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Appetite-Related Gut Peptides in Obesity and Binge Eating Disorder

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Abstract

The worldwide increase in obesity prevalence is a result of positive energy balance, with energy intake exceeding expenditure. The eating behavior in obesity ranges from mild passive overconsumption to excessive overeating with loss of control observed in binge eating disorder (BED). The signaling systems that underlie appetite control in BED are complex and, at this point, not well understood. The present review highlights the current knowledge of key components of the gut peptide system and examines evidence of defects in signaling that differentiate obese binge eaters from obese non–binge eaters. The signaling network underlying hunger, satiety, and metabolic status includes leptin and insulin from energy stores and cholecystokinin, glucagon-like peptide-1, peptide YY(3-36), and ghrelin from the gastrointestinal tract. Of the many gastrointestinal peptides, ghrelin is the only established appetite-stimulating one, whereas cholecystokinin, glucagon-like peptide-1, and peptide YY(3-36) promote satiety. Adipose tissue provides hormonal signals via leptin and insulin to the brain about energy stores and likely from adiponectin and resistin. Binge eating has been related to a dysfunction in the ghrelin signaling system. Moreover, the larger gastric capacity observed in BED may further reduce satiety signals and contribute to overeating.

Keywords

obesity; binge; eating; BED; hormones; appetite; peptide; ghrelin; CCK; leptin

Background

Obesity, which is associated with the metabolic syndrome[1,2] and chronic diseases such as diabetes, hypertension, and heart disease,[3] continues to increase in prevalence in developing countries[4,5] and the United States,[6] where it has reached epidemic proportions.[7] Obesity is highly resistant to treatment, with most of the weight lost regained within 5 years after dieting.[8,9] The nation's medical costs for obesity have been estimated at $70 to $100 billion per year and account for 9% of all health costs. Based on the latest criterion for obesity, body mass index >30 kg/m^2[2,10,11] at least 30% of Americans are obese.[6]

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Binge eating is characterized by eating, in a discrete period of time, an amount of food that is definitely larger than most individuals would eat under similar circumstances, accompanied by a sense of lack of control.[12] The prevalence of binge eating is disproportionately greater within the obese population,[13–15] and binge eaters represent a sizable and distinct subgroup.[15–17] The prevalence of some form of binge eating within the overweight population[18] has been estimated at 25% or higher.[15] Binge eating has also been implicated in the development of obesity[19,20] based on prospective longitudinal studies[21–23] and is a risk factor for weight regain following weight loss.[24]

Most research on binge eating has focused on patients with bulimia nervosa (BN),[25] who engage in binge eating followed by some form of compensation or purging; therefore, this review also covers some gut peptide literature in BN. Those diagnosed with BN, however, make up only a fraction of individuals who regularly binge eat.[26] The much larger group includes those who meet some, but not all, of the research criteria for binge eating disorder (BED).[12,25] BED is defined as recurrent episodes of binge eating (at least twice per week for 6 months) in the absence of the regular use of inappropriate compensatory behaviors, such as vomiting or using laxatives.[12] As noted by Susan Yanovski, “BED provides an opportunity to study the causes and concomitants of binge eating in the absence of compensatory behaviors.”[27] BED is listed in the appendix of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (*DSM IV-TR*), of the American Psychiatric Association[12,15,28] and currently falls into the eating disorder–not otherwise specified category. BED is likely to be included as a recognized eating disorder in the next revision of the *DSM* (*DSM-V*).[29] BED participants have been observed to consume binge meals, both inside and outside of the laboratory.[30–32] They are more resistant to weight loss treatment, have higher dropout rates, and show greater recidivism[33] than other obese participants. Unlike the classic eating disorders of anorexia nervosa (AN) and BN, BED is common in men—about 40% of the BED participants in overweight clinical and community samples.[15] Many obese individuals, 18% to 46% of those enrolling in weight loss programs, meet the criteria for BED.[34] With the rising epidemic of obesity, BED prevalence is also increasing, lending urgency to the study of its pathogenesis.

There is a scientific consensus supporting the clinical validity and utility of the BED diagnosis[35,36] and its distinction from nonpurging BN, who may compensate by other means, such as exercise.[37] The clinical soundness of BED is evidenced by its chronicity[38] and association with overall life impairment and general psychopathology.[15] The lifetime prevalence of other psychiatric diagnoses in those with BED is 60% to 72% as compared with 28% to 49% in controls.[39] Obese BED participants scored higher than matched non-BED obese controls on depression, anger, disinhibited eating,[40] impulsivity,[41,42] and overall psychopathology[43] and scored lower on self-esteem.[44] They had more frequent weight fluctuations and more shape-/weight-related concerns.[37] Compared with patients with BN, they had less restrained eating, less body image disturbance, and either less or similar psychological distress and psychiatric comorbidity.[45] Eating studies have shown that, in BED, binge size is somewhat smaller and eating rate is slower than in BN. Compared with obese non-BED patients, obese BED participants have greater caloric intake during both binge meals and regular meals.[46,47] There is recent evidence for moderate heritability of 0.50 in BED,[48] which implies a biological basis. Thus, there is a clear need to identify

possible disturbances in peripheral peptides involved in regulating food intake in BED. Currently, the biological substrates and mechanisms underlying BED, including the role of gut peptides, are not well understood.

Appetite-Related Peptides

There are 3 different sets of signals from the periphery: one from adipose tissue that exerts long-term regulatory mechanisms on food intake and the other two from the gastrointestinal (GI) tract that exert primarily short-term effects on food intake (Figure 1). This review focuses on the current literature on the peptides and related GI signals. Other signals and agents, such as blood sugar and insulin, circulating non-esterified fatty acids, catecholamines, and 5-hydroxytryptamine, are also involved in the control of food intake[49] but are beyond the scope of this review.

A number of peripheral peptides have been shown to induce satiety signals that act directly on the brain, indirectly via the vagus nerve, or by slowing the gastric emptying rate.[49,50] Such satiety peptides include leptin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY(3-36)), which rise after meals and which suppress food intake when administered peripherally[51,52] or centrally.[49,53] Postprandial CCK levels are apparently lower in individuals with BN.[49,54] This may be a consequence of slower gastric emptying,[54,55] delaying nutrients from reaching the duodenum to trigger CCK release (see the CCK, gastric emptying, and gastric capacity section).

Leptin—Nearly all released by adipose tissue, leptin is considered to be part of a feedback loop, in which low levels signal to the central nervous system (CNS) that energy stores are depleted.[56] Leptin, similar to insulin, decreases appetite when administered centrally by inhibiting CNS neurons that release neuropeptide Y (NPY) and agouti gene-related peptide (AgRP).[49] Leptin also acts on pro-opiomelanocortin (POMC) neurons, which regulate energy homeostasis in the hypothalamus.[57] Both animals[58] and humans[57] with POMC deficiency have increased appetite and are obese. Fasting causes a reduction of POMC mRNA in the arcuate nucleus; however, leptin is able to reverse this effect.[59] Therefore, it is possible that POMC neurons are responsible for most of leptin's actions in the CNS.[60] Fasting leptin is higher in the obese because of the presence of excess adipose tissue, and during weight and fat loss, leptin decreases.[61,62] Leptin increases slowly after meals,[63] which may not become apparent until 2 hours afterward.[64,65] It has been suggested that leptin plays a role in short-term satiety when released by the stomach,[66] a recently discovered small additional source of leptin besides the adipose tissue.[67,68] Overweight and obese women with either BED, subthreshold BED, or no binge eating showed an acute rise in leptin levels, which did not, however, correlate with fullness, following consumption of a brief liquid meal.[66] The meal was relatively high in carbohydrate (55%), which is known to stimulate leptin more than does fat.[69]

Despite its role in the regulation of food intake, leptin injections in obese animals[70] and humans[71] have not been highly efficacious in reducing food intake or body weight. This is likely because of the development of leptin resistance.[72,73] Leptin-resistant individuals, with high plasma levels of leptin, do not adequately decrease food intake in response to leptin.[73]

Fasting leptin is correlated primarily to body fat, regardless of the eating disorder, including AN and BN.[74] However, in one report, fasting leptin was higher in BED patients as compared with weight-matched non-BED controls.[75]

It has been suggested that melanocortin 4 receptor (MC4R) dysfunction may contribute to the development of BED in obese individuals.[76] In a 2003 report in the *New England Journal of Medicine*, obese carriers of an MC4R mutation were all diagnosed with BED, as compared with only 14.2% of obese participants and 0% of normal-weight participants without MC4R mutation.[76] It has also been suggested that MC4R dysfunction may be related to the severity of BED.[77] However, there is significant controversy surrounding these findings, as recent studies have been unable to replicate them.[78–81]

GLP-1—A peptide released in the lower gut, GLP-1, acts as an ileal brake for the upper GI tract and slows gastric emptying of liquid and solid meals. GLP-1 could reduce food intake in part by slowing gastric emptying with resulting greater gastric distension. However, there is also evidence that GLP-1 acts more directly via the vagus nerve as well as centrally.[49] In humans, most studies show decreased food intake after administration of GLP-1, with reduced hunger and increased fullness ratings, without reports of nausea.[49] GLP-1, however, is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of active GLP-1 of only 1 to 2 minutes. Studies are being performed to independently inhibit DPP-4 as well as to use DPP-4–resistant GLP-1 receptor agonists to reduce food intake.[82]

A synthetic analog of GLP-1, which resists DPP-4, exenatide (Byetta) from Amylin Pharmaceuticals, was approved by the Food and Drug Administration in 2005 as an adjunctive therapy in patients with type 2 diabetes already taking either metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but without achieving adequate glycemic control.[83,84] In clinical trials, the drug appeared to also cause modest weight loss and was associated with some side effects, including nausea, diarrhea, dizziness, and headache. About 3% of participants receiving the drug withdrew from the trial because of nausea. The greater incidence of side effects with the analog as compared with the natural peptide is likely due to differences in structure (53% amino acid homology with GLP-1) and function as well as the much longer half-life, 2.4 hours, of the drug, designed to resist DPP-4. The drug is administered by subcutaneous injection 2 or 3 times per day, but a long-acting formulation with once-per-week injections is anticipated.[85] Preliminary data show that fasting and postprandial levels of GLP-1 in BED versus non-BED obese groups do not differ.[86]

PYY(3-36)—Another lower gut peptide, PYY(3-36), is co-localized in the GI tract with GLP-1.[87] PYY(3-36), which penetrates the blood-brain barrier,[88] is also subject to deactivation by DPP-4 and has a half-life in the blood of 9 minutes.[82] Several clinical trials to treat obesity are under way with a PYY(3-36) nasal inhalant.[89] To date, however, intra-nasal PYY(3-36) has not been efficacious in inducing weight loss in obese individuals.[90] Although peripheral PYY(3-36) injections have been shown to suppress food intake in animals,[91] others initially were unable to obtain these results.[92] However, a recent study suggests that daily intermittent intravenous injections are required to produce a sustained effect of PYY(3-36) on food intake and adiposity.[93] PYY(3-36) is likely to reduce food

intake in part by acting on Y2 receptors on vagal afferents, which increase activity in the arcuate nucleus of the hypothalamus. Vagotomy in rats has been shown to abolish the feeding suppression by PYY(3-36),[94] although the concentrations of PYY(3-36) in the ileum and colon were not significantly affected by vagotomy in mice.[95]

Batterham et al[96] showed that PYY (3-36) levels were lower premeal in obese than in lean participants and rose less in the obese postmeal. They also showed that a PYY(3-36) intravenous infusion reduced food intake in both obese and lean individuals and decreased plasma ghrelin without inducing any side effects or nausea. Recently, there have been 2 reports of blunted levels of PYY(3-36) after a meal in the related disorder of BN.[97,98] Preliminary data of PYY(3-36) fasting and postprandial levels in BED versus non-BED obese groups, however, showed no differences.[86] Combining GLP-1 and PYY(3-36) reduces food intake in an additive fashion.[99] The peptides just reviewed as promoting satiety are not all inclusive, and other less established candidates include amylin,[100] pancreatic polypeptide, and oxyntomodulin.[100]

Ghrelin—A more recently discovered gut peptide is ghrelin.[101] A ligand for growth hormone secretagogue receptor, ghrelin is downregulated by excess growth hormone as in acromegaly.[102] Ghrelin is produced mainly by the stomach and when administered increases food intake in animals[103] and humans.[104] In animals, ghrelin enhances gut motility and speeds gastric emptying.[105] The effect on gastric emptying is less clear-cut in humans, where in one study, no effect was seen, as assessed by an acetaminophen tracer,[104] but in another study, fasting ghrelin levels correlated positively with subsequent gastric emptying rate.[106] Evidence is also mixed on whether peripherally administered ghrelin in animals acts via vagal afferents. A vagotomy abolished ghrelin-induced feeding in one study[107] but not in another.[108] Injection of ghrelin centrally[109] stimulates the release of the orexigenic neuropeptides NPY and AgRP in a number of brain areas, especially the arcuate nucleus of the hypothalamus.[110] Ghrelin-producing neurons have been found in the cerebral cortex and in the hypothalamus, where they stimulate NPY neurons.[111] Double-knockout mice for NPY and AgRP do not show the feeding-enhancing effect of ghrelin administration.[112]

In humans, ghrelin rises before meals and falls following meals.[112] The higher the energy value of a meal, the larger the postprandial decline in ghrelin.[113] Ghrelin also follows a diurnal pattern, increasing from the morning to the evening and reaching a higher peak before dinner than before breakfast.[112] This is consistent with the meal pattern in the United States, where dinner is usually the largest meal.[114] The rise in ghrelin from morning to evening appears to be greater in the obese than in the lean.[112] For example, obese participants showed a ghrelin rise of 63 pg/mL from 8 am before breakfast to 5:30 pm just before dinner, while the lean participants showed a rise of only 10 pg/mL during this period. In another study,[115] following several days of fasting, ghrelin rose more during the first 24 hours from morning to night in the obese than in the lean participants. Although BED was not assessed, it is likely that some of the obese were binge eaters, which may have contributed to the findings.

Surprisingly, fasting ghrelin has been found to be 27% lower in obese than in normal-weight individuals.[116] Ghrelin rises following weight loss in obese participants[117] and also rises in

animals during starvation.[118] There are contradictory findings on whether there is a smaller fall in ghrelin after a meal in obese as compared with lean humans.[112,119] The authors reporting the smaller fall in ghrelin propose that the smaller fall in ghrelin maintains hunger.[114] The lower fasting levels in obesity suggest that ghrelin is downregulated in response to overeating or excess body weight.[114,116] Indeed, fasting ghrelin is negatively correlated with percentage body fat, fasting insulin, and leptin, all of which are higher in obesity.[116,120,121] Ghrelin is lower in insulin-resistant obese individuals relative to insulin-sensitive controls.[122] Ghrelin, however, is elevated in Prader-Willi syndrome (PWS), the result of a genetic deletion in chromosome 15, which also leads to mental retardation and short stature and is associated with childhood onset of severe obesity.[123] High ghrelin levels may not account for the increased appetite seen in PWS, as administration of somatostatin to PWS adults reduces ghrelin levels with no effect on appetite.[124] However, somatostatin also inhibits the release of satiety peptides, which may cancel any of the effects on ghrelin. A ghrelin receptor antagonist[125] or antighrelin Spiegelmer, which inactivates ghrelin in the blood circulation,[126] may have the potential to reduce food intake.[114] These approaches have been shown to reduce food intake and body weight in animals.[126,127]

Fasting levels of ghrelin were found to be higher in BN[128] compared with normal participants and highest in AN.[121] In theory, AN participants who continue to starve themselves could develop resistance to their high ghrelin levels.[120] AN patients with the binging/purging subtype had somewhat higher ghrelin than the restricting subtype[129] in one report but not in another.[130] Fasting ghrelin was found to be lower in nonpurging bulimics than in purging bulimics.[130] In 2 recent articles, there was a smaller drop in ghrelin following a meal in BN patients than in controls.[98,131] Ghrelin levels have recently been reported in BED, indicating lower morning fasting ghrelin and a smaller postprandial decline in BED than in non-BED obese individuals.[66,132] The lower ghrelin levels in BED compared with non-BED individuals, although unexpected, are consistent with lower ghrelin levels in obese compared with lean participants and suggest down-regulation of ghrelin by habitual overeating. In another recent report, morning fasting ghrelin was found to be lower in both lean and obese female BED participants, suggesting that BED status, rather than overweight category, was the relevant characteristic.[133]

Obestatin—Obestatin, a 23-amino-acid peptide with a glycine residue at the C-terminal, was reported to be co-expressed with ghrelin, with opposite actions by reducing food intake and weight in animals.[134] Obestatin is postulated to become active by post-translational amidation at its carboxyl terminus.[135] Serum concentrations appear to be unaffected by fasting or refeeding,[134] and it is rapidly degraded when injected into the blood circulation in rats.[136] However, multiple studies have been unable to replicate the anorexigenic property initially reported, the ability to oppose ghrelin-induced stimulation of food intake, or obestatin's inhibition of gastric emptying and jejunal contractile activity in rodents.[137,138] Thus, the precise role of obestatin in controlling appetite and weight remains to be determined.

Adiponectin and resistin—Adiponectin, a peptide produced and released exclusively by adipose tissue,[139] may be an additional adipocyte signaling factor. There are similarities

between adiponectin and leptin; however, plasma levels of adiponectin remain relatively constant throughout the day, are not affected by food intake,[140] and correlate negatively with body mass index.[141] Obese individuals with diabetes have even lower plasma levels of adiponectin than nondiabetic obese individuals.[140,142–145] Diminished adiponectin may be a factor in the development of insulin resistance. Resistin, also known as adipose tissue–specific secretory factor, is another peptide secreted by adipocytes and acts on myocytes of skeletal muscle, hepatocytes, and adipocytes. Opposite in most of its actions to adiponectin, resistin is positively correlated with insulin resistance.[100] Adiponectin and resistin have yet to be studied in BED.

CCK, gastric emptying, and gastric capacity—A number of different GI peptides are known to be anorexigenic, promoting early termination of a meal. Of these, CCK is the most widely studied.[147] After a meal, CCK is released from endocrine I cells of the duodenum and the jejunum.[148] Studies in humans have shown that CCK administration inhibits food intake,[149,150] although a preload is generally necessary to demonstrate a satiation effect.[151] Peripherally administered CCK also acts on CCKA receptors in the gastric antrum, which are involved in the CCK-mediated inhibition of gastric emptying.[152] CCKA receptors are also found in the abdominal section of the vagus nerve,[153] and vagotomy abolishes the anorexigenic effect of the peptide in rats. A relationship between decreased plasma levels of CCK and increased hunger, as well as decreased fullness, has been reported in humans,[154] supporting a satiety role for CCK.

Gastric emptying rate influences the release of CCK, which is triggered by nutrients reaching the duodenum. In BN, fixed liquid meals empty more slowly,[54,55] delaying the duodenal release of CCK,[54,155] which may lead to less satiation.[156] With acetaminophen employed as a tracer,[157,158] gastric emptying of liquids in obese BED participants was not slower, and consistent with this, no significant reduction in CCK levels was observed, unlike that seen in BN.[66]

The capacity of the stomach can also influence satiation and affect the release of peptides. Distention of the stomach activates gastric stretch receptors and mechanoreceptors that transmit satiety signals.[159] A stomach with a large capacity may require a larger than usual meal to generate satiety signals, and consistent with this, gastric capacity correlates highly with test-meal intake.[55] Surgical reduction in gastric capacity to treat obesity reduces meal size, leads to marked weight loss,[160] and usually eliminates binge eating in BED,[161] confirming that a large stomach capacity helps maintain binge eating. Moreover, nonsurgical reduction of stomach capacity by external abdominal pressure[162] or by filling an intragastric balloon also reduces meal intake, especially in the short term.[163] A stomach with increased capacity may also empty fixed liquid meals more slowly, as has been found in BN.[155,164] When gastric capacity was compared between normal-weight individuals with BN, obese individuals, and normal non–binge-eating lean participants, gastric capacity was largest in those with BN, intermediate in the obese participants, and smallest in the lean participants.[164]

When the obese participants were further subdivided into binge eaters and non–binge eaters, the obese binge eaters were similar in stomach capacity to BN patients, while the obese

non–binge eaters were similar to the normal lean participants,[132] even though few of the obese binge eaters met the full criteria for BED. In a more recent study of BED,[132] gastric capacity and emptying as well as levels of glucose, insulin, leptin, CCK, and ghrelin were assessed while fasting and following a test meal. Although not as large as in BN,[55] gastric capacity was greater in obese full-fledged BED than in subthreshold BED or non-BED groups. Gastric capacity was assessed by filling an intra-gastric balloon until maximal tolerance as well as by measuring changes in intra-gastric pressure to determine compliance. Test-meal size correlated with gastric capacity across all groups, and the gastric emptying rate did not differ. The only fasting peptide concentration to differ significantly between groups was ghrelin, which during fasting was lowest in BED, intermediate in subthreshold BED, and highest in the non-BED group. Ghrelin decreased after a fixed meal as expected but decreased the least in BED from a lower baseline. Ghrelin at 30 minutes correlated inversely with gastric capacity: $r = -0.36$, $P < .05$, implying that the large gastric capacity may be responsible for the lower ghrelin level. The lower fasting ghrelin level suggests that binge eating results in downregulation of ghrelin, consistent with lower levels in obese as compared with lean participants.[116] If the extent of the fall in ghrelin after a meal is itself a signal for satiety, the smaller relative decrease in ghrelin postprandially may actually contribute to the binge eating in BED. Overall, these results demonstrate a greater gastric capacity and abnormal ghrelin pattern in BED.

Conclusion

In sum, the major peripheral peptides influencing appetite under normal conditions can be divided into those that help initiate food intake (ghrelin) and decline following meals and those that help terminate food intake and rise following meals (CCK, leptin, amylin, GLP-1, and PYY(3-36)). Except for CCK,[89,165] these appetite-regulating gut peptides can cross the blood-brain barrier, suggesting a central action.[68,166–168] Many of the gut peptide studies comparing lean versus obese groups did not examine or control for binge eating, which may account for some of the differences between these groups, given that BED is much more common in obese than lean populations.[15] Binge eating has been related to a dysfunction in the ghrelin signaling system and to enlarged gastric capacity, which may contribute to the lower ghrelin. Further identifying the dysfunctional gastric and peptide signaling mechanisms in BED may lead to new therapeutic approaches.

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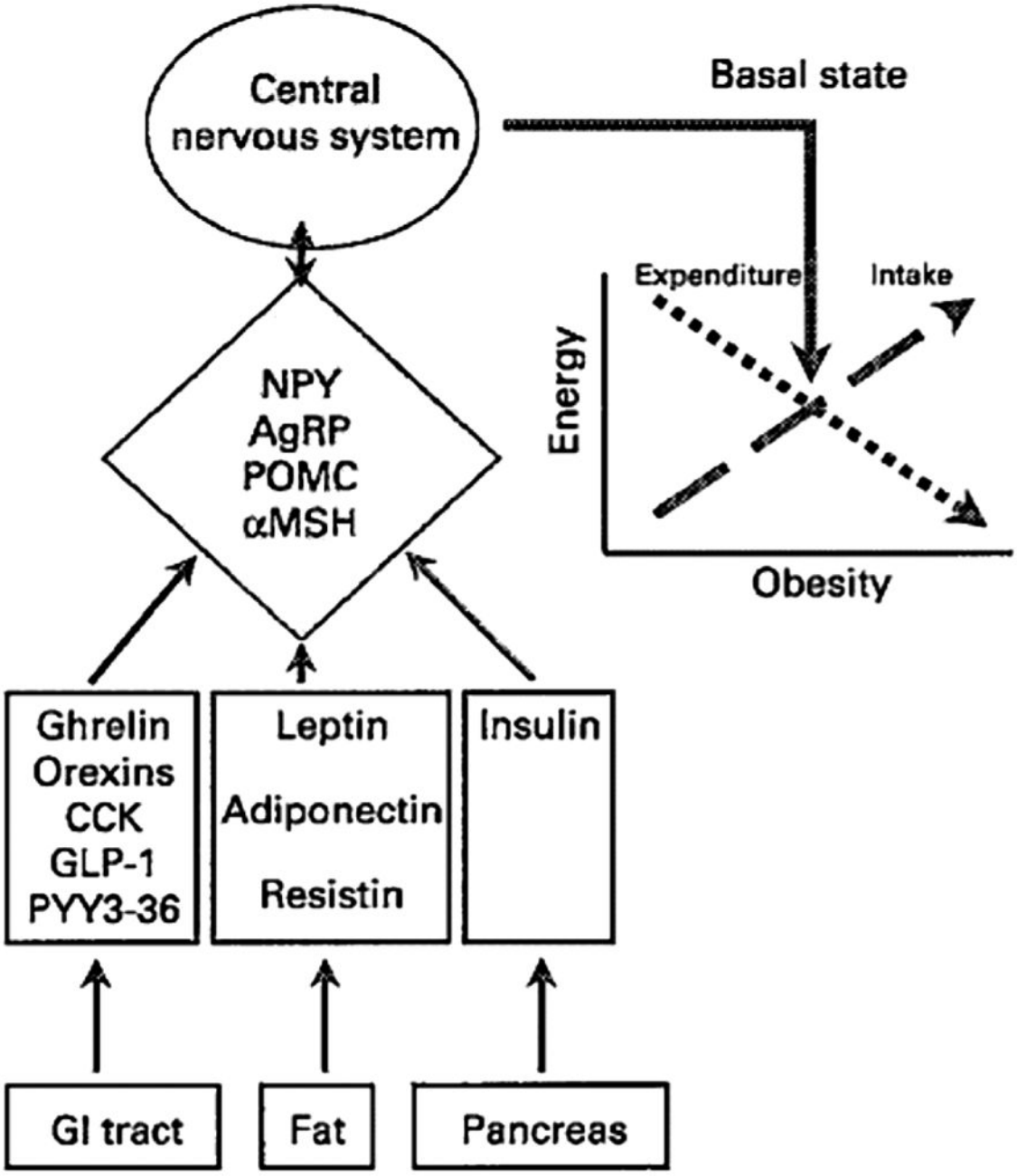

Figure 1.

Major neuropeptide and peptide hormone controls of food intake. The graph illustrates the balance between energy intake and expenditure to maintain a stable fat mass.

NPY indicates neuropeptide Y; AgRP, agouti gene-related peptide; POMC, pro-opiomelanocortin; αMSH, alpha-melanocyte stimulating hormone; CCK, cholecystokinin; GLP, glucagon-like peptide; PYY, peptide YY; GI, gastrointestinal. From Hellstrom et al.[49] Reproduced with permission from The Nutrition Society.