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Review

The role of gut hormones and the hypothalamus in appetite regulation

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Abstract. The World Health Organisation has estimated that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million obese. Obesity is associated with an increased risk of diabetes, cardiovascular events, stroke and cancer. The hypothalamus is a crucial region for integrating signals from central and peripheral pathways and plays a major role in appetite regulation. In addition, there are reciprocal connections with the brainstem and higher cortical centres. In the arcuate nucleus of the hypothalamus, there are two major neuronal populations which stimulate or inhibit food intake and influence energy homeostasis. Within the brainstem, the dorsal vagal complex plays a role in the interpretation and relaying of peripheral signals. Gut hormones act peripherally to modulate digestion and absorption of nutrients. However, they also act as neurotransmitters within the central nervous system to control food intake. Peptide YY, pancreatic polypeptide, glucagon-like peptide-1 and oxyntomodulin suppress appetite, whilst ghrelin increases appetite through afferent vagal fibres to the caudal brainstem or directly to the hypothalamus. A better understanding of the role of these gut hormones may offer the opportunity to develop successful treatments for obesity. Here we review the current understanding of the role of gut hormones and the hypothalamus on food intake and body weight control.

Key words: Appetite, Gut hormone, Hypothalamus

OBESITY has become an important worldwide health issue, with a rapidly increasing prevalence. In the UK, one quarter of adults are obese and one third of all adults are predicted to be obese by 2012 [1]. The World Health Organisation has estimated that by 2015 approximately 2.3 billion adults worldwide will be overweight and more than 700 million obese [2]. In Japan self-reported prevalence of obesity has remained consistently low over the last 30 years. However obesity is now increasing in middle-aged adults and partly associated with a western-style change in diet [3]. There is now clear evidence showing a link between obesity and increased risk of diabetes, cardiovascular events, stroke, cancer [4-6], obstructive sleep apnoea [7] as well as neurodegenerative diseases such as Parkinson's disease [8] and Alzheimer's disease [9].

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Obesity is due to a state in which energy intake exceeds energy expenditure over a prolonged period. In normal subjects, body weight is tightly regulated despite day-to-day variations in food intake and energy expenditure. However, because this system evolved to conserve energy it is biased towards the preservation of energy [10]. Signals relaying information such as the nutritional and energy status of the body, converge within the central nervous system (CNS). In humans it is also of note that psychological and emotional factors can drive food intake in excess of actual need. Furthermore, current modern lifestyles include easily available palatable foods and reduced levels of physical exercise. In rare cases, there are also mutations within genes encoding known appetite regulating hormones, resulting in obesity [11, 12].

Although current pharmacological and behavioural treatments for obesity result in initial weight loss, the effect is transient and followed by weight regain [13]. This reflects the complex systems involved in appetite regulation to avoid large fluctuations in body weight. In contrast, gastric bypass surgery is an established and effective treatment for obesity and results in sus-

tained weight loss [14]. However this treatment is limited due to significant complication rates. Although the mechanism of long-term weight loss following bariatric surgery is yet to be determined, several gut hormones have been implicated. For example, a decrease in circulating ghrelin and an increase in peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) levels have been found following bypass surgery [15-17].

Thus the ability to replicate the gut hormone profile associated with gastric bypass surgery, using pharmacological interventions could offer a promising treatment for obesity [18, 19]. We describe the current understanding of systems involved in appetite regulation within the CNS and gut and illustrate their complexity and potential as therapeutic targets for obesity.

Hypothalamic Control of Feeding

The hypothalamus plays a major role in the control of appetite. Based on early lesioning experiments in the hypothalamus, it was believed that the lateral hypothalamic area (LHA) was the 'hunger centre' and ventromedial hypothalamic nucleus (VMN) acted as a 'satiety centre' [20]. However, it has now been demonstrated that many more hypothalamic nuclei and neuronal circuits are intricately involved in appetite regulation, interacting with the brainstem and higher cortical centres. In addition to peripheral signals relaying via the brainstem and vagus nerve, some authors have suggested the presence of an incomplete blood-brain barrier (BBB) at the median eminence of the hypothalamus and area postrema of the brainstem, allowing peripheral circulating factors direct access to the CNS [21].

Within the arcuate nucleus (ARC) of the hypothalamus, there are two neuronal populations with opposing effects on food intake: neurons which co-express neuropeptide Y (NPY) and agouti related peptide (AgRP) stimulate food intake, whereas neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) suppress feeding. Both populations project to the paraventricular nucleus (PVN), although the ARC also communicates with other hypothalamic nuclei such as the dorsomedial nucleus (DMN), LHA and VMN.

Within POMC neurons, α-melanocyte-stimulating hormone (α-MSH) is produced and this binds to melanocortin-4 (MC4R) receptors in the PVN to suppress food intake [22]. Consistent with this, MC4R knock-out mice exhibit hyperphagia and obesity [23]. Similarly, in humans MC4R mutations account for approximately 6% of severe early-onset obesity and more than 70 different mutations have been associated with obesity [24]. Loos *et al.* [25] found that common variants near the MC4R gene influenced fat mass, weight and obesity risk.

In contrast to the established role of MC4R on food intake, the role of MC3R on appetite control is still unclear. MC3R-deficient mice show increased fat mass and reduced lean body mass [26], but selective MC3R agonists have no effect on feeding [27].

Neuronal expression of CART in the ARC co-localises with POMC and animal studies have demonstrated that intracerebroventricular (ICV) administration of CART inhibits feeding, whereas injection of CART antiserum ICV increases food intake [28]. Interestingly, CART injected directly into the PVN or ARC of fasted rats causes an increase in food intake at 1-4 hours [29], suggesting that CART has alternative effects on food intake depending on the site of administration.

NPY/AgRP neurons have extensive projections within the hypothalamus, including the PVN, DMN and LHA. ICV injection of NPY stimulates food intake in rats [30] and repeated daily injections of NPY result in chronic hyperphagia and increased weight gain [31]. The orexigenic effect of NPY is mediated by stimulation of hypothalamic Y1R and Y5R in addition to local inhibition of POMC neurons in the ARC [32]. In addition, AgRP acts as a selective antagonist at MC3R and MC4R in the PVN [33]. There is also evidence that NPY/AgRP and POMC/CART neurons are influenced by circulating leptin, insulin, glucose, amino acids and fatty acids [34].

In addition to receiving NPY/AgRP and POMC/CART projections from the ARC, the PVN also contains the anorectic thyrotropin-releasing hormone and corticotrophin-releasing hormone. Destruction of the PVN causes hyperphagia and obesity [35].

Other nuclei within the hypothalamus are also implicated in the control of food intake. The LHA contains the orexigenic hormones, melanin-concentrating hormone and orexin, and the DMN receives NPY/AgRP projections from the ARC [36]. In the VMN, brain-derived neurotrophic factor (BDNF) is highly expressed and suppresses food intake through MC4R signalling [37]. Selective deletion of BDNF results in obesity [38]. Figure 1 shows the key neuronal populations involved in appetite regulation and the converging of pe-

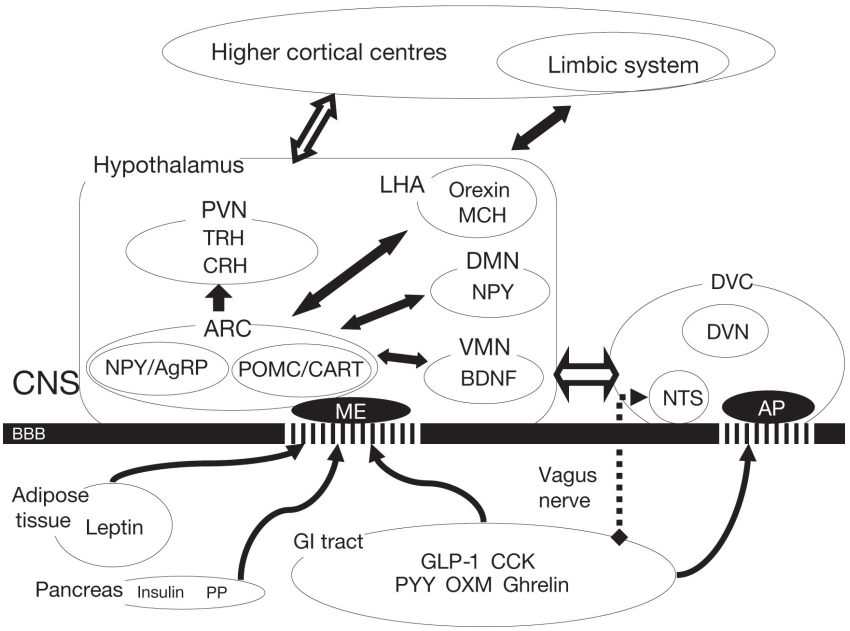

Fig. 1.

Appetite regulation is controlled by complex neuronal pathways which have reciprocal connections between the hypothalamus, brainstem and higher cortical areas. Peripheral signals conveying information can act via neural pathways via the brainstem and hypothalamus directly. Alternatively, due to the presence of an incomplete blood-brain barrier at the median eminence and area postrema, gut hormones and adiposity signals can act via the bloodstream to influence signalling of known appetite controlling pathways such as NPY/AgRP and POMC/CART neurons within the arcuate nucleus. Signals from higher cortical centres are integrated with peripheral signals within hypothalamic nuclei.

CNS, central nervous system; ARC, arcuate nucleus; NPY/AgRP, neuropeptide Y and agouti related peptide; POMC/CART, pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript; PVN, paraventricular nucleus; LHA, lateral hypothalamic area; DMN, dorsomedial nucleus; VMN, ventromedial hypothalamic nucleus; ME, median eminence; DVC, dorsal vagal complex; DVN, the dorsal motor nucleus of vagus; NTS, the nucleus of the tractus solitarius; AP, area postrema; GI tract, gastrointestinal tract; TRH, thyrotropin-releasing hormone; CRH, corticotrophin-releasing hormone; MCH, melanin-concentrating hormone; BDNF, brain-derived neurotrophic factor; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin; BBB, blood-brain barrier.

ripheral and central signals within the hypothalamus.

Brainstem

Within the brainstem, the dorsal vagal complex (DVC) is crucial in the interpretation and relaying of peripheral signals such as vagal afferents from the gut to the hypothalamus [39]. The DVC consists of the dorsal motor nucleus of vagus (DVN), area postrema (AP), and the nucleus of the tractus solitarius (NTS). Vagal afferents from the gut convey information such as gastric distension, gut hormone levels and fatty acids. Transection of all gut sensory vagal fibres results in increased meal size and meal duration [40, 41].

Within the brainstem, vagal afferent neurons have been shown to express a variety of receptors including cholecystokinin (CCK) 1R and CCK2R (at which both CCK and gastrin act) [42], Ob-R [43], Y2R [44], GLP-1 [45] and GLP-2R [46], growth hormone secretagogue receptor (GHS)-R1 at which ghrelin acts [47] and the orexin receptor, OX-R1 [48].

The expression of leptin and insulin receptors, and of glucose sensing mechanisms in the brainstem is similar to that seen in the hypothalamus [49]. There are also neuronal populations known to regulate appetite, such as POMC neurons which exist within the NTS. These demonstrate signal transducer and activator of transcription 3 (STAT-3) activation in response to leptin administration [50]. Furthermore, administration of leptin into the dorsal vagal complex suppresses food intake [49].

Therefore, signals from the periphery have pivotal roles in transmitting information via afferent vagal fibres to the caudal brainstem or directly to the hypotha-

Table 1. Summary of the main gut hormones and adiposity signals that influence food intake and body weight.

	Feeding	Receptor	Major secretion site	Other actions
Gut hormones				
PYY (3-36)	↓	Y2	L cells in gut	Delays gastric emptying
PP	↓	Y4, Y5	PP cells in pancreas	
GLP-1	↓	GLP-1	L cells in gut	Incretin, decreases blood glucose, delays gastric emptying, neurotrophic effect
GLP-2	-	GLP-2	L cells in gut	Intestinal trophic effect
OXM	↓	GLP-1	L cells in gut	
Glucagon	↓	GCGR	Pancreatic α cells	Increases blood glucose levels and insulin secretion
CCK	↓	CCK 1, 2	I cell of small intestine	Gall bladder contraction, relaxation of sphincter of Oddi, pancreatic enzyme secretion
Ghrelin	↑	GHS	stomach	Growth hormone secretion
Amylin	↓	AMY1-3	pancreatic β cells	Decreases blood glucose levels
Adiposity signals				
Insulin	↓	Insulin	pancreatic β cells	Decreases blood glucose levels, stimulates glycogen synthesis
Leptin	↓	Leptin (Ob-R)	adipocyte	Regulation of energy metabolism

PYY, peptide YY; PP, pancreatic polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; OXM, oxyntomodulin; CCK, cholecystokinin; GCGR, glucagon receptor.

lamus to modify appetite. Table 1 lists several peripheral appetite-related signals and their roles.

Reward system

The corticolimbic pathways are thought to be responsible for reward-associated feeding behaviour. Endocannabinoid and opioid receptors are largely distributed within the CNS and play a major role in increased feeding related to reward [51]. The administration of a μ-opioid receptor agonist into the nucleus accumbens preferentially stimulates intake of high fat diet when both fat and carbohydrate diets are presented simultaneously [52]. The endocannabinoid receptor antagonist, rimonabant, was until recently used as a treatment for obesity. However, unacceptable psychiatric side-effects resulted in withdrawal of the drug. Interestingly, leptin has been shown to reduce endocannabinoid levels in the hypothalamus [53].

Gastrointestinal tract

The gastrointestinal (GI) tract is referred to as the largest endocrine organ in the body. More than 30 gut hormone genes are expressed and more than 100 bioactive peptides are produced in the GI tract [54]. Anticipation of a meal and the presence of food in the stomach and the small intestine stimulate secretion of many of these hormones from the gut through mechanical and chemical stimuli. These signals are involved in the initiation of food intake as well as termination of meals. The satiating effect caused by distension of the stomach forms the basis of gastric balloon use in humans as a treatment for obesity [55, 56], although long term data of maintenance of weight loss using this method has been disappointing [57].

Gut Hormones

Peptide tyrosine tyrosine (PYY)

PYY was first isolated as a 36-amino acid peptide from porcine upper small intestine [58] and is a member of the PP-fold family. This family also includes NPY and pancreatic polypeptide (PP). PP-fold peptides act via G protein-coupled receptors: Y1, Y2, Y4, Y5 and Y6 [59]. Two circulating forms of PYY are released by L cells in the distal gut: PYY (1-36) and PYY (3-36). PYY (3-36), the major circulating form, is produced by cleavage of the N-terminal Tyrosine-Proline residues from PYY (1-36) by the enzyme dipeptidyl-peptidase IV (DPPIV) [60]. PYY (3-36) binds with highest affinity to the hypothalamic Y2R

causing a reduction in food intake [61]. It also binds to other Y receptors, although with much lower affinity.

Circulating PYY concentrations are low in the fasted state and rapidly increase following a meal, peaking at 1-2 hours and remaining elevated for several hours [62]. Ingestion of fat results in greater release of PYY than observed with ingestion of carbohydrate or protein meals with a similar caloric content [62]. Peripheral PYY administration causes a decrease in food intake and body weight gain in rats [63]. Similarly, in both lean and obese humans, PYY infusion reduces appetite and food intake [63, 64].

In addition to PYY's anorectic effect on food intake, it also increases energy expenditure [65] and delays gastric emptying in mice [66]. Although studies of circulating levels of PYY in obese and lean people have been conflicting [67, 68], some investigators have found that in obese subjects, circulating PYY levels are low [64, 69]. In contrast, PYY levels in patients with anorexia nervosa are reported to be high [70]. Obese people also have a blunted rise in PYY after a meal, possibly resulting in impaired satiety and hence greater food intake [71].

The anorectic effects of PYY (3-36) may act directly via an incomplete blood-brain barrier (BBB) in the median eminence of the hypothalamus, via vagal-brainstem-hypothalamic pathways, or both. Peripheral administration of PYY (3-36) increases c-fos expression (a marker of neuronal activation) in the ARC and direct injection of PYY (3-36) into the ARC inhibits food intake [63]. This effect is most likely mediated through the Y2R since the anorectic effect of peripheral PYY (3-36) administration is abolished in Y2R-null mice and intra-arcuate injection of a Y2R selective agonist also reduces food intake [63]. Furthermore, it appears that the anorectic effect of peripheral administration of PYY (3-36) in rats is in part due to vagal afferent signalling since the effect is abolished following bilateral subdiaphragmatic vagotomy and brainstem-hypothalamic pathway transectioning [44, 72].

In contrast to peripheral and intra-arcuate PYY (3-36) administration, when given into the third ventricle of the brain [73] or directly into the PVN [74], PYY (3-36) demonstrates an increase in food intake. This may be due to the effects of NPY on Y1R and Y5R, stimulation of which appear to cause an increase in food intake [75]. Therefore, PYY appears to have differing effects on food intake depending on the site of administration.

Pancreatic polypeptide (PP)

PP is secreted from PP cells in the pancreatic islets of Langerhans and is thought to reduce food intake directly through the Y4R in the brainstem and hypothalamus. It may also act via the vagus nerve to reduce food intake since the anorectic effects of PP are abolished by vagotomy in rodents [76]. Y4R expression is found in the AP, NTS, DVN, ARC and PVN [77]. An autoradiography study also identified saturable PP binding sites at the interpenduncular nucleus, AP, NTS and DVN [78], suggesting the major site of action of PP is the brainstem. In a similar manner to PYY, PP demonstrates differential effects on food intake depending on the route of administration. When given peripherally, PP acts as an anorectic hormone, whereas CNS administration stimulates food intake [30]. This may be due to a difference in receptor distribution or activation sites, although the exact mechanism is not yet clear.

Circulating PP concentrations rise after a meal in proportion to the calorific load. Although differences in circulating levels of PP between lean and obese people have been conflicting [79, 80], some studies have demonstrated significantly lower levels in obese subjects [81, 82]. In mice, acute and chronic peripheral administration of PP reduces food intake [76, 83]. In leptin-deficient *ob/ob* mice, repeated intraperitoneal injection of PP decreases body weight gain and ameliorates insulin resistance and hyperlipidaemia [76]. Furthermore, transgenic mice which overexpress PP are lean and demonstrate a reduction in food intake [84]. In normal-weight human subjects, intravenous infusion of PP results in a 25% reduction in 24-hour food intake [85]. Although PP could be a potential target in the search for anti-obesity drugs, it is rapidly degraded in the circulation and therefore the development of Y4 agonists may prove more successful.

Glucagon-like peptide-1

GLP-1, GLP-2, oxyntomodulin (OXM) and glucagon are proglucagon derived peptides. Proglucagon is expressed in the pancreas, L-cells of the small intestine and in the NTS of the brainstem [86, 87]. Glucagon is produced in the pancreas, whereas OXM, GLP-1 and GLP-2 are the major products in the brain and intestine [88].

GLP-1 is co-secreted with PYY from L cells in the intestine and has a potent incretin effect by stimulating insulin secretion in a glucose-dependent man-

ner. In addition, GLP-1 possesses trophic effects on pancreatic β cells [89]. DPPIV degradation and renal clearance rapidly inactivate and remove GLP-1 from plasma circulation [90, 91], resulting in a half-life of 1-2 minutes [92]. GLP-1 has two biologically active forms, GLP-1 (7-37) and GLP-1 (7-36) amide, the latter being the major circulating form in humans [93]. GLP-1 exerts its effect at the GLP-1R to stimulate adenylyl cyclase activity and cAMP production [94]. GLP-1R expression is widely distributed particularly in the brain, GI tract and pancreas [94, 95]. Circulating GLP-1 levels rise after a meal and fall in the fasted state. Recent evidence also suggests that levels rise in anticipation of a meal [96]. GLP-1 reduces food intake, suppresses glucagon secretion and delays gastric emptying [97]. Intravenous infusion of GLP-1 results in a dose-dependent reduction in food intake in both normal weight and obese subjects [98] although obese subjects have a blunted postprandial GLP-1 response compared to lean subjects [94].

Exendin-4, a naturally occurring peptide from the saliva of the Gila monster lizard, is a DPPIV-resistant GLP-1R agonist [99]. It has been licenced for the treatment of type 2 diabetes and has been shown to reduce food intake and body weight, and improve glycaemic control [100]. A once daily subcutaneous GLP-1 preparation, liraglutide, has been developed and demonstrates greater improvements in glycaemic control than exenatide given twice a day [101].

Glucagon-like peptide-2

Like GLP-1, GLP-2 is released from enteroendocrine cells in a nutrient-dependent manner. GLP-2 has been shown to have no effect on food intake in acute or chronic studies in both rodents and humans [102, 103]. However, GLP-2 has an intestinal trophic effect [104, 105] and chronic subcutaneous administration of GLP-2 stimulates crypt cell proliferation. As such, GLP-2 analogues have been developed for use in patients with inflammatory bowel disease [106]. In addition, some studies have demonstrated a reduction in gastric emptying in humans by GLP-2, although the effect is not as potent as GLP-1 [107].

Oxyntomodulin

OXM is another product of the proglucagon gene and is released from L-cells of the intestine in response to ingested food and in proportion to caloric intake [108]. Administration of OXM reduces food intake and increases energy expenditure in both rodents and humans [109-111]. OXM has relatively low affinity for the GLP-1R, binding approximately 50 fold less strongly than GLP-1. However the anorectic effect can be blocked by the GLP-1R antagonist exendin (9-39) [112] and is abolished in GLP-1R null mice [113], suggesting that OXM mediates its effects via the GLP-1R. Alternatively, there may be an as yet unidentified receptor through which OXM mediates an anorectic effect. Certainly, several actions of OXM appear to be independent of the GLP-1R [110, 114, 115]. For example, the cardiovascular effects of OXM are preserved in GLP-1R knock out mice [114]. Like GLP-1, OXM is inactivated by DPPIV and OXM analogues which are resistant to DPPIV degradation are being developed as potential obesity treatments [116].

Glucagon

Glucagon is produced by the α cells of the pancreatic islets. In contrast to GLP-1 and insulin, hypoglycaemia causes an increase in glucagon secretion resulting in hepatic glycogenolysis. Administration of intraperitoneal and subcutaneous glucagon in rats reduces food intake and meal size in addition to reducing body weight gain [117, 118]. Recently beneficial effects of a glucagon and GLP-1 co-agonist on obesity in rodents have been demonstrated [119, 120].

Ghrelin

Ghrelin is the only known orexigenic gut hormone. It was initially identified as an endogenous ligand for GHS-R in rat stomach. However the GHS-R is also expressed in the hypothalamic ARC [121] and levels of circulating ghrelin have been noted to increase before meals and fall rapidly after eating [122]. Both CNS and peripheral administration of ghrelin increases food intake and body weight with a reduction in fat utilisation in rodents [123, 124]. Fasting plasma levels of ghrelin are high in patients with anorexia nervosa [125] and in subjects with diet-induced weight loss [15], whilst obese subjects demonstrate lower fasting ghrelin levels and postprandial ghrelin suppression [126].

Peripheral administration of ghrelin increases c-fos expression in ARC NPY/AgRP neurons [127] and ablation of AgRP and NPY neurons completely abolishes the orexigenic effect of ghrelin [128]. When given centrally, ghrelin causes c-fos activation in several key appetite nuclei including the PVN and DMN. In addition, c-fos activity is increased in the brainstem,

particularly in the NTS and AP [129]. The GHS-R is expressed in the vagus nerve and blockade of gastric afferent vagal nerve in rats abolishes ghrelin-induced feeding and prevents the ghrelin-induced rise in c-fos expression in the ARC [47], suggesting a role for this pathway in mediating some of the orexigenic actions of ghrelin.

Cholecystokinin

CCK was the first gut hormone shown to modulate food intake [130]. CCK is secreted postprandially from the I cell of the small intestine into the circulation with a plasma half-life of a few minutes [131]. CCK levels rise rapidly reaching a peak within 15 minutes after a meal [131]. It is also reported to reduce food intake in humans and rodents [131, 132]. There are two CCK receptor subtypes: CCK1 and CCK2, both receptors being widely distributed in the brain including the brainstem and hypothalamus [133]. The anorectic action appears to be mostly mediated through CCK1R on vagal afferents [134, 135]. Although intermittent CCK infusion to rats at the onset of each meal reduces meal size, it is compensated for by an increase in meal frequency [136]. Furthermore, continuous intraperitoneal infusion of CCK using osmotic minipumps failed to suppress food intake at any time point over a two week period [137].

Amylin

Amylin is stored and released together with insulin in response to food intake. Circulating levels of amylin are higher in obese than lean subjects [138, 139]. Administration of amylin reduces food intake and body weight [140] and has been shown to improve glycaemic control and cause weight loss in patients with type 2 diabetes [141]. The anorectic action of amylin seems to be associated with the serotonin-, histamine- and dopaminergic system in the brain as well as inhibition of NPY release [138].

Peripheral adiposity signals

Adiposity signals are involved in the long-term regulation of energy balance, while gut peptides modulate food intake on a meal-by-meal basis.

Insulin

Circulating levels of insulin and leptin are proportional to adipose tissue and involved in the long-term regulation of energy balance. Insulin is synthesized in the β cells of the pancreas and secreted rapidly after a meal [142]. Circulating insulin crosses the BBB in a dose-dependent manner by a saturable receptor-mediated mechanism [143] and acts at the ARC where insulin receptors are highly expressed [144]. ICV administration of insulin results in a dose dependent suppression of food intake and body weight gain in baboons and rodents [145, 146]. Administration of antisense oligodeoxynucleotides targeting the insulin receptor precursor protein in the ARC results in hyperphagia and increased fat mass in rats [147]. Furthermore, central administration of insulin suppresses the fasting-induced increase in NPY mRNA levels [148] and increases POMC mRNA expression [149].

Leptin

The obese gene coding for leptin was isolated in 1994 [150]. Leptin is secreted by adipocytes with circulating levels proportional to fat mass [151]. Leptin is secreted in a diurnal and pulsatile pattern, with a peak at night [152]. Shifting meal time by 6.5 hours results in a 5-7 hour shift in leptin rhythm, indicating that the pattern of leptin secretion is dependent on daytime feeding rather than the endogenous circadian clock [153]. However, circulating leptin levels do not seem to change acutely following food intake [154].

Leptin is transported across the BBB by a saturable system [155] and exerts its anorectic effect via the ARC. In the ARC, both NPY/AgRP and POMC/CART neurons express leptin receptors [156]. Leptin inhibits NPY/AgRP neurons and activates POMC/CART neurons [22, 157] resulting in reduced food intake [22] and increased energy expenditure [158]. Among the three types of leptin receptors, the Ob-Rb receptor, which is highly expressed in the hypothalamus [159], is thought to be the main receptor involved in appetite regulation. *db/db* mice, caused by a mutation in the Ob-Rb receptor, have an obese phenotype [160, 161]. In addition, leptin-deficient *ob/ob* mice exhibit hyperphagia and obesity and this can be reversed by leptin treatment [162]. In obese children with congenital leptin deficiency, subcutaneous administration of recombinant leptin reduces fat mass, hyperinsulinaemia and hyperlipidaemia [163]. However, obesity in humans is often associated with high leptin levels and failure to respond to exogenous leptin. This leptin resistance may be attributable to reduced leptin

receptor signal transduction [164] or an impaired ability of the BBB to transport leptin [165].

Conclusion

Obesity is the result of an imbalance between energy intake and expenditure. Control of food intake and metabolism is maintained by complex pathways and neuronal circuits which themselves receive peripheral signals such as gut hormones. These can act directly at the hypothalamus or brainstem via the circulation or through vagal afferents to the brainstem. To tackle and solve the current obesity pandemic, development of effective pharmacological treatment is urgently needed. Further understanding of the pathogenesis of obesity and the role of these gut hormones in appetite regulation is essential. Elucidating the mechanism by which gut hormones contribute to long-term lasting weight loss after gastric bypass surgery could provide a real opportunity to develop successful treatments for obese patients.

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