Bowels control brain: gut hormones and obesity

Benjamin C. T. Field, Owais B. Chaudhri and Stephen R. Bloom

Abstract | Food intake and energy expenditure are tightly regulated by the brain, in a homeostatic process that integrates diverse hormonal, neuronal and metabolic signals. The gastrointestinal tract is an important source of such signals, which include several hormones released by specialized enteroendocrine cells. These hormones exert powerful effects on appetite and energy expenditure. This Review addresses the physiological roles of peptide YY, pancreatic polypeptide, islet amyloid polypeptide, glucagon-like peptide 1, glucagon, oxyntomodulin, cholecystokinin and ghrelin and discusses their potential as targets for the development of novel treatments for obesity.

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Introduction

Energy intake and expenditure are regulated by a homeostatic mechanism; in healthy adults, body weight thus remains relatively constant over decades despite large short-term fluctuations in food intake and physical activity. This remarkable feat is achieved by a complex neuronal network, centered on the hypothalamus and brainstem (Figure 1). Afferent signals to this homeostatic network are neuronal, metabolic and hormonal in nature and arise both from the periphery and the central nervous system (CNS). These signals convey information on a multitude of parameters, including the quantity of energy stored in adipose tissue; the presence of inflammatory or toxic substances in the blood; the volume, composition and satiating effect of nutrients in the gastrointestinal tract; and the appearance, aroma and taste of potential foodstuffs. This information is integrated with neuronal contributions from pleasure and reward pathways, as well as higher cognitive functions, such as an awareness of social context. Efferent signals from the homeostatic network are directed to the neuroendocrine axes, autonomic nervous system and diverse regions of the CNS. The result is a finely controlled, continuous adaptation to, and alteration of, a fluctuating energy requirement.

Neuronal control of energy homeostasis

Meal-related hormonal and neuronal signals from the gastrointestinal tract are received via the blood in the area postrema and through vagal afferent fibers in the nucleus of the tractus solitarius (Figure 1). These sensory inputs are transmitted via the parabrachial nucleus and ventral tegmental area to other centers, including the amygdala and nucleus accumbens, where reward is assigned to them in a process involving dopaminergic, opioid and 5-hydroxytryptamine signaling. Inputs from these pathways are integrated with circulating signals of nutritional state, such as fatty acids and the adipocyte hormone leptin, which are detected in the arcuate nucleus via the median eminence.

Leptin-responsive neurons are also present in the brainstem and ventromedial nucleus. Within the arcuate nucleus, the activity of neurons that express pro-opiomelanocortin (POMC) is stimulated by leptin, while that of neurons expressing neuropeptide Y (NPY) is inhibited. Axons from both types of neurons project in parallel to the paraventricular nucleus and lateral hypothalamic area. Release of α-melanocyte-stimulating hormone by POMC-expressing neurons leads to activation of the melanocortin receptor 4 (MC4R), which results in the reduction of food intake and an increased energy expenditure. By contrast, release of NPY activates Y_1 and Y_5 receptors, which increases food intake and reduces energy expenditure. NPY-expressing neurons also release agouti-related peptide, an endogenous antagonist of the MC4R. The response to this dual innervation within the paraventricular nucleus leads to modulation of energy expenditure via the thyroid and adrenal axes and the sympathetic nervous system.

Within the lateral hypothalamic area, second order neurons that express melanin-concentrating hormone and orexins are of importance in modulating food intake. In the ventromedial nucleus, neurons that express brain-derived neurotrophic factor regulate palatable food ingestion via interactions with the amygdala and nucleus accumbens. Motivation and cognition influence energy homeostasis and are influenced in turn by nutritional status, via reciprocal projections between the orbitofrontal cortex, the amygdala, nucleus accumbens, dorsal striatum and other parts of the limbic system.

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Current treatments for obesity

The complexity of the neuronal network that controls energy balance has provided a wealth of CNS drug development targets for novel obesity treatments (Table 1). The number of different targets pursued is illustrative, however, of the challenge of manipulating a homeostatic mechanism with so many layers of apparent redundancy. The vast number of targets also reflects the difficulty of targeting neurotransmitters with diverse roles in other CNS pathways.

Following the withdrawal of marketing authorizations for sibutramine and rimonabant, the only drug currently available in Europe for the treatment of obesity is the pancreatic lipase inhibitor orlistat. When administered in randomized, controlled trials in conjunction with a reduced calorie diet, orlistat causes modest weight loss;[1] however, its use is limited by the unpleasant adverse effect of anal leakage of oily feces. Furthermore, in many patients, the magnitude of weight loss achieved is insufficient to ameliorate the debilitating and life-threatening complications of obesity.

Lessons from bariatric surgery

Among currently available obesity treatments, bariatric surgery alone routinely achieves substantial, permanent weight loss and a reduction in overall mortality, despite the perioperative risk of death from, for example, hemorrhage, sepsis or pulmonary embolism.[2,3] Several procedures are efficacious in reducing body weight, and the field is continuing to develop (Figure 2). Gastric banding, one of the most frequently performed procedures, reduces food intake by limiting the quantity that can be ingested comfortably and by increasing the satiating effect of food.[4] However, compared with gastric banding, appetite and weight loss are usually reduced more efficiently with procedures that incorporate an element of gastrointestinal bypass, such as Roux-en-Y gastric bypass (RYGB).[2,3,5] Furthermore, coexistent type 2 diabetes mellitus is ameliorated much more rapidly by RYGB than by gastric banding, even before substantial weight loss has occurred.[6] These differences in outcome are thought to arise mainly from altered secretion of several gut hormones that occurs after RYGB but not after gastric banding.[7,8]

Dietary restriction and loss of body weight are routinely accompanied by a rapid fall in plasma leptin levels and, consequently, by an increase in hunger.[9] By contrast, appetite is reduced markedly after RYGB, despite substantial weight loss and reduced plasma leptin concentrations.[5] This phenomenon is illustrative of the profound importance of afferent signals from bowels to brain for the regulation of energy homeostasis. The nature of some of these signals is discussed below.

Gut hormones

Peptide YY

Peptide YY (PYY) is an amidated peptide originally isolated from porcine intestine by Tatemoto and Mutt[10] at the Karolinska Institute (Stockholm, Sweden), and named by them after the tyrosine (Y) residues at each end of its 36-amino acid chain. PYY shares considerable sequence homology and a common tertiary structure, the PP-fold, with another gut hormone, pancreatic polypeptide, and with the neurotransmitter NPY. PYY(1–36) is an agonist at three of the mammalian NPY receptors, namely Y_1, Y_2 and Y_5. However, its N-terminus is readily truncated by dipeptidyl peptidase 4 (DPP4),[11] which results in the major postprandial circulating form PYY(3–36).[12] In contrast to the relatively non-selective actions of PYY(1–36), PYY(3–36) is a selective Y_2 receptor agonist.[13]

PYY is synthesized by mucosal enteroendocrine L cells, located predominantly in the distal gut (Table 2).[14] Release of PYY occurs following a meal, in proportion to energy intake, with maximal levels achieved 1–2 h

Key points

- The history of pharmacological therapies for obesity is characterized principally by inefficacy and marked adverse effects
- Robust weight loss can be achieved through bariatric surgery, with associated changes in the intestinal hormonal response to calorie intake
- Gut hormones such as glucagon-like peptide 1, peptide YY, pancreatic polypeptide, glucagon and islet amyloid polypeptide act in an integrated fashion to modulate appetite and energy expenditure
- A potential therapy for obesity might be based on the concept of pharmacological mimicry of the hormonal milieu after bariatric surgery
- Development of such therapies will, however, require improved understanding of the interactions between hormones and of their integration with other signals of nutritional status

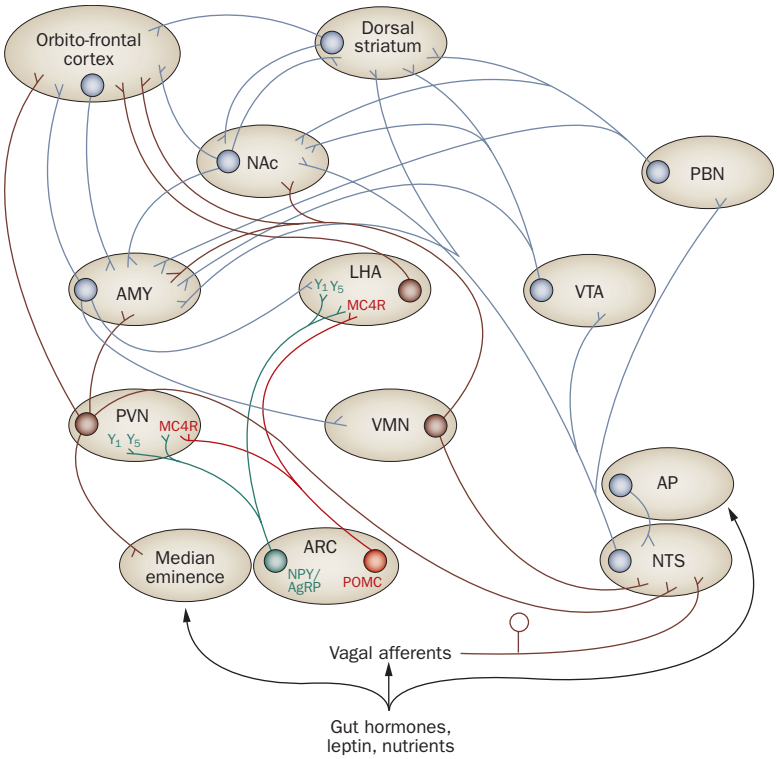


Figure 1 | A complex neuronal network within the CNS controls energy homeostasis. Abbreviations: AMY, amygdala; AP, area postrema; ARC, arcuate nucleus; LHA, lateral hypothalamic area; NAc, nucleus accumbens; NTS, nucleus of the tractus solitarius; PBN, parabrachial nucleus; PVN, paraventricular nucleus; VMN, ventromedial nucleus; VTA, ventral tegmental area.

Table 1 | Selected obesity drug development targets in the CNS

Target	Mode of action	Comments
Antiepileptic	Unknown	Zonisamide and bupropion combination in phase II clinical trials Topiramate and phentermine combination completed phase III clinical trials
Cannabinoid receptor 1	Antagonist	Marketing authorization for rimonabant withdrawn (psychological adverse effects)
Ciliary neurotrophic factor receptor	Agonist	Peptide analog inactivated by antidrug antibodies in phase II clinical trials
Dopamine, 5-hydroxytryptamine and norepinephrine	Reuptake inhibition	Tesofensine in phase II and phase III clinical trials
Dopamine and norepinephrine	Reuptake inhibition	Bupropion currently marketed as aid to smoking cessation
5-hydroxytryptamine	Non-selective agonist	Fenfluramine, dexfenfluramine withdrawn (5-hydroxytryptamine receptor subtype 2b-mediated cardiac valvulopathy and pulmonary hypertension)
5-hydroxytryptamine and norepinephrine	Reuptake inhibition	Marketing authorization for sibutramine suspended in Europe (cardiovascular adverse effects)
5-hydroxytryptamine receptor subtype 2c	Agonist	Lorcaserin completed phase III clinical trials
Leptin receptor	Agonist	Recombinant leptin and pramlintide combination in phase II clinical trials
Melanin-concentrating hormone receptor 1	Antagonist	Orally available compounds cause weight loss in animal models of obesity
Melanocortin-4 receptor	Agonist	Orally available MK-0493 inadequate effect with dose-limiting nausea in phase II clinical trials
Opioid receptor	Antagonist	Bupropion and naltrexone combination completed phase III clinical trials
Orexin receptor 1	Antagonist	In development for treatment of insomnia
Sympathomimetic	Agonist	Phentermine not licensed in Europe (cardiovascular adverse effects)
Y_1 receptor	Antagonist	In preclinical development
Y_2 receptor	Agonist	Intranasal $PYY_{3–36}$ inadequate effect with dose-limiting nausea in phase II clinical trials
Y_4 receptor	Agonist	Various drugs in phase I and phase II clinical trials
Y_5 receptor	Antagonist	Orally available MK-0557 inadequate effect in phase III clinical trial

after meal consumption.[14] Both fasting and postprandial plasma PYY concentrations are increased after RYGB but not after gastric banding.[8] Stimulation of endogenous PYY secretion by nutrients is a complex process, which is enhanced by intraluminal lipid hydrolysis, as well as by a high-protein diet.[15–17]

When intravenously infused to achieve plasma concentrations approximately equivalent to postprandial levels, PYY(1–36) inhibits gastric acid secretion, gastric emptying, mouth-to-cecum transit time and cephalic phase gallbladder contraction in humans.[18–20] The anorectic effect of PYY, however, is mediated not by the relatively non-selective PYY(1–36) but by the selective Y_2 receptor agonist PYY(3–36), via interactions with both the vagus nerve and the hypothalamus. In the vagus nerve, afferent discharges are stimulated by PYY(3–36),[21] whereas, in the arcuate nucleus, PYY(3–36) acts at presynaptic Y_2 receptors to inhibit NPY neurons and disinhibit POMC neurons.[22] These effects translate into reduced body weight in animal models of obesity with repeated administration of the peptide.[23,24]

In humans, intravenous infusion of PYY(3–36) reduces food intake in both lean adults and those with obesity.[25] The range of plasma PYY concentration associated with this anorectic effect is relatively narrow, and nausea occurs when it is exceeded.[26–28] Nausea and vomiting have occurred in association with a rapid rise in plasma PYY concentration in clinical trials of both intranasal and oral preparations of PYY(3–36).[29,30] This acute dose-limiting adverse effect might explain the failure of chronic dosing with intranasal PYY(3–36) to reduce body weight in study participants with obesity.[29] However, sensitivity to the anorectic effect of PYY(3–36) is as strong in humans with obesity as it is in lean individuals.[25] Furthermore, the incidence of nausea after RYGB gradually diminishes with time and weight loss is most prominent in patients who exhibit the greatest postprandial excursions of PYY and other L-cell hormones.[31] Therefore, the Y_2 receptor will probably remain a focus of antiobesity therapy development.

Pancreatic polypeptide

Pancreatic polypeptide is an amidated 36-amino acid peptide that is secreted postprandially under vagal control by pancreatic islet PP cells (Table 2).[32–34] This hormone is a high-affinity agonist of the Y_4 receptor and also exhibits modest agonist activity towards the Y_5 receptor.[35] Transgenic overexpression of pancreatic polypeptide in murine pancreatic islets reduces food intake, while administration of anti-pancreatic polypeptide

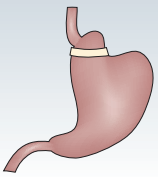
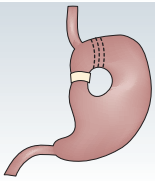
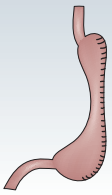
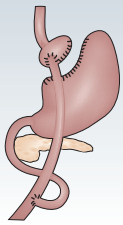
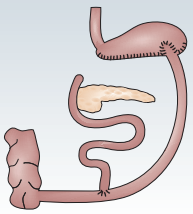
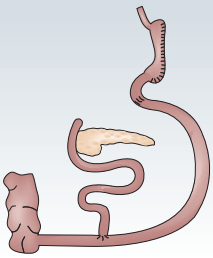
Procedure	Anatomy	Malabsorption	Hormone effect	Diabetes resolution	Weight loss
Adjustable gastric banding		–	Ghrelin ↑ PYY No change GLP-1 No change	With weight loss	+
Vertical banded gastroplasty		–	Ghrelin ↑ PYY No change GLP-1 No change	With weight loss	+
Sleeve gastrectomy		–	Ghrelin ↓ PYY ↑ GLP-1 ↑	With weight loss	++
Roux-en-Y gastric bypass		–	Ghrelin ↑ or no change PYY ↑↑ GLP-1 ↑↑	Rapid	++
Biliopancreatic diversion		+	Ghrelin ↑ or no change PYY ↑↑ GLP-1 ↑↑	Rapid	++
Duodenal switch		+	Ghrelin ↓ PYY ↑↑ GLP-1 ↑↑	Rapid	++

Figure 2 | Comparison of bariatric surgical procedures. Adjustable gastric banding is usually performed laparoscopically. A rigid ring that incorporates a fluid-filled reservoir is positioned around the upper stomach, which restricts gastric volume and outflow. This procedure has replaced vertical-banded gastroplasty, in which a small gastric pouch is formed with staples and outflow restriction is achieved by a rigid, nonadjustable band, positioned at the base of a pouch. In sleeve gastrectomy, the gastric volume is reduced solely by excision of the fundus, which is the principal location of X/A-like cells. In Roux-en-Y gastric bypass, a small stomach pouch is divided from the remainder of the stomach, which remains *in situ* and in continuity with the duodenum. In biliopancreatic diversion, food moves from a gastric pouch, formed by horizontal partial gastrectomy, directly into the ileum. The duodenal switch is a development of biliopancreatic diversion. The procedures differ in that gastric volume is reduced by a sleeve gastrectomy and pyloric function is preserved by surgically connecting the ileum to the duodenum immediately distal to the pylorus. Abbreviations: PYY, peptide YY; GLP-1, glucagon-like peptide-1.

antiserum abolishes this effect.[36] Peripherally administered pancreatic polypeptide acutely reduces food intake and gastric emptying in mice, whereas repeated administration leads to reductions in body weight gain and energy expenditure.[37] These changes are associated with reduced expression of NPY and orexin mRNA in the

Table 2 | Types of enteroendocrine cells and their secreted products

Cell type	Secreted hormone	Location
α cells	Glucagon	Pancreas (islets of Langerhans)
β cells	Insulin, islet amyloid polypeptide	Pancreas (islets of Langerhans)
PP cells	Pancreatic polypeptide	Pancreas (islets of Langerhans)
δ cells (D cells)	Somatostatin	Pancreas (islets of Langerhans)
G cells	Gastrin	Stomach Occasionally in the pancreas
X/A-like cells	Ghrelin, nesfatin-1	Stomach Occasionally in the small intestine
GIP cells (K cells)	GIP, xenin	Small intestine
S cells	Secretin	Small intestine
I cells (CCK cells)	Cholecystokinin	Small intestine
N cells	Neurotensin	Small intestine
L cells	PYY, GLP-1, GLP-2, oxyntomodulin	Small and large intestine

Abbreviations: CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP, glucagon-like peptide; PYY, peptide YY.

hypothalamus.[37] However, the effects of exogenous pancreatic polypeptide on food intake and gastric motility are dependent on intact vagal signaling.[37,38]

In lean humans, intravenous infusion of pancreatic polypeptide, in amounts sufficient to achieve plasma concentrations similar to normal postprandial levels, leads to delayed gastric emptying and reduced acute food intake.[39,40] Similar findings have been made in individuals with obesity secondary to Prader–Willi syndrome.[41] No data have yet been published on the effect of pancreatic polypeptide on energy expenditure in humans. Nevertheless, the anorectic effect of pancreatic polypeptide suggests that Y_4 receptor agonists may be useful in the treatment of obesity.

Islet amyloid polypeptide

Islet amyloid polypeptide (IAPP, also known as amylin) is an amidated 37-amino acid peptide, containing one intrachain disulfide bond, that was first isolated and sequenced from diabetic human pancreas.[42] IAPP is co-secreted with insulin from pancreatic β cells and is the endogenous ligand for a receptor complex comprising the calcitonin G-protein-coupled receptor in association with receptor activity-modifying protein 3.[43] The principal actions of IAPP are the retardation of gastric emptying and the inhibition of meal-stimulated glucagon secretion, thus contributing to the control of blood glucose in an insulin-sparing fashion.[44–47] However, IAPP also has an acute anorectic effect in rodents, mediated via the area postrema.[48] Rodent studies also provide evidence of an anorectic synergy when IAPP is coadministered with either PYY(3-36) or cholecystokinin (CCK).[49,50]

Pramlintide, an analog of IAPP, is licensed in the US, but not in Europe, as an adjunct to insulin treatment for individuals with type 1 and type 2 diabetes mellitus. Pramlintide therapy improves glycemic control, particularly in the postprandial state, and reduces exogenous insulin requirements.[51] Nausea is the most frequent adverse effect associated with the use of this drug. A modest reduction in body weight occurs during chronic treatment—an effect which can be accentuated in humans by coadministration with leptin.[52,53] No published data in humans are available regarding its synergy with either PYY(3–36) or CCK.

Glucagon-like peptide 1

A cleavage product of the proglucagon precursor (Figure 3), glucagon-like peptide 1 (GLP-1) functions both as a brainstem neurotransmitter and as a hormone, with GLP-1(7–36) amide as its major circulating form.[54] GLP-1 is released into the circulation following a meal, in proportion to energy intake, by enteroendocrine L cells.[55,56] Release is stimulated by enteric neuronal signals, as well as by direct interactions between gut luminal contents and receptors expressed on the luminal surface of L cells, such as G-protein-coupled receptor 119 (GPR119).[57,58] Both fasting and postprandial concentrations of GLP-1 are increased after RYGB but not after gastric banding.[8]

GLP-1 functions as an incretin, that is, as a physiological, glucose-dependent, insulin secretagogue, the action of which is to potentiate postprandial insulin release.[59] It also inhibits glucagon secretion, delays gastric emptying[60,61] and inhibits food intake.[62] Chronic subcutaneous infusion of GLP-1 in patients with type 2 diabetes mellitus results in weight loss and improved glycemic control.[63] However, native sequence GLP-1 is not suitable for use as a drug owing to its rapid inactivation by DPP4.[64]

Several GLP-1 receptor (GLP1R) agonist peptide drugs (so-called 'incretin mimetics') are licensed, or in phase II and phase III clinical development, for subcutaneous injection in the treatment of type 2 diabetes mellitus. Exenatide is the pharmaceutical name for exendin-4, a DPP4-resistant peptide originally isolated from the saliva of *Heloderma suspectum*, the Gila monster lizard.[65] Liraglutide is an analog of GLP-1(7–37) with an acylated side chain that binds albumin in the circulation, thereby retarding clearance of the drug.[66] As well as improving glycemic control, this class of drug also reduces body weight.[67–69] Nausea is the most frequent adverse effect, but the difference in the extent of weight loss of patients who have and those who have not experienced nausea is minor.[70]

In addition to parenteral incretin mimetics, oral, nonpeptide GLP1R agonists have been developed,[71] as well as a peptide analog of GLP-1, formulated for oral administration, which is being tested in phase I clinical trials.[72] An alternative to the development of GLP1R agonists is to increase the concentration of endogenous GLP-1 in the circulation, either by inhibiting its degradation or by stimulating its release. The former is accomplished by DPP4 inhibitors, such as sitagliptin and vildagliptin, which are currently licensed for the treatment of type 2 diabetes mellitus. However, DPP4 inhibitors do not cause substantial weight loss, potentially because DPP4 modifies a multitude of peptides with diverse roles. Amongst those peptides is PYY(1–36), the N-terminus of which is truncated by DPP4 to produce

the anorectic Y_2 receptor agonist, PYY(3–36).[11] By contrast, selective GPR119 agonists, which stimulate release of endogenous GLP-1, have exhibited anorectic and weight-reducing properties in early preclinical studies.[73] Several pharmaceutical companies are developing GPR119 agonists as potential treatments for both type 2 diabetes mellitus and obesity.[74]

Glucagon

Glucagon is a 29-amino acid peptide derived from proglucagon (Figure 3) and secreted by pancreatic islet α cells (Table 2). Its principal actions are to stimulate hepatic glycogenolysis and gluconeogenesis and, hence, to maintain blood glucose concentrations in the physiological range during fasting and exercise. Glucagon is also released into the hepatic portal vein at the start of meals.[75,76] In rodents, a high-protein diet elicits the release of glucagon into the hepatic portal vein more efficiently than carbohydrates or fat.[77] The concentration of glucagon in portal blood is greater than that in the systemic circulation, mainly as a result of dilution via the hepatic arterial flow, the major site of clearance of glucagon from the circulation being the renal capillary bed.[78]

Peripherally administered glucagon reduces acute food intake; in rodents, the most potent effect occurs when the hepatic portal vein is infused directly.[79] This anorectic effect is dependent on intact signaling by the hepatic branch of the vagus.[80] In humans, acute food intake is reduced when glucagon is injected intramuscularly at a dose sufficient to cause hyperglycemia and nausea.[81,82] However, nausea is not required to produce the anorectic effect, since low-dose intravenous infusion reduces acute food intake without adverse symptoms.[83]

In addition to altering satiety, glucagon also has inotropic (increased force of heart muscle contraction) and chronotropic (increased heart rate) effects that are independent of adrenergic-receptor activity.[84] Furthermore, at pharmacological blood concentrations, and in the absence of insulin, it also has lipolytic effects.[85] These characteristics potentially increase energy expenditure and thus promote weight loss during chronic hyperglucagonemia. As hyperglycemia and glycosuria can also develop under the same circumstances, the potential role for glucagon receptor (GCGR) agonists in treating obesity and diabetes mellitus is uncertain. Nevertheless, preclinical studies suggest that combining GCGR and GLP1R agonist activity in the same molecule might maximize the effects on food intake and energy expenditure while preventing the development of hyperglycemia.[86,87]

Oxyntomodulin

Oxyntomodulin is another cleavage product of proglucagon (Figure 3). Like GLP-1 and PYY, it is released rapidly from intestinal L cells after meals (Table 2), in proportion to calorie intake, and its secretion is enhanced by RYGB.[88–90] The effects of acute administration of oxyntomodulin in humans include prolongation of gastric emptying, inhibition of gastric and pancreatic exocrine secretion and reduction of food intake.[91–94] In addition, repeated subcutaneous administration causes marked weight loss in patients with obesity.[95] Possibly, weight loss occurs not only as a result of reduced food intake but also owing to increased energy expenditure.[96]

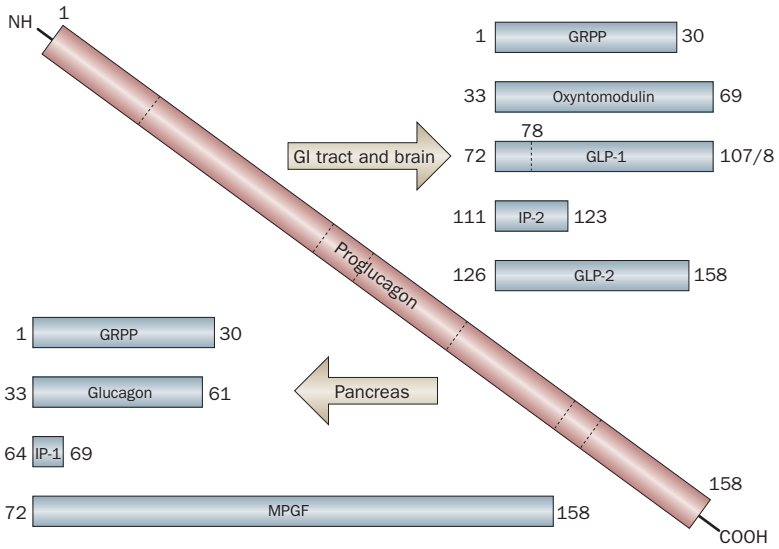


Figure 3 | Tissue-specific proglucagon cleavage. Proglucagon is expressed in the pancreas, gastrointestinal tract and brain. Proteolytic cleavage by prohormone convertases 1 and 2 occurs in a tissue-specific manner. Glucagon is the major secretory product in the pancreas, whereas GLP-1, GLP-2 and oxyntomodulin are synthesized in the gastrointestinal tract and brain. Abbreviations: GRPP, glicentin-related polypeptide; IP, intervening peptide; GI, gastrointestinal; GLP, glucagon-like peptide; MPGF, major proglucagon fragment. Numbers refer to position in proglucagon peptide sequence.

The peptide sequence of oxyntomodulin comprises the entire 29-amino acid sequence of glucagon with a C-terminal octapeptide extension.[97] Limited agonist activity is retained at the GCGR but the anorectic effect of oxyntomodulin is mediated predominantly via GLP1R.[98,99] As with GLP-1, oxyntomodulin is degraded by DPP4 and neprilysin[100,101] and rapidly cleared from the circulation after subcutaneous injection.[95] Nevertheless, the effects of oxyntomodulin in humans on food intake, energy expenditure and body weight, which are achieved without altering glucose homeostasis,[95,96] suggest that it is a potentially valuable target for development of anti-obesity therapies.

Cholecystokinin

CCK is released postprandially by endocrine I cells (Table 2) in the small intestine.[102,103] Circulating in various cleaved forms of different length (for example, CCK-58, CCK-33, CCK-22 and CCK-8) that each contain a sulfated heptapeptide C-terminus, CCK is an agonist of the cholecystokinin receptor type A (CCK-AR, also known as CCK_1R) on vagal afferent fibers.[104] Its effects include stimulation of gallbladder contraction and pancreatic enzyme secretion and retardation of gastric emptying.[105,106] In addition, the release of PYY and GLP-1 after lipid ingestion and the inhibition of ghrelin secretion are dependent on signaling via the CCK-AR.[17,107] As well as having endocrine and possibly paracrine effects, CCK-8 is synthesized and released

as a neurotransmitter within the CNS, binding to both CCK-AR and CCK-BR (CCK_2R).[108]

Sham feeding studies in rats show that infusion of CCK induces the behavioral satiety sequence.[109] However, this distinct role in meal termination may not translate into regulation of long-term energy intake. When CCK is administered chronically to rats by intraperitoneal infusion at the start of every meal, reduced meal size is rapidly compensated for by increased meal frequency.[110] The physiological role of CCK seems to be similar in humans. Food intake is reduced acutely when CCK is administered by intravenous infusion;[111] however, repeated administration of an orally available CCK-AR agonist failed to cause weight loss in obese human volunteers in a phase II clinical trial.[112]

In the light of these findings, the place of CCK in the regulation of body weight, as opposed to satiety, has been in doubt. However, weight loss has been observed in rodents during chronic treatment with parenteral CCK-AR agonists.[113,114] Notably, when rats increase meal frequency to compensate for the reduced intake at meals during repeated CCK-8 infusions, the size of meals nevertheless remains reduced, suggesting that tolerance to treatment potentially does not occur.[110] Furthermore, when CCK is coadministered with leptin in rodents, transport of leptin across the blood–brain barrier is enhanced, which leads to increased phosphorylation of signal transducer and activator of transcription 3 (STAT3) in the arcuate nucleus and increases the loss of body weight.[115] Anorectic synergy of CCK has also been demonstrated in combination with IAPP.[50] These findings suggest that potential still exists for CCK-based antiobesity therapy.

Ghrelin

Ghrelin is a 28-amino acid peptide hormone that is acylated by ghrelin O-acyltransferase (GOAT) and secreted by endocrine cells in the gastric fundus.[116–118] An endogenous ligand for the growth hormone secretagogue receptor type 1 (GHSR), ghrelin stimulates the release of growth hormone from the pituitary gland[117] and also has an important role in appetite regulation.[119] Plasma ghrelin concentration peaks preprandially in humans, both when meals are delivered at scheduled times[120] and when individuals are allowed to eat at will but are deprived of time cues.[121] Furthermore, in humans, intravenous infusion of ghrelin in lean individuals causes a marked increase in appetite and food intake.[122] Ghrelin, therefore, seems to induce hunger and to function as a meal initiator.

A negative correlation exists in humans between fasting plasma ghrelin concentration and BMI.[123] However, this association is not replicated in the postprandial state; ghrelin concentration does not change after a test meal in patients with obesity, whereas it declines markedly in lean individuals.[124] Furthermore, healthy individuals with obesity seem to be more sensitive to the acute orexigenic effects of intravenous infusion of ghrelin than lean individuals.[125] Disruption of ghrelin signaling, either by direct interaction with the GHSR or via a reduced GOAT-mediated acylation of ghrelin may, therefore, prove useful for the treatment of obesity. Conversely, the use of GHSR agonists has been advocated as a potential treatment for cachexia in patients with terminal disease.[126] Through the ability to stimulate release of growth hormone, GHSR agonists could also provide a means of reducing frailty in old age.[127] Nevertheless, the potential for treatment to impair glucose tolerance is of concern, particularly in the latter setting.

Conclusions

The importance of signals arising from the gastrointestinal tract for the maintenance of energy homeostasis is illustrated by the metabolic changes that occur after RYGB. Whereas starvation-induced weight loss is accompanied by downregulation of the thyroid axis,[128] this phenomenon does not occur after RYGB.[129] Furthermore, despite the fall in plasma leptin concentration that accompanies profound weight loss, appetite is permanently reduced after RYGB, which allows sustained control of body weight in the long term. Increased secretion of gut hormones is potentially important in this process, as inhibition of their release leads to increased appetite and food intake.[31]

Recognition of the importance of gut hormones in energy homeostasis has led to efforts to harness their effects in the treatment of obesity. Nevertheless, while food intake can be reduced acutely by administration of hormones or their analogs, this approach does not always translate into weight loss in humans. One possible explanation is that a treatment capable of enhancing mealtime satiety may not necessarily have any effect on either long-term food intake or energy expenditure. Another explanation is that nausea is a common dose-limiting adverse effect in humans, because it represents one end of the spectrum of satiety, the other end being ravenous hunger. By contrast, nausea is absent in some animal species and difficult to measure objectively in others, which might allow greater doses of hormone to be administered in preclinical studies than would be tolerated in humans. As nausea probably occurs at peak plasma concentrations of the drug, its incidence might be minimized by the use of sustained-release formulations. Furthermore, as with bariatric surgery, dietary re-education could be important in avoiding nausea, as endogenous postprandial hormone release and exogenous hormone treatment might have additive satiating and hence potentially nauseating effects. Possibly, nausea might represent a specific physiological effect of one or more hormones, perhaps as part of the response to ingestion of a noxious substance. One might, therefore, speculate that an anorectic effect may be achieved, without nausea, by coadministration of non-nauseating doses of several hormones.

In summary, much is now known of the individual effects on food intake of several hormones released by the gastrointestinal tract. However, while it is likely that these hormones are involved in regulating appetite and energy expenditure, the complexity of the enteroendocrine system is such that many important questions

remain unanswered. The challenge will, therefore, be to understand not only the physiological roles of individual hormones, but also how the multitudes of hormonal, neuronal and metabolic inputs to the CNS are integrated in a comprehensive model of energy homeostasis. Perhaps only once this goal has been achieved will we be able to harness the full potential of the gut to fight obesity.

Review criteria

A search for original articles with publication dates up to and including 2010 was performed in MEDLINE and PubMed. The search terms included "appetite", "satiety", "obesity", "energy balance", "energy homeostasis", "gut hormone" and "bariatric surgery". We also searched the reference lists of identified articles for further papers.

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