

## Peripheral and central signals in the control of eating in normal, obese and binge-eating human subjects

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The worldwide increase in the incidence of obesity is a consequence of a positive energy balance, with energy intake exceeding expenditure. The signalling systems that underlie appetite control are complex, and the present review highlights our current understanding of key components of these systems. The pattern of eating in obesity ranges from over-eating associated with binge-eating disorder to the absence of binge-eating. The present review also examines evidence of defects in signalling that differentiate these sub-types. The signalling network underlying hunger, satiety and metabolic status includes the hormonal signals leptin and insulin from energy stores, and cholecystokinin, glucagon-like peptide-1, ghrelin and peptide YY3-36 from the gastrointestinal tract, as well as neuronal influences via the vagus nerve from the digestive tract. This information is routed to specific nuclei of the hypothalamus and brain stem, such as the arcuate nucleus and the solitary tract nucleus respectively, which in turn activate distinct neuronal networks. Of the numerous neuropeptides in the brain, neuropeptide Y, agouti gene-related peptide and orexin stimulate appetite, while melanocortins and  $\alpha$ -melanocortin-stimulating hormone are involved in satiety. Of the many gastrointestinal peptides, ghrelin is the only appetite-stimulating hormone, whereas cholecystokinin, glucagon-like peptide-1 and peptide YY3-36 promote satiety. Adipose tissue provides signals about energy storage levels to the brain through leptin, adiponectin and resistin. Binge-eating has been related to a dysfunction in the ghrelin signalling system. Moreover, changes in gastric capacity are observed, and as gastric capacity is increased, so satiety signals arising from gastric and post-gastric cues are reduced. Understanding the host of neuropeptides and peptide hormones through which hunger and satiety operate should lead to novel therapeutic approaches for obesity; potential therapeutic strategies are highlighted.

### Signalling systems: Obesity: Hormones

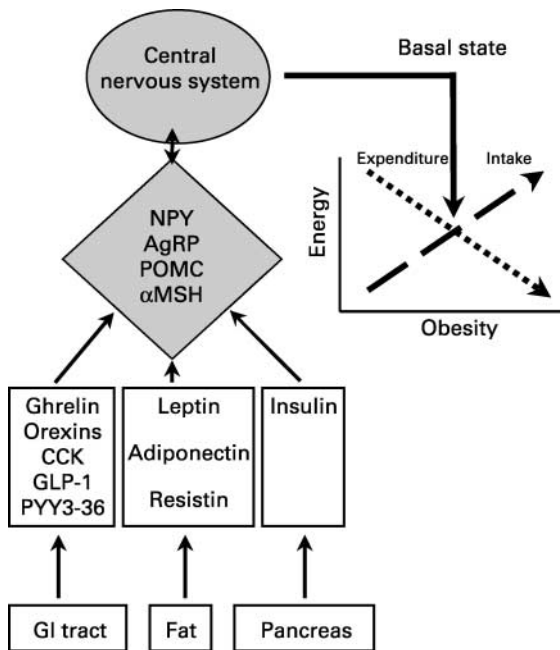
Energy balance is a metabolic state that exists when total energy expenditure equals dietary energy intake. Normally, energy balance is very well regulated. However, in some individuals there is an imbalance between energy intake and energy expenditure in favour of intake, resulting in weight gain and, ultimately, obesity. The prevalence of obesity, associated with chronic diseases such as diabetes and heart disease, keeps increasing in the USA (Flegal *et al.* 2002) and has reached epidemic proportions globally (Hill & Peters, 1998). Obesity is highly resistant to treatment, with most lost weight regained within 5 years. Obesity and the associated insulin resistance are also intimately linked with various medical complications and illnesses, such as hypertension, non-insulin-dependent diabetes mellitus, cancer, IHD and osteoarthritis among others, and represent a major and growing health problem worldwide.

Early research on obesity concentrated almost exclusively on hypothalamic controls of food intake. However,

as early as 1952, Kennedy postulated that the maximum daily intake of food during hyperphagia was determined by some limiting factor in addition to hypothalamic mechanisms (MacDougald & Mandrup, 2002). Today it is accepted that the control of feeding involves not only the central nervous system (CNS), but also the adrenal glands, the pancreas and the gastrointestinal (GI) tract. In addition, recent work has shown that adipose tissue has an important role in the regulation of food intake, as it secretes a number of endocrine and paracrine mediators, including leptin, adiponectin, resistin and TNF- $\alpha$ , which have been shown to influence appetite (Fig. 1). Our understanding of factors regulating food intake has increased greatly during the last 10 years, partly as a result of the discovery of leptin (Zhang *et al.* 1994). That study not only demonstrated that our main store of energy (fat) can signal energy reserves to the CNS, but also spawned an increased interest in the whole field of appetite regulation.

**Abbreviations:** BED, binge-eating disorder; CCK, cholecystokinin; CNS, central nervous system; GI, gastrointestinal; GLP, glucagon-like peptide; NPY, neuropeptide Y; OXA, orexin A; OXB, orexin B; PYY, peptide YY.

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**Fig. 1.** Major neuropeptide and peptide hormone controls of food intake. The graph illustrates the balance between energy intake and expenditure in order to maintain a stable fat mass. NPY, neuropeptide Y; AgRP, agouti gene-related peptide; POMC, pro-opiomelanocortin;  $\alpha$ MSH,  $\alpha$ -melanocyte stimulating hormone; CCK, cholecystokinin; GLP, glucagon-like peptide; PYY, peptide YY; GI, gastrointestinal.

The resulting research has improved our knowledge of the signals underlying energy balance, and the main aim of the present review is to summarise our current understanding of peripheral and central signals in the regulation of food intake in normal and obese human subjects. The focus will be on the various peptide hormones and neuropeptides, and GI signals. However, other signals and agents, such as blood sugar and insulin, circulating NEFA, central catecholamines, 5-hydroxytryptamine and  $\alpha_2$ -adrenoceptors are also important in the control of food intake, but beyond the scope of the present review.

A sizable subset of obese subjects, 18–46% of those enrolling in weight-loss programmes, has binge-eating disorder (BED) (De Zwaan *et al.* 1994), characterised by ingestion of very large meals with loss of control, not followed by purging as in bulimia nervosa (Yanovski, 1993). As noted by Yanovski (1995), ‘binge-eating disorder provides an opportunity to study the causes and concomitants of binge-eating in the absence of compensatory behaviors.’ BED, characterised relatively recently, is listed in the appendix of the *Diagnostic and Statistical Manual IV-TR* of the American Psychiatric Association. BED is found primarily in obese individuals, and patients with BED are generally more resistant to weight-loss treatment, have higher dropout rates, and show greater recidivism after weight loss (Yanovski, 1993) than other obese subjects. With the rising incidence of BED, it is important to study its aetiology and pathophysiology. Currently, the biological mechanisms underlying BED, including the role of the gut–brain axis, are poorly understood. Therefore, another aim of the present review is to examine whether

sufferers from BED and related disorders display disturbances in any of the main signalling systems underlying appetite control.

### Peripheral signals for hunger and satiety

There are three 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 GI tract and pancreas, with orexigenic as well as anorexigenic properties that exert primarily short-term effects on food intake (Fig. 1).

#### Adipocyte signalling

Leptin, secreted from adipose tissue, acts on neurons in the hypothalamus, leading to diminished food intake in animals. Leptin is considered to be part of a feedback loop where low levels of leptin signal to the CNS that energy stores are depleted (Zhang *et al.* 1994). Leptin, similar to insulin, decreases appetite by inhibiting CNS neurons containing neuropeptide Y (NPY) and agouti gene-related peptide. Brain receptors for leptin, as well as insulin, are found (together with receptors for glucocorticosteroids, oestrogen and progesterone) in the periventricular arcuate nucleus in the baso-medial hypothalamus next to the third ventricle, where exchange of molecules across the blood–brain barrier can occur. This area of the brain can be reached by hunger- and satiety-signalling hormones from the bloodstream. Moreover, both leptin and the leptin receptor proteins are present in the fundus of the gastric corpus in man. This suggests a paracrine link by which gastric epithelial cells may be direct targets for leptin (Sobhani *et al.* 2000). In addition, vagal stimulation causes leptin release from the stomach, suggesting that leptin is released during the cephalic phase of gastric secretion to exert another, still unknown, control mechanism (Sobhani *et al.* 2002). The released leptin may also signal satiety to the brain (Bray, 2000).

Since its discovery (Zhang *et al.* 1994), leptin has been shown to be a major regulator of food intake in rodents and genetically engineered animals. However, in human subjects, the balance between control of food intake and metabolism for stable weight control appears far more complex. In human subjects, obesity is associated with high plasma concentrations of leptin. In clinical trials using leptin as an anorexigenic agent, the term ‘leptin resistance’ has been coined for obese people who, in spite of adequate or even high plasma levels of leptin, do not respond to leptin in an orderly fashion resulting in decreased food intake (Heymsfield *et al.* 1999). Dysfunction of leptin systems may explain obesity only in a small number of cases where a specific genetic abnormality to the leptin system has been identified (O’Rahilly, 2003), requiring further exploration of alternative signals.

Another possible signalling factor is adiponectin (ARCP30, AdipoQ, apM1, GBP28), a peptide produced and released to the circulation exclusively by adipose tissue (Scherer *et al.* 1995). Adiponectin is a member of the complement C1q factor family and displays structural

homology with the TNF family (Shapiro & Scherer, 1998). There are important differences between adiponectin, insulin and leptin. Unlike leptin, plasma levels of adiponectin remain relatively constant throughout the day and are not affected by food intake (Hotta *et al.* 2000). Expression of adiponectin is decreased in obese and leptin-deficient ob/ob mice (Hu *et al.* 1996; Pajvani *et al.* 2003), and in human subjects there is a negative correlation between BMI and plasma levels of adiponectin (Matsubara *et al.* 2002). Obese diabetic subjects have even lower plasma levels of adiponectin than non-diabetic obese people (Hotta *et al.* 2000; Berg *et al.* 2002; Hug & Lodish, 2002; Tsao *et al.* 2002; Ukkola & Santaniemi, 2002), suggesting that diminished adiponectin plays a role in the development of insulin resistance in non-insulin-dependent diabetes mellitus.

Resistin, also known as adipose tissue-specific secretory factor, is another hormone secreted by adipocytes and acts on skeletal muscle myocytes, hepatocytes and adipocytes. Opposite in directional effects to adiponectin, higher resistin may decrease insulin sensitivity, leading to non-insulin-dependent diabetes mellitus (Steppan *et al.* 2001).

Two additional peptides have been described recently, fasting-induced adipose factor, also known as hepatic fibrogen-angiopoietin-related protein (Kersten *et al.* 2000; Kim *et al.* 2000) and the perilipins (Londos *et al.* 1996; Tansey *et al.* 2001). Animal studies have shown that the fasting-induced adipose factor peptide is predominantly expressed in adipose tissue, and that fasting-induced adipose factor in white adipose tissue and liver is strongly upregulated by fasting. Fasting-induced adipose factor might also act as an apoptosis survival factor for vascular endothelial cells and has therefore been discussed in the context of metabolic and cardiovascular complications of obesity (Trayhurn & Beattie, 2001). The perilipins are the most abundant proteins coating the surfaces of lipid droplets in adipocytes and are found at lower levels surrounding lipid droplets in steroidogenic cells. Perilipins drive the fat accumulation in cells through triacylglycerol storage in adipocytes by regulating the rate of basal lipolysis. Perilipins are also required to maximise hormonally stimulated energy utilisation by lipolysis (Londos *et al.* 1996; Tansey *et al.* 2001). Whether these peptides also play a role in signalling energy stores to the CNS like leptin has yet to be determined.

### Gastrointestinal signalling

There are now a number of GI peptide hormones whose activity can be related to a variety of food-related gastric and intestinal cues (Read *et al.* 1994). Distention of the stomach activates gastric stretch receptors and mechanoreceptors that transmit satiety signals (Schwartz *et al.* 1993). The stomach also serves as a food reservoir, with a capacity that can limit meal intake. Although the specific relationship between these gastric signals and the release of GI neuropeptides related to appetite has not been elucidated adequately, recent research has clarified the effects of many of the neuropeptides.

The only known GI peptide hormone with confirmed orexigenic properties is ghrelin, first identified in the

gastric mucosa (Kojima *et al.* 1999). Ghrelin, a ligand for growth hormone secretagogue receptor, is produced mainly by the stomach and, when administered, increases food intake in animals (Tschop *et al.* 2000) and human subjects (Wren *et al.* 2001) without affecting gastric emptying. Plasma levels of ghrelin peak before a meal, then decrease to a nadir and again increase to a peak that is reduced by the next meal (Cummings *et al.* 2001). Effects of ghrelin on eating may be mediated via the arcuate nucleus and the solitary tract nucleus (nucleus tractus solitarius) in the brain. Ghrelin also stimulates the release of growth hormone (Takaya *et al.* 2000) and is involved in the hypothalamic regulation of metabolic control and energy balance (Cummings & Foster, 2003). Ghrelin opposes leptin by stimulating different neuropeptides in the hypothalamus (Nakazato *et al.* 2001). The finding that appetite-stimulating effects of ghrelin have little impact on GI functions (Wren *et al.* 2001) suggests a central nervous effect of ghrelin. Ghrelin concentration is 27% lower in obese subjects than in normal-weight subjects (Tschop *et al.* 2001) and is negatively correlated with BMI (Shiyya *et al.* 2002). Fasting ghrelin concentration is greatest in anorexia nervosa, consistent with ghrelin concentration rising in animals during starvation (Asakawa *et al.* 2001), while weight gain in anorexia nervosa decreases plasma ghrelin concentration (Otto *et al.* 2001). The increase in ghrelin concentration during starvation may promote eating and the fall in ghrelin concentration in obesity may be a secondary response to over-eating (Tschop *et al.* 2001) rather than causal (Geliebter, 2002). Indeed, fasting ghrelin concentration is negatively correlated with body fat (%) and fasting insulin and fasting leptin concentrations, all of which are elevated in obesity (Tschop *et al.* 2001; Shiyya *et al.* 2002). Even if ghrelin is not a primary causal factor in obesity, a ghrelin antagonist may still help reduce food intake in obesity.

Orexins are novel appetite stimulating neuropeptides that appear to play a role in regulation of food intake, arousal and energy homeostasis (Kirchgeßner, 2002). Initial reports suggested that orexin A (OXA) and orexin B (OXB) were produced exclusively by a small group of neurons in the lateral hypothalamic area (Sakurai *et al.* 1998). However, neurons in the GI submucosal and myenteric plexuses, and endocrine cells in the intestinal mucosa and pancreatic islets have recently been shown to display OXA and orexin receptor immunoreactivity (Kirchgeßner & Liu, 1999; Näslund *et al.* 2002). OXA inhibits fasting GI motility in the rat and modulates both insulin and glucagon release from the endocrine rat pancreas (Nowak *et al.* 2000; Ouedrago *et al.* 2003). Moreover, orexin-positive neurons in the gut, like those in the hypothalamus, are activated by fasting, indicating a functional response to the nutritional status of these cells (Kirchgeßner & Liu, 1999). Recently, orexin receptors have been found on vagal afferent neurons in both rats and human subjects and OXA inhibited vagal responses to cholecystokinin (CCK; Burdyga *et al.* 2003). Plasma concentrations of OXA are increased during fasting in human subjects (Komaki *et al.* 2001) and are lower in obese subjects compared with normal-weight subjects in the fasted state (Adam *et al.* 2002). Taken together, these results imply a

role for OXA in the control of food intake, but the precise nature of any such involvement remains to be clarified.

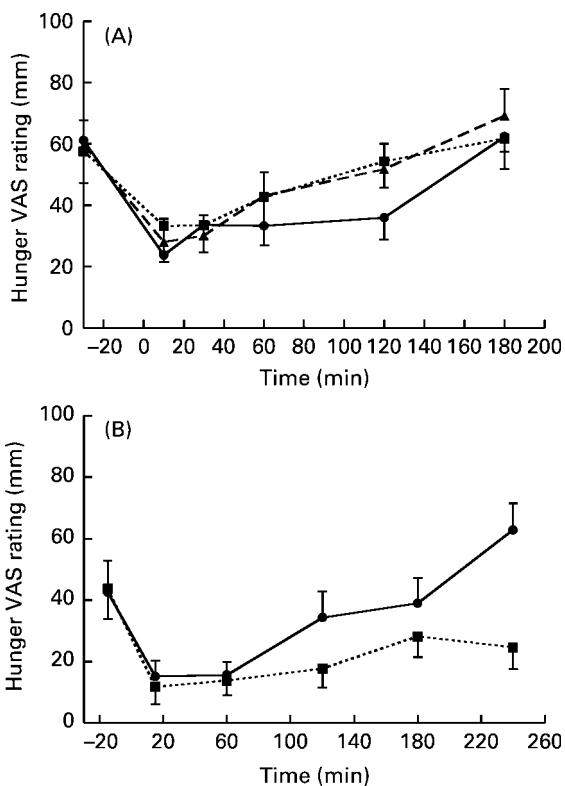
Conversely, a number of different GI peptide hormones are known to be anorexigenic, promoting early termination of the meal. Of these, CCK, glucagon-like peptide (GLP)-1 and peptide YY (PYY) 3-36 have received recognition as physiological regulators of food intake. CCK is the most widely studied GI peptide regulating food intake control, and research on CCK has been widely reviewed (Ritter *et al.* 1999). After a meal, CCK is released into the bloodstream from endocrine I cells of the duodenum and the jejunum (Buchan *et al.* 1978). Studies in human subjects have shown repeatedly that CCK inhibits food intake (Kissileff *et al.* 1981; Ballinger *et al.* 1995), although a concurrent gastric preload is generally necessary to achieve a satiety effect with CCK in obese and normal subjects (Lieveise *et al.* 1993). Peripherally administered CCK also acts on CCK<sub>A</sub> receptors in the gastric antrum; these receptors are involved in the CCK-mediated inhibition of gastric emptying (Reubi *et al.* 1997). CCK<sub>A</sub> receptors are also found in the abdominal part of the vagus nerve (Mercer & Lawrence, 1992) and vagotomy abolishes the satiating effect of the peptide in rats. A relationship between decreased plasma levels of CCK and hunger, as well as decreased fullness, has also been reported in

human subjects (French *et al.* 1993), supporting a role for CCK as a physiological mediator of satiety.

GLP-1 and GLP-2 are produced and secreted from endocrine L-cells found in the mucosa of the ileum and colon. After food ingestion, both peptides are released in equimolar amounts to the circulation (Bell *et al.* 1983; Holst, 1997). GLP-1 is a major contributor to the ileal brake mechanism of the upper GI tract, thereby modulating gastric emptying and acid secretion (Näslund *et al.* 1999b). GLP-1 also exerts dual actions in regulation of blood glucose concentrations through insulinotropic and glucagonostatic actions (Ørskov, 1992). Since GLP-1 slows gastric emptying of liquid as well as solid meals (Wettergren *et al.* 1993; Näslund *et al.* 1999b), metabolic requirements for insulin after food intake are reduced (Nauck *et al.* 1997). Accumulating evidence indicates that effects of GLP-1 on GI functions are mediated via the vagus nerve both in animals and human subjects (Imeryuz *et al.* 1997; Wettergren *et al.* 1997; Tolessa *et al.* 1998; Wettergren *et al.* 1998).

GLP-1 also exerts dual actions on feeding behaviour and satiety: intracerebroventricular injection of GLP-1 in rats inhibits food and water intake (Lambert *et al.* 1994; Tang-Christensen *et al.* 1996; Turton *et al.* 1996) and induces *c-fos* expression in the paraventricular nucleus of the hypothalamus (Turton *et al.* 1996). Administration of the GLP-1 receptor antagonist, exendin(9-39)amide, intracerebroventricularly to satiated rats resulted in increased food intake, but not in fasted rats (Turton *et al.* 1996). Furthermore, rats receiving continuous intracerebroventricular treatment with exendin(9-39)amide not only increased food intake, but also significantly increased their body weight (Bloom, 1997). No effect was seen with intraperitoneal injections, suggesting central signalling as the mode of action of GLP-1 in satiety. In human subjects, most, but not all (Long *et al.* 1999), studies report decreased food intake after administration of GLP-1, including studies in normal weight, diabetic and obese subjects (Flint *et al.* 1998, 2000; Näslund *et al.* 1998b, 1999b; Gutzwiller *et al.* 1999a,b; Toft-Nielsen *et al.* 1999) (Fig. 2). Reduced food intake is consistent with ratings of reduced hunger, and increased fullness following GLP-1 infusion (Gutzwiller *et al.* 1999b; Näslund *et al.* 1999a).

In contrast to GLP-1, the role of GLP-2 in regulation of food intake is inconsistent. GLP-2 is primarily known to exert trophic effects on the intestinal mucosa (Tsai *et al.* 1997), leading to advances in the treatment of short bowel syndrome (Lovshin & Drucker, 2000). GLP-2 has been reported to affect gastric motor activity in pigs (Wøjedemann *et al.* 1998). In addition, GLP-2-containing neurons connect the nucleus tractus solitarius with the medial hypothalamus, where GLP-2 receptor mRNA is expressed (Tang-Christensen *et al.* 2000). Furthermore, central administration of GLP-2 to rodents reduced food intake compared with placebo, suggesting that GLP-2 may be another satiety-promoting peptide (Tang-Christensen *et al.* 2000). However, this does not seem to be the case in human subjects. Gastric emptying studies including ratings of satiety have failed to verify any effect of GLP-2 (Schmidt *et al.* 2003) (Figs 2 and 3), and peripheral administration of GLP-2 did not influence appetite and *ad libitum*



**Fig. 2.** Hunger ratings in two sets of experiments with intravenously administered glucagon-like peptide-2 (A) at 0.75 (■) or (▲) 2.25 pmol/kg per min or glucagon-like peptide-1 (B) at 0.75 pmol/kg per min (■) or sodium chloride solution (9 g/l; ●). VAS, visual analogue scale. Values are means with their standard errors shown by vertical bars. Mean values for glucagon-like peptide-1 were significantly different from those for sodium chloride solution: \* $P < 0.05$  (From Näslund *et al.* 1999b; Schmidt *et al.* 2003).



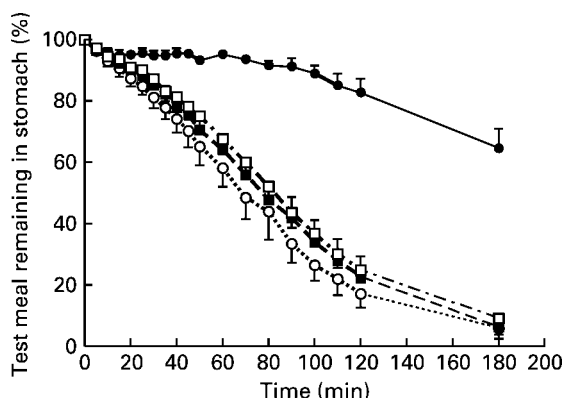
food intake (Sørensen *et al.* 2003). Why the effects of GLP-2 on appetite in rodents and human subjects seem to differ is unclear and requires substantiation.

PYY itself is well defined as an orexigenic neuropeptide (Morley *et al.* 1985; Hagan, 2002). However, the truncated form of PYY, PYY3-36, has anorexigenic effects, is released postprandially from the GI tract in proportion to the energy content of a meal and induces satiety (Batterham *et al.* 2002). PYY3-36 exerts its action as an agonist on  $Y_2$  receptors, thereby suppressing NPY-driven hunger feelings. PYY infusion was shown recently to reduce food intake in obese and lean subjects; moreover, fasting plasma PYY was lower in the obese than the lean subjects (Batterham *et al.* 2003).

Neuropeptidergic control of appetite is also regulated through insulin from the  $\beta$ -cells of the pancreatic endocrine islets of Langerhans, which, like leptin, downregulate NPY and agouti gene-related peptide, resulting in decreased appetite and food intake. Insulin also stimulates melanocortin-producing neurons in the hypothalamus (Porte *et al.* 2002).

#### *Distortion of gastric satiety cues in obesity and binge-related disorders*

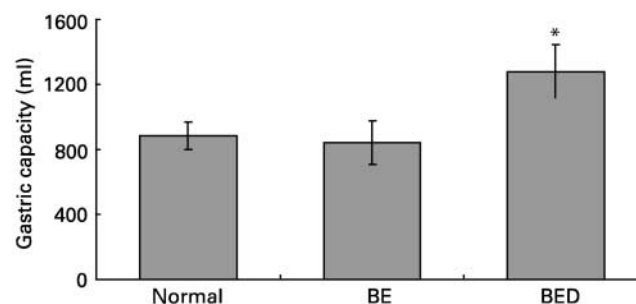
As we have seen, except for PYY3-36, which is reduced in obesity, there is no clear evidence of differences in peptide hormones between normal and obese subjects that could explain higher food intake as a component of obesity (the lower levels of ghrelin would suggest reduced appetite). Importantly, obese subjects in general have a larger than normal gastric capacity (Geliebter, 1988) as do normal-weight individuals with bulimia nervosa (Geliebter *et al.* 1992). A stomach with a large capacity may require a larger meal than usual to generate satiety signals, including release of satiety-related GI peptides and, indeed, gastric capacity correlates highly with test-meal intake (Geliebter *et al.* 1992). Further evidence for the importance of gastric



**Fig. 3.** Gastric emptying curves from two different sets of experiments where glucagon-like peptide-1 (0.75 pmol/kg per min; ●) or sodium chloride (9 g/l; ○) and glucagon-like peptide-2 (0.75 pmol/kg per min; ■) or sodium chloride solution (9 g/l; □) were given intravenously for 180 min to eight healthy volunteers. Values are means with their standard errors shown by vertical bars. Mean values for glucagon-like peptide-1 were significantly different from those for sodium chloride solution:  $P < 0.001$  for time effect, treatment effect and time  $\times$  treatment interaction for glucagon-like peptide-1 (From Näslund *et al.* 1999b; Schmidt *et al.* 2003).

capacity is the observation that surgical reduction in gastric capacity reduces meal size and induces marked weight loss (Brolin, 1992). Surgical reduction in capacity can also eliminate binge-eating in BED (Adami *et al.* 1999), confirming that a large stomach capacity helps maintain binge-eating. Moreover, non-surgical reduction of stomach capacity by external abdominal pressure (Geliebter *et al.* 1986) or by filling an intragastric balloon also reduces meal intake, especially in the short term (Geliebter, 1988).

A stomach with increased capacity may also empty fixed liquid meals more slowly, and slower emptying has been seen in bulimia nervosa (Geraciotti & Liddle, 1988; Geliebter *et al.* 1992). When gastric capacity was contrasted between subjects with bulimia nervosa, obese subjects and matched controls in the same laboratory, gastric capacity was largest in the subjects with bulimia nervosa, intermediate in obese subjects and smallest in normal-weight subjects (Geliebter & Hashim, 2001). Delayed gastric emptying by promoting greater gastric distension is generally associated with greater satiety, but it may also diminish intestinal satiety cues, including delaying the duodenal release of CCK as in bulimia nervosa (Geraciotti & Liddle, 1988). Although impaired CCK effects in obesity in general have not been found, the observation that obesity includes a number of clinically distinct sub-groups, most clearly non-BED and BED, raises the possibility that obese subjects with BED have similar changes in gastric capacity and CCK release to bulimia nervosa. Indeed, when obese subjects were sub-classified as binge-eaters and non-binge-eaters, binge-eaters were similar in stomach capacity to bulimia nervosa patients, while the non-binge-eaters were similar to normal subjects (Geliebter *et al.* 1992). However, only a few of the subjects with binge-eating in that study had full-fledged BED. The possibility that obese patients who meet full diagnostic criteria for BED had even greater changes in gastric capacity and consequent satiety signalling was assessed in a recent study of BED (Geliebter *et al.* 2004). In that study, and in a number of the studies referred to in the present review, gastric emptying of liquids was estimated with the tracer paracetamol, which is rapidly absorbed from the duodenum after leaving the stomach (Sanaka *et al.* 1997, 1998), and correlates well with radiolabelling and intragastric suction. In brief, gastric



**Fig. 4.** Gastric capacity, based on volume tolerated, in obese patients classified as having binge-eating disorder (BED), sub-threshold BED (BE) or non-bingeing (normal). Values are means with their standard errors shown by vertical bars. Mean value was significantly greater than those of BE or normal groups:  $*P < 0.05$ . (From Geliebter *et al.* 2004.)

capacity and gastric emptying, and levels of glucose, insulin, leptin, CCK and ghrelin, were assessed while fasting and after a test meal in obese patients who were diagnosed with BED ( $n$  11), binge-eating but not full BED ( $n$  13) or normal without binge-eating ( $n$  13). Gastric capacity was greater in the BED than binge-eating or normal groups, as assessed by filling the stomach with an intragastric balloon until maximal tolerance and by measuring intragastric pressure to determine compliance, although not as great as that reported previously in bulimia nervosa (Geliebter *et al.* 1992) (Fig. 4). Test-meal size correlated with gastric capacity across all subjects. Gastric emptying did not differ significantly among groups. The only fasting hormone concentration to differ significantly between groups was ghrelin, which was lowest during fasting in BED, intermediate in binge-eaters and highest in the normal subjects. Ghrelin decreased after a fixed meal as expected, but decreased the least in BED from a lower baseline. Ghrelin at 30 min correlated inversely with gastric capacity:  $r = -0.36$ ,  $P < 0.05$ . The lower fasting ghrelin suggests that binge-eating results in downregulation of ghrelin, consistent with lower levels in obese subjects as compared with lean subjects (Tschöp *et al.* 2001). 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 nevertheless contribute to the binge-eating in BED. Overall, these results demonstrate a greater gastric capacity and abnormal ghrelin pattern in BED.

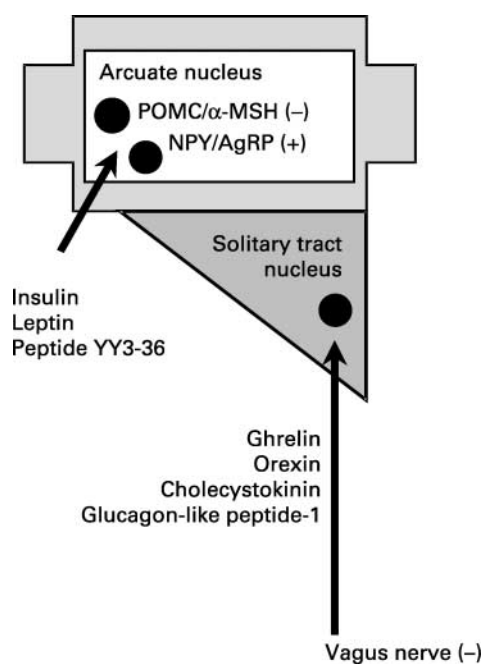
Another peptide that could contribute to obesity is GLP-1. It has been reported that the plasma increase of GLP-1 after a meal is attenuated in obese subjects (Ranganath *et al.* 1996, 1999; Näslund *et al.* 1998a). As GLP-1 strongly inhibits gastric emptying by about 50% 3 h after

a meal (Fig. 3), low GLP-1 concentrations in obese subjects may promote earlier onset of subsequent meals. Moreover, when obese patients undergo jejunio-ileal bypass, their gastric emptying rate is slowed and GLP-1 response to the ingested meal restored (Näslund *et al.* 1998a). In families with morbid obesity, there is a genetic linkage between islet 1 locus on chromosome 5q and the ancestor for GLP-1, namely the proglucagon gene. Since islet 1 locus is a positive regulator of proglucagon gene transcription, this may influence GLP-1 elaboration and release to the circulation (Clement *et al.* 1999). Thus, a defect in this system may result in decreased plasma levels of GLP-1 with short postprandial satiety periods and short meal intervals, resulting in increased daily food intake. None of these studies of GLP-1 has examined any distinction between BED and non-binge-eating groups, and future research needs to integrate these approaches to allow more detailed evaluation of the importance of GLP-1.

#### Interactions between peripheral and central homeostatic controls of eating in normal and obese men

So far, the present review has examined peripheral and central homeostatic controls of appetite separately, but of course these signals ultimately are integrated in order to direct food intake. The classic model of central nervous regulation of food intake was the 'dual-centre model' (Stellar, 1954), which suggested that different neuronal nuclei in the hypothalamus governed food intake by modifying hunger and satiety. However, this model has since been shown to be simplistic, and neural structures beyond those described in the dual-centre model (the lateral and ventromedial hypothalamic nuclei) are now strongly implicated in the regulation of appetite. For example, both the arcuate nucleus and the periventricular nuclei are important centres in the control of food intake, while the nucleus of the solitary tract serves as a gateway of signals from the GI tract that are relayed to the hypothalamic level (Fig. 5). In addition, there is increasing recognition that non-homeostatic mechanisms, particularly reward processes, play an important role in short-term control of food intake, although these processes are beyond the scope of the present review.

The arcuate nucleus seems to be of central importance for the inflow of peripheral signals mediating information on metabolic storage and needs. In the arcuate nucleus there are two different populations of cells with an explicit role in food intake (Fig. 2). One of these cell populations contains NPY, which is a powerful stimulator of feeding behaviour in animals (Chamorro *et al.* 2002), whereas the other contains pro-opiomelanocortin, which is split into  $\alpha$ -melanocyte stimulating hormone; this then inhibits eating by acting on melanocortin receptors (Wikberg *et al.* 2000). Peptide hormone receptors are located on these two cell populations, both of which are controlled by leptin and insulin; these inhibit the NPY-containing neurons and stimulate the pro-opiomelanocortin-containing neurons. The relevant postsynaptic NPY receptors are mainly of the  $Y_1$ -type, whereas presynaptic inhibitory  $Y_2$ -receptors are located directly on the NPY neurons (Fuxe *et al.*



**Fig. 5.** Schematic illustration of peripheral and central signalling for the control of food intake. POMC, pro-opiomelanocortin;  $\alpha$ MSH,  $\alpha$ -melanocyte stimulating hormone; NPY, neuropeptide Y; AgRP, agouti gene-related peptide.

1997; Broberger *et al.* 1999). Interestingly, PYY3-36 released from the GI tract after food intake is the natural ligand for these  $Y_2$  receptors (Batterham *et al.* 2002). This implies that feedback signals from the GI tract not only act on the brain stem, but also on the hypothalamus. Within the arcuate nucleus there is also inhibitory cross-talk between the two neuropeptide systems, with NPY neurons exerting inhibitory input on  $\alpha$ -melanocyte stimulating hormone neurons and agouti gene-related peptide, adding to the inhibition of the feeding-suppressive  $\alpha$ -melanocyte stimulating hormone system (Broberger *et al.* 1998; Hahn *et al.* 1998). In cells considered to be targets for the innervation of NPY- and pro-opiomelanocortin-containing neurons in the lateral hypothalamus, another two orexigenic peptides, OXA and OXB (Sakurai *et al.* 1998), have been found.

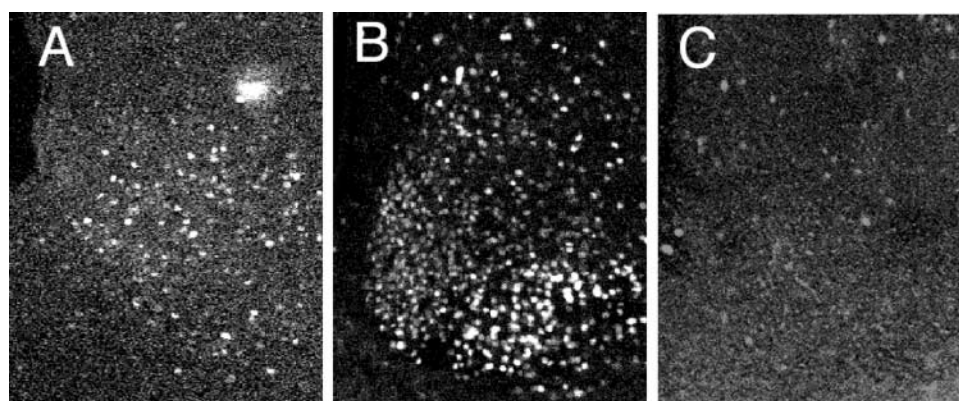
The anorexigenic peptide GLP-1 is found in the nucleus tractus solitarius and in dorsal and ventral parts of the medullary reticular nucleus, corresponding to brain stem regions that receive vagal afferents from the gut (Jin *et al.* 1988). GLP-1 immunoreactive nerve fibres are also found in the hypothalamic paraventricular nucleus with fibres projecting to the lateral hypothalamus and periventricular strata (Shimizu *et al.* 1987; Jin *et al.* 1988; Kreyman *et al.* 1989). Interestingly, when OXA and GLP-1 are administered peripherally, they selectively activate *c-fos* expression in the lateral and baso-medial hypothalamus respectively (Levin, J Ma, Tong, PM Hällstrom, AL Kirchgessner and E Näslund, unpublished results; Fig. 6), again indicating that GI signalling exerts a dual input both at a hypothalamic and brain stem level.

What then are the major central and peripheral signals associated with meal termination? A classic finding was that decerebrate rats are capable of terminating their eating upon distension of the stomach with activation of stretch receptors, but were incapable of increasing energy intake in response to energy dilution (Grill & Norgren, 1978). Structures in the brain stem appear to primarily control meal volume, energy content and duration, whereas the hypothalamus primarily senses and balances the metabolic status in the control of food intake. These feedback mechanisms involve a host of peptide hormones located at various points along the GI tract. In addition to their central

receptors, signals mediated from peripheral receptors are transferred via the vagus nerve to the nucleus tractus solitarius in the brain stem (Raybould, 1998). The peripheral and central vagus systems sense mechanical distension and chemical stimulation by different nutrients. These signals do not only affect the sensory nerve fibres directly, but are also released in the form of hormones to the circulation. Important examples of this are CCK and GLP-1. The effects of these peptides are likely to be mediated through the vagus nerve. In the vagus, the satiating effects of CCK are mediated by the  $CCK_A$  receptor (Hewson *et al.* 1988; Reidelberger *et al.* 1991), while the effects of GLP-1 are mediated through its distinct receptor. Furthermore, sensory vagal ganglia in the rat, predominantly those expressing the  $CCK_A$  receptor, contain high levels of cocaine- and amphetamine-regulated transcript, which itself is associated with reduced food intake (Broberger *et al.* 1999). In general terms, the vagus nerve is activated by CCK and GLP-1 as the stomach is distended by food and nutrients are being delivered to the small intestine. Next, in the brain, vagal nerve fibres release cocaine- and amphetamine-regulated transcript in the nucleus tractus solitarius of the brain stem, where its satiety-promoting effect is greatest.

#### Pathways to the development of future anorexic drugs

Of the various mechanisms reviewed here, the melanocortin system has attracted greatest interest from a pharmaceutical perspective. Mutations in the melanocortin-4 receptor are not as uncommon as deleterious mutations in other systems regulating fat storage and may contribute to the early development of morbid obesity (Yeo *et al.* 1998). Melanocortin-4 receptor mutation was recently found to be much more common in BED than in non-BED obese subjects (Branson *et al.* 2003). The melanocortin-4 receptors involved have a limited distribution, which might reduce the risk of side effects. The neuropeptides acting within this area also seem to be extremely effective. For example, in the rat, central injection of agouti gene-related peptide causes long-standing satiety for up to 1 week after administration (Hagan *et al.* 2000). Research with GLP-1 and PYY also suggests clinical potential. Treatment with



**Fig. 6.** Mean numbers of *c-fos*-positive neurons in the arcuate nucleus in control rats ((A), 30.2 (SEM 1.7)) and orexin A ((B), 114.0 (SEM 6.9)) and glucagon-like peptide 1 ((C), 25.0 (SEM 2.3)) -treated rats. (From Levin J Ma, Tong, PM Hällstrom, AL Kirchgessner and E Näslund, unpublished results.)



GLP-1 in overweight subjects reduced their appetite and daily intake, leading to weight control (Näslund *et al.* 1999b; Näslund *et al.* 2004). Furthermore, infusion of physiologically appropriate of PYY3-36 decreased rated appetite and reduced daily food intake (Batterham, 2002) in normal and obese subjects (Batterham *et al.* 2003). This is in contrast to other satiety-stimulating peptide hormones such as CCK, where the latency period to the next meal was shortened and therefore the daily intake was unchanged. Although CCK today is less attractive as a target treatment, it may be beneficial when combined with a centrally acting 5-hydroxytryptamine-1A receptor agonist (Poeschla *et al.* 1993), since this receptor is considered pivotal for satiety feelings caused by peripheral peptide administration. Thus, in cases where single peptide treatments do not work, a dual treatment modality may be of choice for control of peripheral and central signalling in eating behaviour. It is also important to recognise that different treatment strategies will be needed to distinguish between binge-related and non-binge-related obesity.

## Summary

The present review highlights the complexity of both the central and peripheral signalling systems underlying homeostatic controls of food ingestion and the complexity of obesity. Historically, there have been numerous breakthroughs, such as the initial discovery of CCK, the more recent discoveries of leptin, ghrelin and GI peptides, all of which have been heralded as likely to lead to major breakthroughs in the treatment of obesity. In practice, the multiplicity of controls greatly reduces the likelihood of treatments based on modification of any one signalling system. However, recent advances in the understanding of GLP-1, ghrelin and PYY and studies showing altered gastric capacity in obesity and BED pave the way for more novel single or combined pharmaceutical approaches to therapy, as well as greatly increasing our basic understanding of the underlying controls of appetite. Future research should be focused on the possible interactions between these systems, and how they relate to different forms of obesity and disordered eating.

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