GLP-2 = glucagon-like peptide 2; GRPP = glicentin-related pancreatic peptide; MPGF = major proglucagon fragment; OXM = oxyntomodulin. Numbers refer to amino acid residues.

The brain and satiety

Once a meal is ingested, satiety hormones are released from the gut in a coordinated manner and contribute both to effective digestion and a feeling of fullness. As described above, central circuits in the brain integrate these satiety signals, along with important signals of long-term energy status, such as leptin and insulin, in order to produce a coordinated response to the change in nutritional status.

The hypothalamus and brainstem are important regions regulating energy homeostasis, and the arcuate nucleus of the hypothalamus has recently been identified as a region vital for the reception and integration of signals from the periphery. This nucleus is situated at the base of the hypothalamus, and is exposed to the circulation as it is close to the median emi-

nence – a region lacking a complete blood–brain barrier. Peripheral signals of satiety interact with receptors expressed on the arcuate nucleus, and thus alter neuropeptide release from two neuronal populations within the hypothalamus. One population of neurones co-expresses the orexigenic neuropeptides agouti-related peptide (AgRP) and NPY; the other population releases cocaine and amphetamine-regulated transcript (CART) and propiomelanocortin, which inhibit feeding[4] (Fig 3). Propiomelanocortin is a precursor protein which gives rise to α-melanocyte stimulating hormone, an important anorexic neuropeptide which forms part of the melanocortin system, and is antagonised by AgRP. Both of these neuronal populations in the arcuate nucleus project to the paraventricular nucleus and other nuclei involved in energy regulation within the hypothalamus.[4]

The hypothalamus integrates input from the brainstem and corticolimbic regions concerned with sensations of reward. Extensive reciprocal connections exist between the hypothalamus and brainstem, particularly the nucleus of the solitary tract.[4] Like the arcuate nucleus of the hypothalamus, the brainstem is well placed to receive circulating signals, being close to an area with an incomplete blood–brain barrier – the area postrema. In addition, the brainstem receives vagal input from the gastrointestinal tract and afferents from the glossopharyngeal nerve. Projections from the nucleus accumbens to hypothalamic structures such as the arcuate nucleus, paraventricular nucleus and lateral hypothalamic nucleus may also influence the homeostatic mechanisms controlling food intake.[4]

Defects in neuropeptide circuits can deregulate energy homeostasis, resulting in obesity. For instance, up to 5% of severely obese patients have mutations in their melanocortin 4 receptor. However, in most obese individuals there is no single gene defect and although genetic factors certainly predispose to obesity, environmental factors are powerful influences which can override homeostatic mechanisms. Eating palatable food is a pleasurable experience which activates a diffuse network of reward centres, connected by mu-opioid signalling. Structures such as the amygdala and nucleus accumbens are thought to process the feeling of desire for palatable and calorie-dense food.[32] Interaction between the ingestion of palatable food, the activation of reward centres such as the amygdala and nucleus accumbens and subsequent alteration of hypothalamic neuropeptide circuits may be an important mechanism of disordered energy homeostasis.

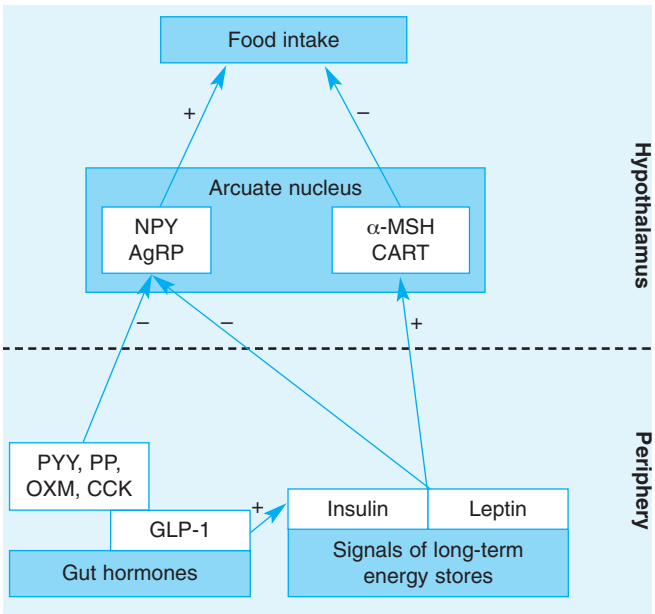

Fig 3. Schematic representation of actions of gut hormones and long-term adiposity signals on neuronal populations in the arcuate nucleus. a-MSH = alpha-melanocyte stimulating hormone; AgRP = Agouti-related peptide; CART = cocaine and amphetamine-regulated transcript; CCK = cholecystokinin; GLP-1 = glucagon-like protein 1; NPY = neuropeptide Y; OXM = oxyntomodulin; PP = pancreatic polypeptide; PYY = peptide YY. + signifies net stimulation; – signifies net inhibition.

Future direction

Obesity is a disease which adversely affects the cardiovascular system, alters pulmonary function, disorders the immune system, and alters the endocrine system, resulting in morbidity and mortality. The normal homeostatic mechanisms which operate to tightly regulate the balance between energy intake and energy expenditure break down in obesity and this may, in part, be a reflection of a relative deficiency of satiety signals such as PYY, GLP-1 and PP. Manipulation of gastrointestinal hormones therefore holds out the prospect of an effective and well-tolerated treatment for obesity. Drugs targeting appetite-signalling neuropeptides in the brain, downstream of gut hormones, also affect other central nervous system functions which use the same receptors. Agents based on the gut hormones themselves would have the advantage of targeting specific appetite circuits within the brain, and may indeed be the secret to satiety.

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