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Review Article

Current and emerging concepts on the role of peripheral signals in the control of food intake and development of obesity

F. A. Duca[1,2] and M. Covasa[1,3]*

[1]*INRA and AgroParis Tech, UMR 1319, MICALIS, Neurobiology of Ingestive Behavior, 78350 Jouy-en-Josas, Cedex, France*
[2]*University Pierre and Marie Curie, Paris 75005, France*
[3]*Department of Basic Medical Sciences, College of Osteopathic Medicine, Western University of Health Sciences, Pomona, CA 91766, USA*

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Abstract

The gastrointestinal peptides are classically known as short-term signals, primarily inducing satiation and/or satiety. However, accumulating evidence has broadened this view, and their role in long-term energy homeostasis and the development of obesity has been increasingly recognised. In the present review, the recent research involving the role of satiation signals, especially ghrelin, cholecystokinin, glucagon-like peptide 1 and peptide YY, in the development and treatment of obesity will be discussed. Their activity, interactions and release profile vary constantly with changes in dietary and energy influences, intestinal luminal environment, body weight and metabolic status. Manipulation of gut peptides and nutrient sensors in the oral and postoral compartments through diet and/or changes in gut microflora or using multi-hormone 'cocktail' therapy are among promising approaches aimed at reducing excess food consumption and body-weight gain.

Key words: Satiation: Cholecystokinin: Glucagon-like peptide: Peptide YY: Taste: Microbiota

Obesity rates continue to rise worldwide, with no immediate cure in sight. While increased food intake coupled with decreased energy expenditure generally accounts for rising obesity rates, this equation is influenced by a multitude of factors including genetic, physiological, neural, metabolic, social and environmental factors (for a review, see Berthoud[(1)]). With large-scale attempts at increasing energy expenditure mostly unsuccessful, the necessity for therapy in combating obesity has led to important advances in understanding the mechanisms controlling meal size and energy regulation. Throughout a meal, ingested nutrients interact at multiple sites generating signals regarding energy load, meal composition and size. Signals from the oral cavity, gastrointestinal (GI) tract, adjacent alimentary organs, and muscle and adipose tissue all converge in the brain to control short-term food intake and achieve long-term energy balance. The present study reviews new emerging evidence for the role of GI signals in controlling appetite and energy balance, their adaptive functions in the face of constant environmental changes and their potential therapeutic role in the prevention, perpetuation and treatment of obesity. Since peripheral signals are sensed by the brain and the ongoing bidirectional dialogue between the gut and the brain is pivotal to the control of energy intake, the key brain areas integrating this complex information, the sensing neurons and central peptides involved in the regulation of energy homeostasis will also be briefly mentioned.

In today's modern society, where there is an abundance of food, most meals are not initiated by physiological need ('hunger'); therefore, the main action of most peripheral signals is not to initiate feeding, but to control the size of the meal once eating begins. The GI tract is host to a vast array of chemical and neural signals controlling food intake. These signals arising from the periphery are classically divided into short-term 'episodic' signals, which are rhythmically released in response to eating such as GI peptide hormones,

Abbreviations: AgRP, agouti-related peptide; ARC, arcuate nucleus; CCK, cholecystokinin; CD36, fatty acid translocase CD36; D2R, D2 receptor; DA, dopamine; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; GOAT, gastric *O*-acyl transferase; GPCR, G-protein-coupled receptor; HF, high fat; LCFA, long-chain fatty acid; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY; T1R, type 1 taste receptor.

* **Corresponding author:** M. Covasa, fax +33 1 34 65 24 92, email mcovasa@jouy.inra.fr

and long-term 'tonic' signals, such as insulin, leptin and adipokines, that are released in proportion to the amount of fat stores, reflecting the metabolic state[2,3]. Some of the GI peptides such as cholecystokinin (CCK) generate signals leading to meal termination (satiation), while others such as peptide YY (PYY)(3–36) also play a role in controlling eating during the postprandial period (satiety). Most short-term, episodic peptide signals are secreted from the gut in response to specific nutrients, and act on local sensory nerves, relaying messages to the hindbrain that contribute to satiation and/or satiety[4]. Although known for their short-term effects, new accumulating evidence suggests a broader role in the long-term regulation of appetite and energy balance[5]. Tonic signals reflect energy storage levels and, via an endocrine mode of action, regulate body weight and stored energy by acting on hypothalamic neurons[2]. A constant reciprocal relationship exists between episodic and tonic signals, with episodic signals overcoming tonic influences, thus driving eating even in an energy-repleted condition such as obesity, while, on the other hand, tonic signals can modulate the strength of episodic signalling, therefore contributing to the short-term control of food intake.

Gut–brain integration

Satiation, adiposity and other neural signals, such as gastric distension, are integrated in the caudal brainstem and/or hypothalamus where an appropriate response is generated, ultimately affecting meal size and energy homeostasis, as depicted in Fig. 1. The caudal brainstem is a key recipient integrating not only sensory information from neural gustatory and gut vagal afferents that synapse in the nucleus of the solitary tract[1], but also humoral information from endocrine signals, via area postrema such as leptin, ghrelin and amylin which all contain receptors in the caudal brainstem[6–8]. While decereberate animals can effectively control meal size through caudal brainstem integration, they lack the ability to seek food and compensate total energy intake when fasted, demonstrating the role of higher-order hypothalamic input in the regulation of weight gain[9].

The hypothalamus, specifically the arcuate nucleus (ARC), is the main relay station that receives and integrates nutritional information via circulating hormones and metabolites through a saturable carrier across the blood–brain barrier[10–12], and/or from direct access through the incomplete portion of the blood–brain barrier[13]. In addition, hypothalamic nuclei receive indirect information from peripheral signals via brainstem neural pathways[14]. Finally, dopaminergic and endocannabinoid systems that are involved in food reward, as well as higher-order brain inputs related to emotions, motivation and learned behaviour, also converge in the hypothalamus[15]. Taken together, the hypothalamus coordinates multiple levels of information and provides subsequent efferent signals to regulate overall energy homeostasis. A major site for this regulation within the ARC is through two populations of neurons with opposing effects on food intake. There are an anorexigenic group containing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript, and an orexigenic group containing neuropeptide Y (NPY) and agouti-related peptide (AgRP), that branch and relay information to other areas involved in food intake and energy homeostasis, such as the lateral and ventromedial hypothalamus, the paraventricular nucleus and the nucleus of the solitary tract[16]. Therefore, the overall control of food intake and regulation of body weight occurs predominantly in the central nervous system. However, peripheral inputs have a major impact on the subsequent actions of the central nervous system, since they relay first-hand primary information regarding the current meal and the metabolic status of the body.

Oral nutrient sensing

In obesity, an increased motivation to eat overrides homeostatic regulation, resulting in sustained and escalating overeating despite normal or excessive energy storage. Sugars and fats are palatable to both humans and animals, and are preferred and consumed in large quantities[17]. Thus, identification of mechanisms involved in the detection of chemical compounds such as sugars and fats has major nutritional and clinical significance. In the past decade, the field has made significant progress with the discovery and characterisation of sweet taste receptors of the type 1 taste receptor (T1R) family, their expression, distribution, functional role and the molecular components of taste transduction signalling pathways (for a review, see Bachmanov & Beauchamp[18]). Chemosensing of nutrients begins in the oral cavity where taste signalling molecules are contained in epithelial cells of specialised taste buds that undergo a cascade of intracellular events leading to neurotransmitter release and activation of gustatory afferent nerve fibres[19]. On the tongue, the G-protein-coupled receptors (GPCR) T1R2 and T1R3 form a heterodimeric combination to detect sweet tastants while the T1R1/T1R3 combination and the type 2 taste receptor family are responsible for amino acid (umami) and bitter tastes, respectively[20–22]. The vast overconsumption of sugar in the Western diet provides a possible role for sweet taste in the development of obesity. Knockout mice of either T1R2 or T1R3 have a dramatic loss of sweet taste perception, while abolishing both T1R2 and T1R3 receptors leads to a complete loss of sweet taste, demonstrating the importance of these proteins in sweet detection[23]. Furthermore, genetic variations in the genes encoding these receptors are associated with differences in sensitivity to sweet taste in both rodents and human subjects[24,25]. An association between sugar consumption and variation in the *TAS1R2* gene has recently been reported in two obese populations[25]. Although genetic association studies lack functional links, nevertheless, this finding suggests that increased sugar consumption may be a result of genetic variations and subsequent change in sweet taste sensitivity. Whether genetic variations in sweet tasting, either induced or spontaneous, are linked to increased obesity, or whether individuals with defects in sweet taste perception are less obese is not clear. Interestingly, obese individuals do have altered sweet taste perception[26] and 'liking' for sweetness in the obese increases as a function of sweetness and BMI[27]. However, Grinker and co-workers[28,29] reported

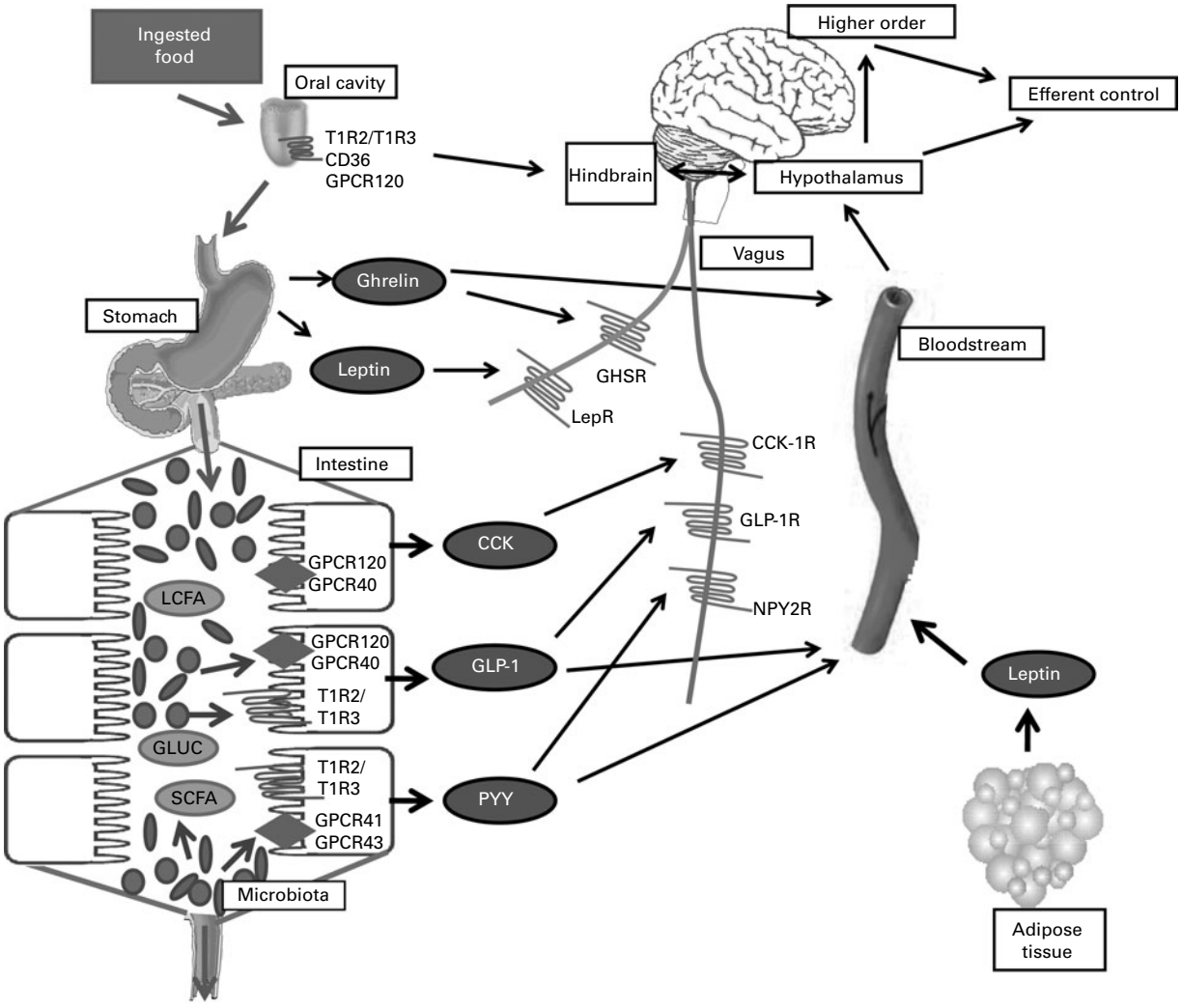

Fig. 1. Food intake is controlled by complex neural, hormonal and metabolic signals. In the oral cavity, nutrient and non-nutrient tastants activate several taste proteins, such as type 1 taste receptor (T1R) 2/3 and fatty acid translocase CD-36 (CD36). This sensory input is processed by the hindbrain, further stimulating ingestion. The presence of nutrients triggers the release of gastrointestinal (GI) peptides from the stomach and intestine that either act locally on specific receptors distributed along vagal afferents which synapse with the first-order neurons in the hindbrain, or enter the bloodstream (along with signals from the adipose tissue such as leptin) and activate receptors located on hypothalamic neurons. The release of these GI signals, especially in the distal intestine, is also affected by the microflora within the gut. Gut microbiota dispersed primarily throughout the distal intestine (represented by oval and round shapes in the intestinal lumen) influences peptide secretion possibly through nutrient receptors, such as T1R2/R3 and G-protein-coupled receptor (GPCR) or bacterial by-products such as SCFA, that serve as ligands for GPCR. These signals, along with other sensory inputs, are integrated with circuits from higher-order brain areas which in turn alter food intake, energy expenditure and body adiposity. With the exception of ghrelin that has a stimulatory effect on food intake, the final actions of these peptides are inhibition of food intake. LCFA, long-chain fatty acid; GLUC, glucose; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY; CCK-1R, cholecystokinin-1 receptor; GHSR, growth hormone secretagogue receptor; LepR, leptin receptor; GLP-1R, glucagon-like peptide-1 receptor; NPY2R, neuropeptide Y 2-receptor.

no difference in the sensitivity for sweets between obese and normal-weight individuals. In rodents, obese-prone as well as obese rats lacking a functional CCK-1 receptor show an increased avidity for high concentrations of sucrose solutions compared with their lean counterparts[30,31]. These obesity-induced changes in sweet taste responses were completely reversed after weight loss, suggesting that they were secondary to the obese state[31]. Together, these findings underscore the importance of both the effects of genotype on sweet preferences as well as the prevailing dietary environment and pathological conditions such as obesity that can modify and account for individual differences in food preferences.

Dietary fats are also detected in the oral cavity mainly through tactile (texture) and olfactory cues, although gustatory cues have also been suggested[32]. Several detection mechanisms for NEFA have been reported in rodents. They act through the Kv1·5 delayed rectifying potassium channel and the fatty acid translocase CD36 (CD36), coined the putative NEFA receptor[33,34]. Localised in circumvallate and foliate taste buds[35], CD36 mediates preference for both long-chain fatty acids (LCFA) and TAG in rodents and deletion of its gene greatly reduces fat preference and intake in mice[35,36]. Additionally, deletion of the gene abolishes digestive secretions initiated by orally deposited LCFA, further demonstrating

its role as a lipid sensor. However, development of fat preference can be acquired independent of CD36 through other modalities such as learned associations or post-oral reinforcing actions of fat[36]. Recent evidence shows that despite the reported role of CD36 in glucose and lipid metabolic abnormalities, there was no association between CD36 gene variants and obesity risks[37]. However, diet-induced obese rodents exhibited a decreased expression of CD36[38]. Thus, the degree of the direct involvement of CD36 in modulating fat intake and preference and associated metabolic disorders still requires greater evaluation.

In addition to CD36, several GPCR identified on the lingual epithelium have been shown to bind to short- (GPCR41 (NEFA2), GPCR43 (NEFA3)), medium- and long-chain (GPCR40 (NEFA1) and GPCR120) NEFA[39]. As with CD36, GPCR120 and GPCR40 knockout mice displayed decreased preference to LCFA[40]. Their presence and functions in human lingual tissue, however, are not known. Furthermore, the picture of fat taste detection in humans is less clear with no identified receptors for TAG, the main form of dietary lipids, and a lack of knowledge of possible transduction mechanisms. Further, we still do not fully understand whether lipids are processed by the somatosensory or the gustatory system. Although CD36 is expressed in human taste cells, and may be involved in dietary LCFA detection[35], the role of the gustatory apparatus in fat detection and preference in humans remains largely unresolved. However, recent findings have shown that hypersensitivity to lipids in human subjects was associated with a lower BMI, as well as a decreased consumption of lipids and total energy[41]. Thus, this represents a prolific and promising area for research aiming at developing strategies for modulating taste receptor functions to curb appetite given that taste is a major factor accounting for increased preference for palatable foods resulting in excess weight gain.

Gut chemosensation

The finding that the molecular sensing elements and pathways that mediate oral taste signalling are also present and operate in the GI tract[42–44] has added a new dimension to the role of the gut in controlling appetite. For example, T1R, type 2 taste receptors, α-gustducin and transient receptor potential member 5 lingual taste molecules are all expressed in the upper GI mucosa[45,46] and are subject to dynamic metabolic control of the intestinal luminal environment. In addition, they co-localise with gut peptide producing cells[47,48] in the intestinal epithelium and mediate peptide release[43,49]. Specifically, the T1R2/R3 sweet taste receptor found on the tongue is also present in enteroendocrine L-cells of mice and humans[43,46,50,51], and is required for glucagon-like peptide-1 (GLP-1) release after a glucose load[43]. Similarly, α-gustducin co-localises with GLP-1 in the intestinal epithelium[48], and T1R3 and α-gustducin knockout mice have impaired GLP-1 release[43,49]. In human subjects, administration of lactisole, a T1R3 antagonist, dose-dependently decreased the glucose-stimulating release of both GLP-1 and PYY[49]. Also, specific GPCR have been identified in enteroendocrine cells, providing a mechanism for lipid-induced secretion of GI peptides. For example, GPCR120 and GPCR40 have been implicated in CCK and GLP-1 release via LCFA, while GPCR41 knockout mice have a blunted release of PYY[42,44,52,53]. As shown in Fig. 1, these data demonstrate that taste and nutrient receptors in the gut provide feedback information in response to luminal nutrients through mediating hormone secretion. However, the ability to manipulate these receptors and with them peptide secretion so far has proved elusive. Several groups have shown that artificial sweeteners known to bind to T1R3 were unable to stimulate GLP-1 release, while glucose is more effective than fructose in inducing release[54]. Therefore, while the ability to enhance satiation signalling could be beneficial for the treatment of metabolic disorders, non-taste mechanisms are major factors influencing gut peptide release.

Gut peptides

Recent successes from bariatric surgery in achieving massive weight loss in morbidly obese patients, which are associated with enhanced secretion of anorexigenic peptides, have propelled gut hormones to the forefront of research seeking an alternative, non-surgical, treatment for obesity. A growing number of neural and humoral factors are released from the gut during feeding, and they play a prominent role in the cascade of events controlling appetite.

Ghrelin

In addition to gastric mechanoreceptors that respond vagally to stretch and tension[55], the stomach is the site of release for ghrelin, the only known peripheral orexigenic hormone[56–58]. Produced mainly by the X/A-type cells in the gastric mucosa[59,60], plasma ghrelin levels are high during fasting, greatly decreased during re-feeding and rise before the onset of a meal, defining the peptide as a possible meal initiator[61,62]. However, the ability of ghrelin to initiate intake has recently been contested by the fact that ghrelin levels actually peak in response to habitual meal patterns, thus rising in anticipation of meal, and perhaps better preparing the GI tract for an upcoming meal[63]. Des-acyl ghrelin is the prominent form in the plasma[64], but the biologically active form requires acylation by the gastric *O*-acyl transferase (GOAT) enzyme[65]. Ghrelin activates NPY/AgRP neurons within the ARC[66,67] through growth hormone secretagogue receptor-1a. Thus, the orexigenic effect of ghrelin is dependent on the release of NPY and AgRP and their subsequent inhibitory action on POMC neurons[68]. In addition to a central action, vagal afferents innervating the stomach express the ghrelin receptor, indicating a possible peripheral mechanism[69,70]. Furthermore, ghrelin down-regulates anorexigenic peptide receptors for PYY, GLP-1 and CCK[71,72], thus strengthening its orexigenic effects.

Although initial pharmacological data provided strong evidence on the role of ghrelin in the control of food intake, more recent studies using targeted deletion of ghrelin and its receptor[73,74], ghrelin overexpression[75] or manipulation of ghrelin activation pathways[76] have raised new and intriguing

British Journal of Nutrition

questions on the functional role of ghrelin. For example, abolishing ghrelin or ghrelin receptor activity in obese mice results in decreased food intake, body weight and adiposity and improvement in metabolic parameters[73,77,78]. Furthermore, transgenic mice overexpressing ghrelin are resistant to high-fat (HF) diet-induced obesity[75]. This differential effect of ghrelin on feeding and obesity when animals are on a HF diet suggests a crucial role of ghrelin as a key homeostatic signal modulating energy balance and lipid metabolism. Indeed, GOAT, the enzyme responsible for ghrelin acylation, is regulated by dietary lipids, such as medium-chain fatty acids acting as substrates[76]. This suggests that the GOAT–ghrelin system acts as a lipid 'sensor' to inform the hypothalamus of available energy for distribution. The role of ghrelin on hypothalamic and peripheral lipid metabolism has been shown in several papers and recently reviewed[79]. Although much remains to be done in identifying the physiological and neuronal pathways of ghrelin's role under various feeding and metabolic conditions, it is clear that ghrelin has an important physiological and pathophysiological role in appetite as an anticipatory meal signal and as a signal for energy deficits. Consistent with the latter, ghrelin is a promising candidate for obesity management.

A role of ghrelin in long-term weight regulation has been suggested. For example, ghrelin increases the production of fat storage proteins, resulting in intracytoplasmic lipid accumulation[80], reduces fat utilisation, increases adipose tissue and promotes weight gain[56]. While individuals with the Prader–Willi syndrome have elevated levels of ghrelin even before the onset of obesity[81,82], an inverse correlation exists between ghrelin levels and obesity-related parameters such as BMI, visceral adiposity, hyperleptinaemia, abnormal glucose homeostasis and insulin resistance[83,84]. Plasma ghrelin levels are reduced in obese individuals compared with normal-weight individuals, an effect that may result in limiting intake[85]. However, unlike lean individuals, the obese fail to significantly decrease ghrelin levels after a meal, suggesting a role for ghrelin in overconsumption due to a blunted postprandial response[85]. Adding to this, the beneficial weight loss from bariatric surgery may be due in part to changes in ghrelin release[86]. Most evidence shows that ghrelin fasting and postprandial levels are decreased significantly after gastric bypass but others have reported unchanged or even increased levels of plasma ghrelin after surgery which had been attributed to differences in pre- and post-operative conditions and surgical methods[86]. The mechanisms for reduced plasma ghrelin levels after gastric bypass are not clearly known, although the loss of ghrelin-producing cells and the absence of gastric mucosal contact with nutrients have been suggested as possible causes[87]. Additionally, gastric bypass surgery in rodents lowered growth hormone secretagogue receptor-1a protein expression in the hypothalamus, providing another mechanism for weight loss after surgery[88].

Approaches aimed at blocking the activity of ghrelin (e.g. anti-ghrelin vaccines)[89] and its receptor[77] or inactivating the acylation process using GOAT enzyme inhibitors have all been proposed as a potential target for obesity treatment[90]. However, ghrelin receptor antagonists have had mixed results, and although the anti-ghrelin vaccine proved effective in animal models, it failed to reduce weight in obese human subjects[91,92]. On the other hand, GOAT antagonists that reduce acyl ghrelin prove to be promising, with recent results showing decreased hunger, body weight and fat mass in HF-fed mice[93]. Furthermore, rodents treated with a ghrelin-specific RNA spiegelmer, an L-isomer oligonucleotide, which binds and blocks acylated ghrelin, have decreased food intake and body weight; however, it has yet to be tested in human subjects[78,94]. Finally, some, but not all, linkage and genomic studies showed associations between several ghrelin variants and the obese phenotype, further implicating ghrelin as a major candidate involved in long-term energy balance (for a review, see Barnett *et al.*[93]).

Cholecystokinin

In the proximal intestine, CCK released from mucosal enteroendocrine I-cells, mainly in response to fats and proteins, stimulates pancreatic secretion, bile release, gallbladder contraction, slowing of gastric emptying and inhibition of food intake, thus controlling the passage of the ingesta[95]. Most of CCK's actions, including control of food intake, are mediated through CCK-1R acting through a paracrine mode of action on vagal afferent neurons[96]. CCK interacts with other signals such as gastric distention[97], oestradiol[98], 5-hydroxytryptamine[99,100] and leptin[101] to enhance its anorexigenic effects while also mediating the effect of other signals such as ghrelin[102], PYY[102,103] and apoA-IV[104].

Although predominantly viewed as a short-term satiation signal, there is also evidence that CCK plays a role in the pathogenesis of obesity in human subjects. For example, *CCK-1R* gene promoter polymorphism is associated with body fat[105] and obese carriers of variants in the *CCK* gene have an increased risk of eating large portion sizes, with a 60 % increased risk for carriers of CCK_H3[106]. Further, obese women have lower fasting plasma CCK concentrations and exhibit a blunt postprandial CCK response, possibly indicating a dysfunctional secretion and thus a decrease in the signalling pathway[107]. However, plasma CCK concentration in obese subjects remains elevated following consumption of a fatty meal, which could lead to CCK-1R desensitisation[108]. Manipulation of endogenous CCK levels either through diet (e.g. addition of LCFA), by inhibiting CCK degradation, or through chronic exogenous administration of CCK have all been shown to decrease energy intake and/or body weight[96]. Whether these approaches can lead to sustained changes in CCK responses without the development of tolerance effects, resulting in a consistent reduction in appetite, in obese subjects requires further investigation. However, recent findings showing that CCK-58 is more potent than CCK-8 in reducing food intake[109] and that morbidly obese subjects have elevated CCK levels even 20 years after jejunoileal bypass[110] strengthen the role of CCK as a therapeutical candidate in obesity management. Furthermore, pharmacological studies employing CCK-1R agonists have been promising, with, at least, initial studies showing a significant weight loss[111]. Studies using longer forms of CCK, such as CCK-58

that prolong the intermeal interval[112], may prove more beneficial in curbing intake. Lastly, CCK may have a role in long-term energy balance by interacting with leptin[113–115] and amylin[116]. Indeed, administration of CCK with either leptin or amylin increases the magnitude of feeding suppression while CCK/leptin enhances body-weight suppression[113,114,116,117]. Uncovering the most effective strategy of manipulating the CCK system leading to enhancement of the effects on intake, adiposity and other metabolic improvements remains a promising area of intense investigation.

Glucagon-like peptide-1

Another major hormone that exerts a profound effect on eating behaviour, GI functions, nutrient utilisation and energy homeostasis is GLP-1. GLP-1 is a post-translational product of the proglucagon gene expressed in the α-cells of the pancreas, L-cells of the small intestine and colon, and neurons in the central nervous system[118]. Secretion of GLP-1 is governed by a neural–humoral reflex, the presence of nutrients and other endocrine factors in the intestinal tract[119]. GLP-1 is present in two forms, GLP-1(1–36) and GLP-1(1–37), which undergo enzymatic cleavage to yield the bioactive forms of the peptide: GLP-1(7–36) and GLP-1(7–37)[120,121], which enter the circulation via the lymphatic system[122]. Most of the peptide is rapidly degraded by dipeptidyl peptidase IV[123], which results in a relatively short half-life in the circulation[124] and limits its effects on weight loss. GLP-1 has potent effects on (1) regulating GI functions such as gastric emptying, motility and pancreatic secretions[125–128], (2) suppression of food intake[129–131] and (3) regulation of blood glucose levels by stimulating insulin secretion[132]. Both systemic and central exogenous GLP-1 are effective in decreasing food intake[130,131,133] by acting either locally through vagal afferents or centrally through brain neurons arising from the hindbrain that maintain synaptic connections with hypothalamic areas[131,134–136]. Indeed, recent work by Kanoski *et al.*[137] shows that the suppressive effects of long-lasting GLP-1 agonists are not exclusively mediated by a peripheral action, but also require some central activation, while others have shown that blood-borne GLP-1 does not require peripheral participation[138,139]. However, the role of endogenous GLP-1 as a true satiation peptide is still contentious, and it may only have a role in decreasing appetite during times of low intake, not during large meals. This is evidenced by the fact that GLP-1R antagonism only increases intake during the light, but not the dark, cycle, which is the largest meal for a rodent[135,140]. Furthermore, although circulating GLP-1 remains elevated for several hours[141], it does not appear to promote satiety, as it is unable to increase the intermeal interval[138]. GLP-1 also interacts with both central[142,143] and peripheral[144,145] peptides that control food intake, as well as with long-term energy-regulating hormones such as leptin[146,147].

In pathological states characterised by imbalanced energy homeostasis, studies have shown that while fasting levels are maintained, GLP-1 secretion is markedly decreased[148–150]. Interestingly, though, is the fact that potency of GLP-1 appears to be maintained in obese models, although a HF diet can abate the anorexic response[150,151] (F. A. Duca and M. Covasa, unpublished results). Further proof for GLP-1's role in weight-loss treatment comes from data showing a dramatic fasting and postprandial increase in plasma levels of GLP-1 after gastric bypass surgery[86]. Whether these changes have a direct bearing on weight loss is not known, particularly given the rapid degradation of GLP-1 in the blood. However, other sources of GLP-1 signalling that avoid peptide degradation via activation of vagal afferents[134,138] or the caudal brainstem[152] or entrance into the lymphatic system[122] may be partly responsible for its delayed effects on weight loss[153]. Given all this, several GLP-1R agonists (exenatide and liraglutide) or dipeptidyl peptidase IV inhibitors have been developed to prolong its anorexigenic effects. Although originally developed for treating diabetes, both liraglutide and exenatide produced significant weight loss[154,155]. In a smaller study, dual treatment of extenatide and insulin to type 2 diabetic obese patients yielded a 12·8 % reduction in body weight after 1 year[155]. Although more studies on obese patients are needed, the initial success of GLP-1 treatment coupled with the fact that sensitivity seems to be maintained in obesity establishes GLP-1 as a promising therapeutic target.

Peptide YY

Co-secreted with GLP-1 from enteroendocrine L-cells in response to a meal[156], PYY mediates several GI functions such as inhibition of gastric emptying and secretion, GI motility, gall bladder emptying, and pancreatic and intestinal secretion. PYY(3–36) is the active and major circulating form, resulting from the cleavage of PYY(1–36) by dipeptidyl peptidase IV[157]. PYY levels are increased within 15 min following a meal and remain elevated for up to 6 h[156]. The anorectic effect of centrally and peripherally administered PYY(3–36) is mediated by NPY2 receptors in the ARC, down-regulating orexigenic NPY mRNA[158,159] while possibly up-regulating POMC mRNA[159,160], although the effect on POMC has been challenged[158,161,162]. However, PYY may also act on vagal afferents that express Y2 receptors[163], since vagotomy abolishes the suppressive effect of exogenous PYY[134,163].

The fact that PYY plasma levels stay elevated long after a meal suggests a role for PYY in satiety[164]. Additionally, several studies have shown a positive correlation between postprandial PYY levels and ratings of satiety in human subjects[165,166]. Therefore, treatment strategies involving PYY may target lowering body weight via enhanced satiety. PYY may indeed have a role in the pathogenesis of obesity as diet-induced obese rats display reduced levels of PYY[166,167], and human studies have shown a negative correlation between fasting PYY and BMI in adults[168], as well as a decreased postprandial response[166]. Furthermore, PYY levels are greatly increased in both fasted and fed animals following gastric bypass surgery[169,170], suggesting an important role of PYY in weight loss. The increased PYY levels in gastric bypass patients can last for years[110], a phenomenon attributed to

alterations in L-cell functions[169]. Finally, chronic administration of PYY reduces body weight in animal models, while PYY-null mice developed hyperphagia and increased adiposity that was subsequently reversed by PYY(3–36) treatment[171]. However, to date, therapeutic treatments with PYY(3–36), its analogues or combination therapy have had only modest results[172,173]. Nevertheless, because PYY increases the intermeal interval, it makes it an interesting peptide with potential therapeutic effects particularly when combined with other satiation peptides such as GLP-1 or oxyntomodulin to reduce long-term energy intake[145,174].

Other gut anorexigenic peptides

Several other peptides are released from the gut in response to nutrients which include gastrin-releasing peptide, apoA-IV, enterostatin, pancreatic polypeptide, amylin, glucagon and oxyntomodulin (OXM), to name a few. While a role for most of these peptides in obesity treatment remains uncertain and is still under consideration, the effects of OXM, which has potent anorectic, incretin and energy expenditure properties[175,176], look more promising with recent data showing decreased food intake and sustained weight loss in diet-induced obese mice following infusion with an OXM analogue[177].

Gut peptide interactions

Control of food intake is orchestrated, in part, by highly complex interactions between gut peptides. Since single hormone therapy poses several challenges, including rapid peptide degradation, tolerance, redundancy and compensatory mechanisms, the use of multi-hormone therapy has proved more effective. Roth *et al.* showed that treatment of PYY, a GLP-1 analogue, or amylin with co-administration of leptin all decreased weight in obese rats, but only amylin and leptin had a synergistic effect. This treatment of pramlinitide (an amylin analogue) and metreleptin (recombinant leptin) elicited a weight loss of 12·7 % in obese human subjects[178,179]. The addition of CCK with leptin and pramlintide may prove to be even more effective than either the two treatments alone, since CCK and leptin co-treatment in rodents synergistically reduces meal size and reduces body weight[113,114]. Treatment with all three peptides increased weight loss by 40 % compared with just the leptin and pramlinitide combination in obese rats[180]. Furthermore, combination of low doses of PYY(3–36) with OXM or GLP-1 in human subjects resulted in a 42·7 and 27 % reduction, respectively, in energy intake compared with controls and was significantly greater than that produced by either hormone independently[145,174]. Thus, 'cocktail' treatments appear to be more effective in suppressing energy intake and sustaining weight loss. Attempts have been made at replicating complex neurohormonal responses following a meal by designing treatment combination targeting both episodic and tonic signals, such as CCK, amylin and leptin[180]. The ability of a multi-faceted treatment to decrease meal size while simultaneously increasing the intermeal interval and background tonic signalling may result in significant energy reductions and long-term weight loss. Additionally, the synergistic property of 'cocktail' therapy allows for lower doses of peptides within the treatment, thus limiting potential tolerance effects normally observed with long-term single drug treatment. In summary, manipulating gut hormones through dietary or combination therapy to mimic a more complete post-ingestive response could prove an effective treatment approach to curb appetite and weight gain. However, to date, their effects in humans are largely unknown but the initial success in animals is promising.

Modulation of gut peptides by the gut luminal environment

Dietary influences

Responses to GI appetite-related signals are not fixed, and they change considerably in response to the dietary and endocrine milieu. Some changes can lead to defects in release, or functionality, of the peptides resulting in increases in food intake and ultimately obesity. For example, rats adapted to a HF diet become less sensitive to both exogenous and endogenous CCK as well as to gastric and intra-intestinal lipid loads, and exhibit hyperphagia and weight gain (for a review, see Covasa[181]). The reduced sensitivity to CCK after HF exposure occurs both in rat pups[182] and adults[183,184] and can be reversed when switched to a low-fat diet[182]. These behavioural responses have been associated with rapid physiological, enzymatic and molecular changes in CCK and CCK-dependent physiological functions and signalling pathways, as well as with reduced neuronal activation in enteric, vagal and the nucleus of the solitary tract neurons, areas densely populated with CCK-1 receptors[181]. Similarly, human subjects adapted to a HF diet reported greater hunger during a duodenal lipid infusion[185], and had increased daily food consumption and body weights[186]. The effects of HF feeding are not limited to CCK. Similarly, long-term exposure to a HF diet resulted in both decreased sensitivity to an exogenous analogue of GLP-1 and decreased plasma GLP-1[150] (F. A. Duca and M. Covasa, unpublished results). Furthermore, Chandarana *et al.*[169] have recently shown that while short-term HF diet exposure did not alter fasting circulating acyl-ghrelin, total PYY or active GLP-1 concentrations, prolonged exposure with the development of obesity significantly diminished the levels of these peptides. These lower levels of circulating peptides such as PYY may result in increased intake in obese human subjects[166]. Obesity is often associated not only with changes in responsiveness to peripheral peptides and nutrients but also with central peptides, in several obese models. For example, HF feeding significantly increases the expression of centrally acting peptides such as orexin[187], galanin[188], AgRP[189] and NPY[190] in the hypothalamus. Thus, potentiating positive feedback involving orexigenic signals, coupled with decreased negative feedback from anorexigenic signals, following HF feeding may be responsible for the overconsumption on a HF diet. It is clear that the obese state is associated with changes in hormone release induced by food

intake, but it remains uncertain how obesity influences hormone concentrations or changes in sensitivity to the hormones that might exacerbate the obese condition.

Microbiota influences

In addition to the presence of nutrients, the intestinal epithelium comes in direct contact with trillions of diverse, complex bacteria and other micro-organisms collectively termed the microbiota. Growing evidence demonstrates that the gut microbiota contributes to the development of diet-induced obesity[191–193]. For example, colonisation of adult germ-free mice with a distal gut microbial community harvested from conventionally raised mice leads to a dramatic increase in body fat within 10–14 d, despite an associated decrease in food consumption and increased energy expenditure[194]. Additionally, germ-free mice are resistant to diet-induced obesity when fed a HF/high-sugar 'Western' diet[195,196]. Interestingly, the obese phenotype is transmissible: germ-free mice that receive an 'obese microbiota' display significantly greater fat mass than those that received a 'lean microbiota'[197]. Finally, the diet can profoundly alter the composition of the gut microbial population[198–200], possibly contributing to weight gain.

In addition to its profound effect on modulating host energy homeostasis and metabolism[201], as shown in Fig. 1, there is evidence that microbiota-generated by-products affect the functional expression of intestinal nutrient-responsive GPCR[202,203], GI hormones[204], and nutrient transport and taste[205]. Studies examining a direct role of the microbiota in the control of food intake and body adiposity are in infancy; however, indirect evidence suggests a role of the gut microbiota in the secretion and function of GI peptides, such as 5-hydroxytryptamine, GLP-1, GLP-2, PYY and ghrelin[206–209]. Additionally, obesity has been associated with diet-induced, low-grade gut inflammation or the 'metabolic endotoxaemia' condition resulting from a substantial increase in bacterially derived lipopolysaccharide and increased gut permeability, a condition improved by altering the gut microbiota[210], involving GLP-2[207]- and endocannabinoid[211]-dependent mechanisms. This implicates the gut microbes as targets in metabolic disorders such as obesity and diabetes. As such, decreasing inflammation by increasing microbial fermentation, either through the diet or the aid of prebiotics, results in lowered appetite, elevated plasma levels of GLP-1[206,208], GLP-2[207] and PYY[208,212], and decreased levels of ghrelin[206]. Thus, the microbiota profile can be modified in the interest of improving metabolic parameters such as glucose homeostasis and leptin sensitivity, and to control the activity of gut hormones through its effects on enteroendocrine cell number and increased cell differentiation[213]. Furthermore, SCFA, by-products of polysaccharide degradation by the gut microbiota, are ligands for intestinal GPCR which are candidate mechanisms for peptide release[214]. They induce enhancement in colonic motility via 5-hydroxytryptamine release[209,215] and stimulate leptin and PYY secretion[202]. We have recently shown that mice devoid of the gut microbiota exhibit altered expression of lingual and intestinal epithelium GPCR for both sweet and lipid tastants[205] (F. A. Duca and M. Covasa, unpublished results). Furthermore, germ-free mice have decreased expression of the intestinal satiety peptides CCK, GLP-1 and PYY and lower levels of circulating leptin, PYY and ghrelin. These changes were associated with altered preference for, and intake of, sugars and oils[205] (F. A. Duca and M. Covasa, unpublished results). These data show that the microbiota has a potent modulatory role for the signalling elements known to be involved in the control of food intake and regulation of energy balance, resulting in behavioural changes. Thus, microbial components target molecular regulatory systems with a major role in metabolism, nutrient sensing and absorption, gut barrier integrity, gut hormones, systemic inflammation and fat tissue metabolism. The precise mechanisms responsible for these changes including their overall significance as it relates to weight gain are largely unknown, although several mechanisms have been put forward mainly involving the suppression of the intestinal lipoprotein lipase inhibitor Fiaf, inactivation of AMP-activated protein kinase pathways and efficient energy extraction from complex carbohydrates[201]. Nevertheless, it is evident that changes in the gut microbiome with a shift towards improving efficiency of energy extraction and excess energy availability are neither sufficient nor can they explain the dramatic rise in the obesity epidemic within the past years. Despite major advances at the host–microbial interface and the intriguing link with the host metabolic phenotypes such as obesity and diabetes, significant work still lies ahead in deciphering the mechanisms by which the microbiota affects the regulatory systems governing energy homeostasis. Studies so far have generated more questions than answers. A major challenge is the inherent difficulty of teasing apart the complex interactions between the microbiota and the host at multiple levels that expand through several physiological and neural systems from the periphery to the brain. Because of this, some previous results are inconclusive, even controversial, with multiple confounding variables making it difficult to distinguish and separate the effect from the cause or contributing factors. Thus, it is imperative that future studies (1) uncover the identity of specific species of bacteria that are associated with obesity, (2) identify the molecular targets and understand the mechanisms of action, and (3) develop the delivery tools, including 'targeted' prebiotic and probiotic treatment to manipulate the microbiota profile acting on specific pathways to sustain desired intake and weight, and alleviate metabolic parameters associated with obesity. This may be especially important, since current exogenous peptide administration treatments can induce side effects and have short-lived success rates from developed tolerance, while the option of altering endogenous GI peptide levels through microbiota manipulations could be safer and long-lasting. Nevertheless, based on the existing body of evidence, the gut microbiota qualifies as an important additional factor to an already complex and redundant homeostatic and appetite-controlling system, which, undoubtedly, adds a new and critical dimension to our understanding of the role of the gut in the control of food intake, obesity and associated metabolic disorders.

Hedonic influences and interactions with homeostatic controls

Despite the strong regulation of the homeostatic system, it has become apparent that the non-homeostatic (hedonic or food reward) system plays an integral role in feeding behaviour. In obesity, an increased motivation to eat overrides homeostatic regulation resulting in sustained and escalating overeating despite normal or excessive energy storage. Palatable foods can be overconsumed for their pleasurable effects, with hedonic responses generated in the cortico-limbic structures overriding physiological control of appetite (for reviews on the hedonic system, see reports by several researchers[216–218]). Interestingly, obesity is associated with alterations in the reward system, specifically the mesolimbic dopamine (DA) pathway, possibly resulting in overeating of palatable foods[31]. For instance, obese individuals have blunted striatal activation in response to highly palatable foods, and individuals with a point mutation in the DA D2 receptor (D2R) are predisposed to obesity and substance abuse[219,220]. In line with this, D2R levels are decreased in several models of obesity, and obesity-prone rats have lower basal and stimulated DA levels[221]. Furthermore, sites in the lateral hypothalamus which receive input from hedonic striatal projections are less responsive during obesity and overeating, and striatal D2R knockdown rats have blunted rewarding lateral hypothalamus stimulation[222]. Thus, obesity is associated with hyporesponsivity of the mesolimbic dopamine pathway possibly through decreased D2R signalling, leading to overconsumption in order to alleviate deficits in reward signalling. However, it is still debated as to whether these alterations are a cause or consequence of the obese state[218]. Recent work comparing individuals with a low or high risk for obesity development shows that normal-weight individuals predisposed to obesity exhibit elevated dorsal striatum responses to food reward[223,224]. This led to the suggestion that reduced dorsal striatum responses to food and decreased D2R availability reported in the obese are indicative of a consequence rather than the cause of hyperphagia[225]. Thus, the current 'feed-forward' model postulates that increased initial responses of the DA system reflect enhanced responses to palatable foods and subsequent overeating. This, in turn, leads to the down-regulation of DA signalling, abrogating striatal responses to food intake and a return to prior reward experience from increased consumption.

While the reward system can override homeostatic signals, we also know there is a high degree of interaction between the two systems that influence appetite behaviour. For example, activation of the leptin receptor in the ventral tegmental area inhibits DA neurons and subsequent food intake, while leptin decreases both basal and food-evoked levels of DA[226,227]. However, leptin appears to be necessary for normal mesolimbic DA signalling, as *ob/ob* mice have reduced DA production and decreased DA release in the nucleus accumbens, which are corrected with leptin treatment[228]. More importantly, leptin resistance also results in altered DA signalling, indicating that while leptin is necessary for normal DA signalling, exogenously administered and obesity-induced leptin resistance causes hyposensitivity of the mesolimbic DA system[221,229]. On the other hand, leptin is also regulated by D2R activation, as the injection of a D2R agonist reduces leptin levels, and D2R knockout mice have increased leptin signalling and sensitivity[230]. Furthermore, studies show that ghrelin stimulates DA release and increases activity in reward areas of the brain in human subjects[231,232]. Thus, in addition to increased intake through alterations in homeostatic signalling, leptin resistance can cause an inopportune hyposensitivity of the hedonic system possibly exacerbating energy excess. Taken together, it is clear that a significant interaction between the homeostatic and hedonic systems occurs to affect food intake, yet potent hedonic signalling can overcome physiological appetite signals resulting in overeating. On the other hand, DA circuitries, for example, are a major site of receipt and convergence of post-oral, metabolic, hormonal and visceral cues that interact with and modulate cognitive and reward functions that drive consumption. A clear understanding of controlling this delicate reciprocal balance between the hedonic and homeostatic processes to meet energy needs, as well its dynamic and complex neurocircuitries in altered food intake and obesity, is still lacking and under intense investigation.

Perspectives and conclusions

The knowledge on the role of the GI tract in the control of food intake and the regulation of body weight is rapidly evolving. Our constant discoveries of the complexity of systems and pathways involved in this process have moved the field beyond the rather simplistic view that obesity is a simple result of excess energy balance. Clearly, food consumption is controlled by a multitude of complex factors involving metabolic and hedonic components that converge and interact at various levels of the gut–brain axis. Disruptions in both the homeostatic and hedonic systems can result in chronic positive energy balance and ensuing obesity. Although significant progress has been made recently in identifying the neural substrates and brain circuitries involved in responses to overconsumption of palatable food and weight gain, it is not clear how precisely the hedonic system influences food intake or yet how it overcomes the homeostatic system. Similarly, the influence of intrinsic or diet-induced alterations on the responsiveness of the reward and metabolic systems, and how these effects contribute to overeating and obesity, remains unclear. The evidence that oral and post-oral signals are disrupted in obesity has generated interest in developing therapeutic strategies against obesity. It has become increasingly obvious that monotherapies, or by targeting single homeostatic or hedonic components, are largely insufficient and ultimately ineffectual in producing the desired weight-loss effects. Thus, taking advantage of the interactions that normally occur between various gut hormones involved in appetite and energy regulation proves a more promising strategy in controlling meal size and subsequent weight gain. Using combination therapies, it may be possible to simulate physiological levels of key GI signals, such as those observed in bariatric surgery patients with severe weight loss. The therapeutic success of combining

short- and long-term signals in rodents warrants further investigation, and long-term human clinical studies should be conducted as these 'cocktail' therapies may prove to be the most effective treatment for sustained weight loss. Furthermore, diet has a major role in modulating the release and action of gut hormones and dietary manipulations can result in changes in sensitivity to both hedonic and metabolic appetite-related signals that affect the behavioural control of intake. More work should be directed towards understanding how diet-induced adaptational changes can lead to deficits in the sensitivity of the reward as well as post-absorptive metabolical signalling, and how these effects contribute to overeating and obesity. At the same time, studies examining factors controlling food intake need to consider the profound impact that alterations in energy balance exert on hormone and nutrient levels which in turn influence brain regions involved in ingestive behaviour, thereby perpetuating obesity. In line with this, critical areas for future research should also involve investigating potential mechanisms that predispose individuals to obesity. This will provide useful insights into inter-individual variability in the aetiology of obesity.

Finally, the microbiota residing in the GI tract has a major impact on enteroendocrine gut functions and molecular chemosensory machinery that influence host physiology and metabolism, and affect adiposity and obesity. Future work should focus on understanding the intricate mechanisms by which nutrients and nutrient-sensing molecules, non-nutrient tastants, as well as microflora all affect GI peptide secretion, and how this can be modulated in the face of constant changes of the gut environment to control ingestion. For instance, recent work in rodents with prebiotic treatment shows significant decreases in inflammation and weight; however, studies involving long-term prebiotic treatment in human subjects are scarce and needed. Thus, developing effective treatments for obesity will ultimately require a comprehensive understanding of the complexity of systems that regulate body weight and their interactions. Although much remains to be done, the novel discoveries and experimental approaches captured in the present review will undoubtedly continue to raise more questions and pose new challenges in our quest to finding a cure to curb obesity.

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