

# Adiposity and the Gut - The Role of Gut Hormones

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**Abstract:** The WHO has declared that obesity is one of the top five risk conditions in the world. Body adiposity occurs as a consequence of an imbalance between food intake and energy expenditure. The hypothalamus integrates complex neural and humoral signals that coordinate the initiation and termination of feeding and regulates energy expenditure. In the last decade there has been considerable interest in the role of gut hormones in governing hunger and satiety signals in the brain. Ghrelin, a small peptide synthesized in the stomach, stimulates food intake while peptide YY (PYY), oxyntomodulin (OXM), glucagon like peptide-1 (GLP-1), cholecystokinin (CCK) and pancreatic polypeptide (PP) inhibit appetite.

To date, pharmacological approaches used to alter gut hormones administration may provide physiological and therapeutic solutions for appetite control and long-term anti-obesity therapy. Here we review the recent advances in this field.

**Keywords:** Gut peptides, PYY, Oxyntomodulin, GLP-1, Ghrelin, obesity.

## INTRODUCTION

*Prevention is better than cure:* from the early days this has been the focus of many clinicians, scientists and researchers in attempts to find preventive measures before the occurrence of disease. Early diagnosis can avert a lot of pain and disability, not to mention savings on the high cost related healthcare problems, both for the individual as well as the community.

In an evolutionary sense, the population today is comprised of the survivors of those who were able to lay down fat in times of plenty and conserve energy for times of need. In the current era of what is described as "The Toxic Environment", food is plentiful while the need is at its lowest due to high technology and low physical activity. A natural consequence of which is increased *Body adiposity*, defined as abnormal storage/accumulation of fat in proportion to body size.

The WHO has declared that obesity is one of the top five risk conditions of ill health and disease in the world. It substantially increases the risk of type II diabetes, hypertension, stroke, cardiovascular disease, respiratory problems and sleep apnoea, gall bladder disease and osteoarthritis. In addition, obesity is associated with increased risk of endometrial, breast and colon cancer. Estimates have shown that obesity accounts for about 50,000 deaths/year in the UK and 112,000 deaths/year in the USA.

The annual cost of obesity healthcare-related issues is estimated to amount to £3.3-3.7 billion in the UK [1] and \$100 billion in the USA [2]. It has been suggested that BMI can predict the average annual healthcare cost as well as work absence even after adjustment for age, sex, race, smoking and educational status [3]. Therefore, the growing

epidemic of obesity is recognised to be an alarming health and economic problem.

Furthermore, being obese is recognised as a social stigma associated with stress. In a multidisciplinary longitudinal study, poorer employment and relationship outcome were shown to be associated with persistent obesity in women [4]. The increase in its prevalence is not only confined to western societies but it is a growing epidemic worldwide including developing countries with traditionally lowest rates.

Of greater concern is the rising prevalence in childhood obesity with its associated co-morbidities [5]. In 2004, the Commons Health Select Committee predicted that "*if the rapid acceleration in childhood obesity in the last decade is taken into account, by year 2020 half of the British children would be obese*" [1]. This is associated with an increase in type 2 diabetes in children.

In July 2005, the Food Standard Agency (FDA) launched a consultation document on proposals to introduce targets for nutrient content of some manufactured foods used in school meals in an attempt to support Ofcom's work to further regulate the advertising and promotion on children's foods that are high in fat, salt and sugar content [6,7]. In addition, there has been much recent news and media coverage to increase public awareness and education on obesity-related issues. Government panels, disease associations, medical societies and healthcare professionals are calling for immediate actions to tackle the obesity epidemic.

Weight reduction programs based on calorie restrictions, increased physical activity and behaviour therapy have been shown to be effective but are short lived. It is the maintenance of reduced body weight that constitutes the problem. Most people re-gain on some (if not all) of their lost weight.

Lifestyle changes and the use of pharmaceutical agents have not achieved optimal solutions for weight loss and its maintenance. Currently, only a limited number of pharma-

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ceutical agents are available, and only three (orlistat, sibutramine and recently rimonabant) are licensed for the treatment of obesity. In addition to their limited long-term effectiveness, they are not without side effects [8-12].

Bariatric surgery, though most successful in maintaining long-term weight loss, is not without risk. Minimally invasive laparoscopic gastric banding is now increasingly popular in the management of obesity and the maintenance of weight loss. It has been shown to be more effective than lifestyle change and pharmacotherapy, with lower risks of morbidity and mortality [13]. However, the more invasive types of bariatric gastric surgery have been shown to be associated with high risk morbidity and mortality [14]. Better understanding of the *homeostatic mechanisms* that regulate body adiposity is now required. Recently gut hormones/peptides have been shown to play a key role in appetite control and energy homeostasis. This has been the focus of an intense research effort with the aim of generating long-lasting, safe and effective solutions for the control of appetite and maintenance of body weight. This review will examine these mechanisms and discuss possible targets for pharmaceutical intervention.

### HOMEOSTATIC CONTROL IN THE PATHOPHYSIOLOGY OF BODY ADIPOSITY

In addition to neural signals, psychological and habitual behaviour in the control of appetite, recent advances have highlighted the importance of gut hormones as regulatory factors [15-18]. Despite considerable inter and intra-diurnal variations in calorie intake, long-term energy intake and energy expenditure are precisely matched [16,19,20]. Many factors have been identified in the control of eating. The hypothalamus is the principal region in the central nervous system that regulates energy intake and energy expenditure. To accomplish this, the appetite centre in the hypothalamus (central) requires integrating complex neural and hormonal signals from a peripheral satiety system which includes the gut and adipose tissue. Short-term signals from the gut primarily regulate satiety while long-term signals from adipose tissue encode energy stores [21-23].

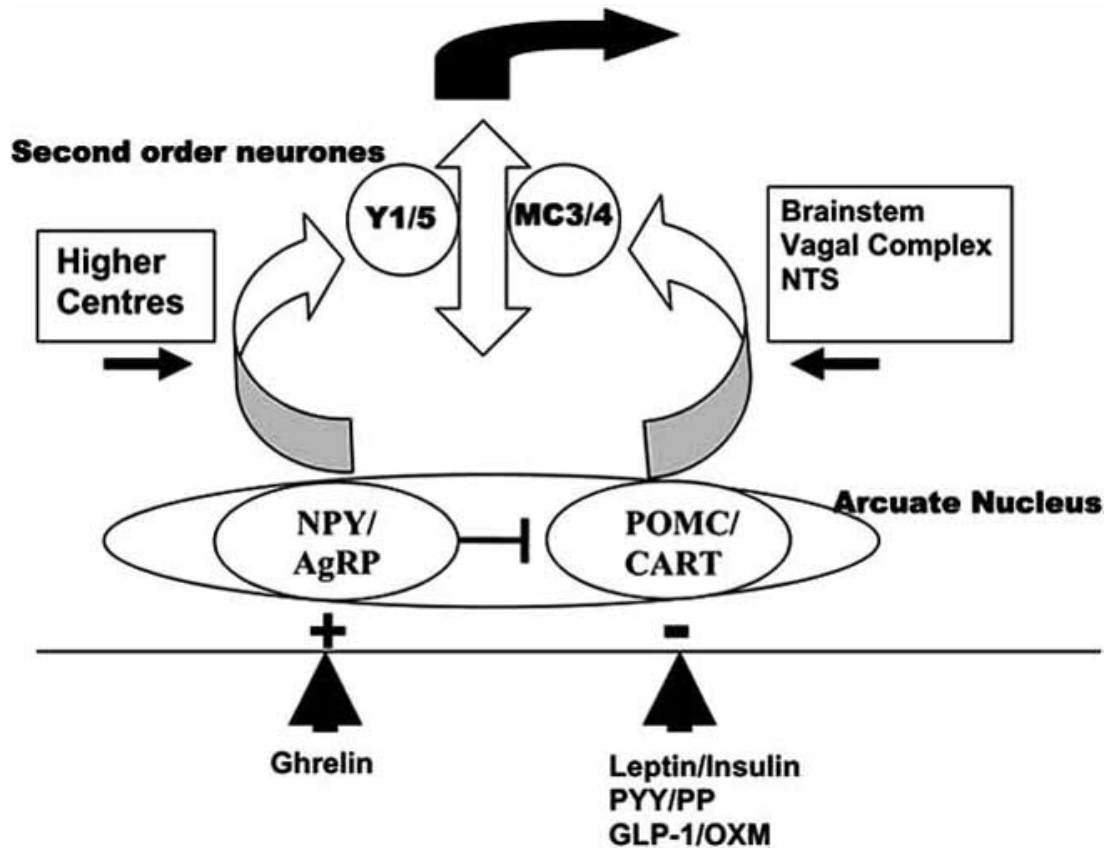
Multiple visual, olfactory and auditory cues received by the CNS influence food intake prior to ingestion of food [20,24,25]. While these signals stimulate the initiation of food intake, termination of food intake has been shown to be encoded by short-term satiety signals from the gut [20,26]. This was based on animal experiments involving regulation of food intake in response to distension of the stomach as well as caloric content of nutrients [24]. Distension of the small intestine was also shown to reduce food intake in rats [27]. Interestingly, recently hepatic chemoreceptors [28,29] and meal composition have been shown to influence satiety signal levels from the gut [30]. Activation of neuronal expression within the hypothalamus observed following administration of gut peptides support the notion that signals from the gut are communicated to the appetite centres in the hypothalamus [16,22]. In turn, the hypothalamus coordinates these signals to the brainstem and higher centres in the brain for the regulation of food intake and energy expenditure [16,23,31].

### THE BRAIN/ HYPOTHALAMIC CIRCUITRY

The hypothalamus is a central part of the control pathways of the limbic system. It is surrounded by the anterior nuclei of the thalamus, septum area and portion of the basal ganglia anteriorly, amygdala posteriorly and paraolfactory area and hippocampus laterally. This prime position facilitates its connections with afferent input from the periphery, via the brainstem, and higher brain centres that are involved in the control of food intake and energy homeostasis. Therefore, despite its small size, it plays a major role in controlling the vegetative and (neuro)endocrine functions of the body. It integrates neural signals via vagal stimuli, chemical and hormonal signals from the gut and adipose tissue, and sensory signals from higher centres in the brain that influence feeding behaviour Fig. (1). The nucleus tractus solitarius (NTS), with anatomical proximity to the area postrema in the brainstem also plays a role. NTS acts as a switchboard that regulates autonomic tone. It receives and processes incoming signals from the periphery and modulates both the sympathetic and vagal outflow in an integrated and reciprocal manner.

Nuclei in the hypothalamus have multiple functions. In addition to their function in controlling emotional behaviour, they have been shown to be involved in the control of food intake and energy expenditure [22]. The lateral nuclei on each side of the hypothalamus are what have been described as the "feeding centre" as they are associated with hunger. Their stimulation results in an increased feeling of hunger and appetite, leading to an increased desire of food intake. On the other hand, stimulation of the ventromedial nuclei, known as the "satiety centre", causes suppression of appetite and thereby reduced food intake. Experimental studies have shown that destruction of these nuclei results in opposing actions i.e. loss of appetite and hyperphagia respectively. The paraventricular nuclei (PVN), dorsomedial nuclei (DMN), perifornical nuclei and the mammillary body are also involved in the regulation of food intake and energy expenditure.

The arcuate nucleus (ARC) has been shown to be of prime importance in the regulation of food intake/satiety perception and energy expenditure. Its position at the base of the hypothalamus with an "incomplete" blood brain barrier allows its direct exposure to factors in the general circulation such as hormones and peptides from the gastrointestinal tract. It contains two subsets of neurons; a stimulatory neuron (orexigenic) containing Neuropeptide Y (NPY) and agouti related peptide (AgRP), and an inhibitory neuron (anorexigenic) containing pro-opiomelanocortin (POMC) (Fig. (1)). The latter is a precursor of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) and cocaine and amphetamine-regulated transcript (CART). These two sets of neurons function paradoxically to each other; when one subset is activated the other is inhibited. Stimulation of the NPY/AgRP neurons increases food intake and reduces energy expenditure and activation of POMC neurons suppresses food intake and increases energy expenditure. This has been supported by animal studies in which intracerebroventricular injection of POMC-derived peptides ( $\alpha$ -MSH) was shown to inhibit food intake [32], while central injections of AgRP significantly increased food



**Fig. (1).** Hypothalamic Circuitry in regulation of food intake and energy expenditure.

intake [33]. While the stimulatory effects of AgRP on food intake have been attributed, at least in part, to blocking neuronal activation in the PVN [34], NPY, which has a shorter half life compared to AgRP, has been proposed to exert its effects via the Y receptors. Six Y receptor subtypes have been described (Y1-Y6) [18,35], and NPY has a higher affinity to the Y1 and Y5 receptors. These are also available in high abundance in the NTS.

The -MSH acts on melanocortin receptors in the second order neurons in the hypothalamus. Five melanocortin receptors have been identified; MC3 and MC4 receptors are shown to be involved in appetite regulation. However, receptors for the CART neurons have not been identified so far. The AgRP is an antagonist of the MC3/4 receptors [34]. Mutations in the melanocortin system, including the POMC gene, MC4R and AgRP have been shown to be associated with obesity [36-38].

POMC immunoreactivity and cell bodies have also been shown in the NTS and other areas of the brainstem including the ventrolateral medulla and the lateral reticular nucleus [39]. Most of these brainstem POMC neurons originate from the ARC [40]. Indeed, two different neuronal pathways have been identified to initiate from the ARC; one travelling through the dorsomedial tegmentum to reach the lateral reticular nucleus and the NTS, and the other passing through the ventrolateral tegmentum to reach the ventrolateral medulla, nucleus ambiguus and the NTS [39]. The presence of these neuronal connections, the MC4R [41] and leptin receptors [42] in the NTS may elucidate the important role of

the NTS in the regulation of energy homeostasis not only through conveying signals from the periphery to the higher brain centres, via the vagal afferents, but also through a central melanocortin system and leptin receptors. In support of this, administration of leptin [42] or an MC3R/MC4R agonist into the fourth ventricle was shown to cause a reduction of food intake, while administration of an MC3R/MC4R antagonist resulted in an increase in food intake [43].

In addition, ARC neuronal projections activate neurons in the PVN and the dorsomedial nuclei in the hypothalamus. These activated pathways are integrated in the PVN, along with received signals from the sympathetic and vagal afferent fibres via the NTS, and project to higher centres in the brain that are involved in energy homeostasis. PVN also coordinates input from melanin concentrating hormone (MCH) producing neurons in the lateral hypothalamus, the area postrema, the brainstem and amygdala that have an impact on food intake. The latter two have some areas that increase and other areas that are involved with the inhibition of food intake. It is worth noting that areas in the brain stem and amygdala control salivation, licking, chewing and swallowing.

#### THE GUT- BEYOND THE DIGESTIVE PROCESS

The gastrointestinal (GI) system is a port through which food and nutritive substances, vitamins, minerals and fluids enter, get digested, absorbed and the remainder expelled from the body. It has a *mechanical* function acting as a

container, grinder, and propeller of food substances by the action of smooth muscles. *Digestion* of food substances involves the breakdown of complex molecules to simple single units by the action of digestive enzymes. This makes nutritive substances ready for *absorption* by the epithelial surface lining the gut.

In addition, the GI tract produces and secretes biologically active polypeptides/hormones (gut hormones) by nerve endings and glandular cells in the mucosa. These peptides exert their actions in a paracrine fashion, via the circulation and/or by acting directly on the CNS. They also respond to the gut's nutrient content, producing signals which are transmitted through the vagal or sympathetic afferent fibres to the appetite centres in the brain [16]. Interestingly, many of the gut peptides are also produced in the CNS and act as neurotransmitters [16].

In the last 20 years, gut hormones have been the focus of intense research which has highlighted their important role in the regulation of food intake and energy homeostasis.

The numerous gut hormones shown in (Table 1) include peptide PYY3-36, oxyntomodulin and GLP-1 that inhibit appetite (anorexigenic). They act as short-term satiety signals following food intake. PYY3-36 has been demonstrated to inhibit food intake in both animals and humans [18,37,44,45]. The ability of patients to maintain long-term weight loss following bariatric surgery has been attributed, at least in part, to the high levels of PYY3-36 postoperatively [46]. Most recently, the appetite inhibitory effect of oxyntomodulin in humans was confirmed and was shown to continue over 4 weeks resulting in a significant weight loss [47]. GLP-1, the product of proglucagon with structural homology to OXM, is a powerful incretin [48], and it inhibits gastric emptying and glucagon secretion [49-51]. GLP-1 also suppresses appetite and food consumption following its peripheral administration in normal and diabetic humans [52-54].

Ghrelin, produced in the stomach, is the only gut hormone known to stimulate feeding (orexigenic). Vast interest has been shown recently in the effects of ghrelin on food regulation [30,55,56]. The role of ghrelin agonists and antagonists have been extensively investigated in cachectic and obese patients respectively [23,56,57]. Suppressed ghrelin levels in patients following bariatric surgery might be another factor in the long-term maintenance of weight loss [23,58]. CCK is a satiety signal that provides information about the chemical properties of food. It binds to receptors in the liver, activates vagal afferents or access the CNS via the circulation [59-61].

## ANOREXIGENIC PEPTIDES

### Oxyntomodulin

Oxyntomodulin (OXM) is a 37 amino acid peptide produced by the L-cells of the small intestine along with GLP-1. OXM and GLP-1 are products of the proglucagon gene (PPGP) produced by the action of prohormone convertase enzymes 1 and 2 [62,63]. The proglucagon gene product is also expressed in the pancreas and the CNS [64,65]. OXM comprises glucagons and an 8 amino acid carboxy terminal peptide [64,65]. Posttranslational process-

ing of this gene product results in a larger inactive peptide, glicentin, which contains the glucagon sequence. GLP-1 and GLP-2 are cleaved out and secreted separately. Glicentin is later cleaved to glucagon-related pancreatic peptide (GRPP) and oxyntomodulin [16,64].

Levels of OXM vary throughout the day. Highest levels are detected in the evening, which then gradually fall to very low levels in the early hours of the morning [66]. It has been shown that food ingestion and caloric content of the meal are factors that influence its release [62]. Like other gut peptides, OXM has many actions; in addition to inhibition of gastric acid secretion and motility [67], animal studies have shown that it decreases enzyme secretion by the pancreas and increases intestinal glucose absorption [68,69].

The actions of OXM are thought to be mediated through the glucagon and GLP-1 receptors (GLP-1R) [70]. However, it is worth noting that OXM has been shown to bind the GLP-1R with a lower affinity compared to GLP-1 [71]. Interestingly, while exendin 9-39 (a GLP-1 agonist and a GLP-2 antagonist) has been shown to block the actions of both GLP-1 and OXM [72], its direct administration into the arcuate nucleus was shown to abolish the peripheral effects of OXM only, with no observed effects on GLP-1 [19]. Furthermore, intra-peritoneal (IP) administration of OXM and exendin 9-39 has been shown to result in c-fos (marker of neuronal activation) expression in the arcuate nucleus only [19,70]. This pattern is different from that seen with GLP-1 administration [19]. The above suggests that GLP-1R is not the only receptor through which OXM can mediate its actions [47]; other mechanisms might be involved. For example, suppression of ghrelin following OXM administration might be one such mechanism. In keeping with this, a reduction in circulating ghrelin levels was reported in both animals (20%) [19] and humans (44%) [72] following peripheral administration of OXM.

Recently, OXM has been identified as an anorexigenic gut peptide [72]. Animal studies have shown that both central and peripheral administration of OXM inhibits food intake [73,74]. This effect was shown to continue with chronic administration of OXM both centrally to ICV and intra-peritoneally, resulting in reduced weight gain [74]. It is thought that this weight reducing effect is due to a dual action of OXM; a reduction in food intake and an increase in energy expenditure [74]. The appetite-inhibitory effect of OXM has also been shown in humans [72]. A significant (19.3%) reduction in hunger scores and calorie intake in a free choice buffet meal was reported in thirteen healthy normal weight volunteers following an intravenous infusion of OXM [72]. In this randomised double-blind placebo controlled cross-over study, the effect of OXM persisted for 12 h post infusion [72]. In a recent study, Wynne *et al.* [47] showed that OXM did not lose its effect with repeated administration over one month and consequently caused a significant weight loss. Twenty six healthy (but overweight) volunteers were enrolled in this study. They were randomised (double blind) to have subcutaneous injections of active OXM or placebo three times daily for thirty days. Exercise and diet were fixed in both groups. A 5.5 lb reduction in weight was observed in the active group, compared to 1lb in those on placebo [47]. Interestingly, a

Table 1. Anorexigenic and Orexigenic Gut Hormones

peptides	Site of synthesis	Stimulus	Actions	Mediation of action	Molecular forms
<i>Orexigenic</i> OXM	L-cells of distal ileum and colon Pancreas CNS	Meal Calorie content Fat	Inhibits food intake Inhibits gastric acid secretion Inhibits gastric motility Reduces pancreatic enzyme secretion	GLP-1 Receptor Glucagon receptor Suppression of ghrelin	-
GLP-1	L-cells of distal small ileum, colon Pancreas CNS	Meal	Incretin effect on insulin secretion Suppresses glucagon release Promotes pancreatic $\beta$ -cell growth Inhibits food intake Delays gastric emptying Inhibits gastric secretion Inhibits lipase secretion	GLP-1 Receptor	GLP-17-36 GLP 17-37
PYY3-36	L cells of distal ileum, colon, rectum CNS	Meal Fat and protein Calorie content CCK, Gastric acid, Bile acid, Bombesin, IGF-1	Inhibits food intake Reduces gastric motility Inhibits gallbladder secretion Inhibits pancreatic secretion	Y2 Receptor Inhibits NPY	PYY 1-36 PYY 3-36
PP	PP cells in islets of Langerhans CNS	Meal Circadian rhythm	Inhibits pancreatic enzyme secretion Inhibits food intake Gall bladder relaxation	Y4 Receptors	-
CCK	I cells of duodenum, jejunum; CNS Enteric nerve ending	Food ingestion, protein, fat	Stimulates gall bladder contraction Stimulates pancreatic exocrine secretion Delays gastric emptying Inhibits gastric acid secretion Reduces food intake Increases satiety Stimulates bowel motility	CCK A/1 CCK B/2	Multiple Intestinal CCK-33, CCK-8
<i>Orexigenic</i> Ghrelin	Stomach small bowel colon Hypothalamus	Fasting Circadian rhythm	Promote GH release Increases food intake Promotes gastric motility Promotes PP release	GHS Receptor	-

CCK: cholecystokinin; CNS: central nervous system; GHS: growth hormone Secretagogue; GLP-1 glucagon-like peptides-1; PP: pancreatic polypeptide; PYY: peptide YY

significant increase in adiponectin and a reduction in leptin levels were also observed in the active group [47]. These findings further support the suggestion that OXM exerts its anorexigenic effect through different mechanisms; a direct effect on the hypothalamus, possibly via the GLP-1R, a direct and an indirect acute effect via suppression of ghrelin and a long-term effect via leptin and adiponectin. This

suggests that OXM is a promising candidate for investigation as a therapeutic agent in the treatment of obesity [47].

#### Glucagon Like Peptide-1 (GLP-1)

GLP-1 is also a product of post translational processing of proglucagon. It is produced by the L-cells in the distal ileum [75]. Two forms of GLP-1 have been identified; GLP-

17-36 and GLP-17-37. They are secreted in response to food intake as well as neural and hormonal signals [76-78]. Both forms are equally potent, however, they have a very short half life ( $t_{1/2}$  1-2 min) because they are rapidly inactivated and cleared from the circulation by the enzyme exopeptidase dipeptidyl peptidase IV (DPP IV) [79].

GLP-1 has several actions; centrally, it is involved in neuroprotection and regulation of learning and memory. In addition, its action on the hypothalamus in reducing food intake is well established [80,81]. Peripherally, on the GI tract, it reduces gastric secretion and motility [82] and increases gastric satiety. Since the peptide is produced in the GI tract but exerts its effect on the CNS, it has been suggested that it reaches the CNS by transmission via the dorsal vagal complex through the area postrema [83]. Therefore, an intact vagal nerve and somatostatin activation are required to mediate most of its actions. However, its effect on lipase secretion appears to be locally induced and independent of vagal innervations. In keeping with the signal transmission to the CNS, increased c-fos expression has been shown following peripheral GLP-1 administration.

In rodents, both central and peripheral [52] administration of GLP-1 have been shown to inhibit food intake and chronic administration to result in weight loss [81]. A similar effect has been demonstrated in humans where peripheral administration of GLP-1 resulted in inhibition of food intake in normal [84], diabetic [85-87] and non diabetic obese men [84,88]. Repeated subcutaneous injections of GLP-1 over 5 days resulted in a 15% reduction in calorie intake and, subsequently, a 0.5 kg weight loss in obese subjects [88]. This indicates that the food inhibitory effect of GLP-1 is preserved in obese subjects [88]. Interestingly, obese subjects have been shown to have low levels of GLP-1 that normalise following weight loss [89].

In addition to GLP-1's central effect on the appetite centres in the brain, its local effects in reducing gastric emptying and thereby increasing gastric satiety have been suggested to contribute to its inhibitory effect on food intake [50,51]. GLP-1 is also an incretin mimetic that has been found to up-regulate insulin gene expression [90]. It has been shown to stimulate pancreatic  $\beta$ -cell proliferation and to promote islet cell neogenesis [91]; an action thought to be mediated through the GLP-1R. Various studies have shown postprandial glucose-lowering effects of GLP-1 through stimulation of insulin and inhibition of glucagon secretions. Reduced gastric emptying due to GLP-1 further assists in lowering blood glucose levels by slowing the rate of transit of nutrients from the stomach to the small intestine [51,92,93]. This has been demonstrated by normalisation of blood glucose levels following intravenous and subcutaneous infusions of GLP-1 in poorly controlled diabetics. In addition, repeated subcutaneous infusions over a period of 6 weeks have resulted in a 1.3% reduction in HbA1c and a 2kg weight loss [54].

In light of the above, GLP-1's use as a therapeutic agent in the treatment of diabetes has received wide acceptance. Obesity is a recognised feature of the metabolic syndrome and type 2 diabetes, therefore, GLP-1 has a dual benefit on these patients; regulation of their glycaemia and weight control. However, the principal limitation in the use of native

GLP-1 is its short half life in the circulation due to degradation by DPP IV. Therefore, interest has been focussed on the development of DPP IV inhibitors or long acting GLP-1 agonists. Exendin 4, a 39 amino acid peptide isolated from the venom of the lizard *Heloderma Suspetum* has a sequence homology with the GLP-1 molecule (the N-terminal region of both molecules are identical). Exendin 4 is an agonist of GLP-1R and has a greater half life (33 min) in human serum, as it is resistant to DPP IV cleavage. Recently, exendin 4 was launched as an effective anti-diabetic agent with weight control properties (discussed below).

### **PYY and PP**

PYY and PP, along with NPY, belong to the same family of peptides named PP fold peptides. They have structural homology; being 36 amino acids with several tyrosine residues. They all form a tertiary structure which is characteristically u-shaped; a double helix, one and one polyproline, connected by a  $\beta$ -turn [22]. The PP fold peptides appear to exert their effects through the various Y receptors (Y1-6) [35]. Interestingly, the classification of these Y receptors is based on their affinity to the different fragments of PYY, PP and NPY peptides and analogues.

PYY is derived from the gut and was first isolated in 1980 [94]. It is virtually absent in the stomach, but is produced throughout the intestine, predominantly by the L-cells in the ileum, colon and rectum [95]. PYY has been shown to have a 42% and 70% structural homology with GLP-1 (with which it also co-localises in the gut) and NPY respectively. There is evidence that PYY is also produced by the pancreas and the CNS [96].

PYY is released postprandially and appears in the circulation 15 minutes following food ingestion. Postprandial plasma levels plateau after 1-2 h, but remain elevated for up to 6 h. However, once released, the native form PYY1-36, is rapidly cleaved by DPP IV to PYY3-36 [97]; the circulating form of PYY. The release of PYY has been shown to be influenced by a number of stimuli including caloric content and composition of the meal [98]. CCK, gastric acid, infusion of bile acid to the ileum and colon, insulin like growth factor-1 (IGF-1) [99], bombesin and calcitonin gene related peptide (CGRP) are other factors that have been shown to stimulate the release of PYY. In addition to the above chemical stimuli and direct food contact with the gut, evidence suggests that neural signals are important for its release, for example an intact vagal nerve. This was proposed following an increase in circulating PYY levels shortly after food ingestion, but well before nutriment reached the distal part of the small intestine or colon; the main site of PYY production [100]. In contrast, release of the peptide is inhibited during fasting [18] and by GLP-1 [101], however, gastric distension has been shown to have no significant effect.

In addition to the above physiological factors affecting the release of the peptide, it has been shown that PYY increases in a number of gastrointestinal diseases and surgical procedures [102-104]. These include inflammatory bowel diseases, bowel surgery and malabsorption status such as tropical sprue, chronic pancreatitis and coeliac disease [105]. This observed increase in PYY has been proposed to

serve two purposes; while it might be responsible, in part, for the weight loss observed in these patients through reducing their appetite, the elevated PYY levels have also been suggested to contribute to the recovery of the disease process in the gut [58,106]. The latter is thought to be through delaying gastric emptying and inhibiting gall bladder contractions [107]. Elevated levels of PYY have also been shown in association with other cachectic conditions. Recently, Le Roux and co-workers [108] have demonstrated an exaggerated response of PYY release (46-60% increase) 30 minutes following a meal in 6 patients with cardiac cachexia compared to age, sex and BMI matched normal controls [108]. Cachexia associated with chronic kidney disease (CKD) is another example where PYY levels are elevated [109]. Furthermore, higher PYY concentrations were shown in the CSF of patients with eating disorders such as Bulimia nervosa and binge-eating disorders [110], compared to patients with anorexia nervosa [111]. In contrast, fasting levels of PYY were not elevated in morbidly obese patients and relatively lower (compared to lean subjects) PYY levels were found in obese subjects. Interestingly, the latter patients retained a PYY response (increased level) to food ingestion, though to a lower extent compared to lean subjects [18].

The above supports the concept that PYY3-36 has an important role in the control of food intake and energy regulation. Indeed, in the last decade, a number of studies have demonstrated that PYY3-36 exerts anorexigenic effects. In both animal and human studies, PYY3-36 has been shown to inhibit food intake and reduce weight gain [18,44,112] in addition to its actions as a satiety hormone [113,114]. In mice, peripheral [37,44,112,115] and central [44] administration of PYY was shown to acutely reduce food intake. Batterham *et al.* [44] showed that the food inhibitory effects of PYY3-36 continued on chronic peripheral administration of the peptide, which resulted in reduced weight gain in the treated animals [44]. A single infusion of PYY3-36 in humans also caused a 30% and 31% reduction in food intake 2 h post infusion in obese and lean subjects respectively [18]. In this study, the appetite reducing effect of PYY3-36 was shown to persist for 24 h in all the subjects.

The above studies have generated a lot of interest in PYY3-36 and its role in explaining the pathophysiology and underlying mechanisms of obesity [16]. However, the findings in the animal studies have been controversial [58,116-118] because of variable results obtained by different investigators. Nonetheless, the acute effects of PYY3-36 on food inhibition have been reproduced in a number of studies in rodents [119,120] and in primates [121]. Pitnner and co-workers showed repeated injections of PYY caused a significant inhibition of food intake and weight reduction in animals [122]. Daily intermittent IV injections of PYY3-36 in rats for 10 days were shown to cause a sustained reduction in daily food intake (20%) and reduced body weight and adiposity [123]. The following hypotheses have been suggested to explain the discrepancies in those studies:

1. different methodologies and protocols [116]
2. different strains of animals [116]

3. different handling of animals and the stress conditions under which the experiments were conducted [116]
4. different immunoassay methods use for PYY measurements [58]
5. PYY concentration in different age groups [124]

The effect of PYY has also been reproduced in humans; Degen and co-workers have recently investigated the effects of escalating doses of PYY on food intake in twenty eight healthy volunteers [125]. These investigators have shown that PYY caused a significant reduction in food (35%,  $p<0.001$ ), calorie (32%,  $p<0.001$ ) and fluid (18%,  $p<0.01$ ) intake [125].

PYY3-36 may also improve insulin sensitivity. Long-term peripheral administration of PYY3-36 was shown to improve glycaemia in animal models [122]. This was attributed to the reduction in food intake, visceral fat and weight in those animals. All these further support a possible therapeutic role of PYY in obesity.

It has been shown that PYY exerts its effects through binding to the Y receptors. Of the six classes identified to date [16,35], PYY3-36 has been shown to have a higher affinity to the Y2 receptor [44]. Binding to the Y2 receptors is thought to inhibit the orexigenic NPY neurons with a reciprocal activation of POMC in the arcuate nucleus, resulting in appetite suppression [17,126]. In support of this, a Y2 receptor antagonist was shown in mice to completely block the anorexigenic effect of PYY3-36 [44,127]. In addition, appetite suppression could not be accomplished following PYY3-36 administration in Y2 receptor knock-out mice [44]. This might suggest a potential therapeutic role for PYY agonists and/or Y2 receptor antagonists in the treatment of obesity. In addition to its affinity to Y2 receptors, PYY3-36 binds to Y1 and Y5 receptors, though with a lower affinity compared to Y2 receptors. Peripheral administration of PYY 3-36 was also shown to cause c-fos activation and expression in the arcuate nucleus [44].

### Pancreatic Polypeptide (PP)

PP, another anorexigenic peptide, is produced by the PP cells of the islets of langerhans [128-130]. It was known well before the discovery of PYY [131] and has been shown to act via the Y4 receptors. Its release is biphasic, being highest in the evening [132]. Circulating levels are increased by ghrelin, motilin and secretin [133-135] and reduced by somatostatin [136]. As with PYY, higher levels were found in anorectic compared to obese subjects [137,138]. This has put PP under investigation to explore its anorectic properties. Indeed, a peripheral administration of PP was shown to reduce food intake in animals [129,139] as well as humans [18,140]. In 10 healthy volunteers calorie intake was reduced by 21% within 2 h and 33% within 24h following PP infusion at a rate of 10 pmol/kg/min [141]. However, similar to PYY, conflicting results has limited its current therapeutic role as an appetite-regulatory peptide [22].

### Cholecystokinin (CCK)

CCK is one of the oldest known and most extensively investigated gut peptides [60,61]. It was originally isolated from the I cells of the intestine in the duodenal and jejunal

mucosa, but other forms have also been isolated from the ileal mucosa, the blood and the brain [60]. They are all derived from a single gene, but posttranslational processing results in multiple forms that differ in size and molecular weight [60,142]. Two forms are produced in the intestine; CCK33 and CCK8. In the brain, CCK is one of the most abundant peptides [143], and it acts as a neurotransmitter in the enteric nerve endings.

The role of CCK as a regulatory factor in the digestive process is well established. It is released postprandially in response to fat and protein ingestion [144-146]. It facilitates their digestion by stimulating intestinal motility, gall bladder contraction, and increased pancreatic exocrine secretions. CCK is also known to cause satiety. This is accomplished by CCK's effect on slowing gastric emptying and inhibiting gastric acid secretion. In addition, CCK has been shown to inhibit food intake in both humans and rodents [147,148]. However, studies on long-term administration of CCK demonstrated that its food inhibitory effect is short-term. These studies showed that though CCK continued to cause inhibition of food intake, it also caused an increase in meal frequency, thereby causing no weight reduction [149].

It has been shown that CCK exerts its actions through two receptors; one identified mainly in the gut, CCK1 (CCK A), but also present in the brain and the other distributed mainly in the brain, CCK2 (CCK B) with existence in the gut [59,150]. Peripheral administration of CCK has been shown to activate c-fos expression in the brainstem, NTS, and dorsal vagal nucleus [151]. Rats lacking functional CCKA receptors are diabetic, hyperphagic and obese [28,143]. However, receptor deficient mice have normal body weight [152], which suggests that other pathways might also be involved. For example, neuronal connections have been shown to be required for the mediation of CCK actions on the CNS [153]. This was concluded subsequent to studies showing no inhibitory effect of CCK on food intake following vagotomy [154,155].

The above demonstrates that though CCK plays an important role in the digestive process, it has no long lasting effect on food inhibition. Therefore, there have been no advances in its therapeutic role as a potential agent in the treatment of obesity.

### **Ghrelin**

Ghrelin was discovered in 1999 as the endogenous ligand for the growth hormone secretagogue receptor [156]. It is a 28 amino acid peptide, produced and secreted primarily by the stomach [156,157]. Ghrelin is also produced in the duodenum and, to a lesser extent, in the rest of the small intestine [56,156,158-163]. Once released, ghrelin enters the circulation, crosses the semi intact blood brain barrier (in the region of ARC) and reaches the brain. There is also evidence for ghrelin synthesis, though in minute amounts, in the hypothalamus adjacent to the orexigenic neurons; NPY and AgRP. However, this remains controversial [22,164-166] and its physiological role needs to be established.

There is ample evidence to support the orexigenic effect of ghrelin and its role in the regulation of food intake. This effect is thought to be mediated via the orexigenic peptides NPY/AgRP in the hypothalamus. In support of this, NPY-Y1

receptor antagonists [161,167-169] have been shown to abolish the orexigenic effects of ghrelin. C-fos activation following central and peripheral ghrelin administration has been shown in the ARC, the area postrema and the NTS [167,170-173].

Ghrelin levels have been shown to be highest before a meal and suppressed postprandially. In keeping with this, in both animal and human studies, ghrelin has been shown to contribute in signalling the pre-prandial hunger and meal initiation [156-158]. Ghrelin also stimulates gastric motility and acid secretion in the cephalic phase response of food intake [169]. In rats, IP and central administration of ghrelin into ICV was shown to increase food intake [174-176]. This was also shown in humans in whom intravenous ghrelin administration, though short lived, resulted in an increase in appetite and food intake [177]. Despite the above evidence for its orexigenic effects, it appears that ghrelin is not the only factor responsible for the initiation of food intake. Sun *et al.* [166] showed no significant alterations in food intake or body weight in ghrelin-null animals [166], and recently, ghrelin infusions were shown to have no effect on food intake in six men and one woman with previous complete truncal vagotomy [55]. The latter suggests that an intact vagal nerve is required for ghrelin to exert its stimulatory effect on food intake.

Several factors have been shown to influence the release of ghrelin. These include meal calorie content and composition (discussed below) and the nutritional status of the individual. Ghrelin increases during fasting, peaks just before meal intake and is suppressed in response to meal ingestion. It has been shown to be inversely related to BMI with obese subjects having lower basal levels. However, these subjects have been shown to maintain, though to a lower extent, ghrelin suppression postprandially [30, 160,178]. The latter may explain persistent eating habits in obese patients. On the other hand, the level is increased during fasting, cachexia [108,109], in states of malnutrition [179,180] and in patients with anorexia nervosa [111]. This may be explained as a physiological response of the body to normalise food intake in those conditions. In contrast, ghrelin levels were shown to be reduced following a Roux en-Y gastric bypass, though other forms of bariatric surgery were not associated with a reduction in ghrelin level, despite massive weight loss [181]. Removal of gastric fundus, the primary site of ghrelin production, was suggested to explain the findings in the Roux-en Y type of surgery [182-184], although the real mechanism is still unknown. However, mechanical restriction due to reduced stomach size, hence reduced meal portions, as well as the decreased ghrelin levels have been suggested as causative factors for the maintenance of weight loss in these patients.

As mentioned earlier, ghrelin levels appear to also be influenced by direct nutrient sensing, caloric content as well as stomach volume load. Carbohydrates, and to a lesser extent fat, have been shown to reduce, while protein appears to stimulate, ghrelin release in normal [30,185-187] and type-1 diabetic patients [188]. Furthermore, ghrelin suppression was shown to be induced by glucose, but not water, infused into the stomach. This suggests that caloric content, rather than stomach volume load (distension), is

more important in the regulation of ghrelin [189]. However, the micronutrient content cannot totally explain the postprandial suppression of ghrelin; other factors might be involved. Ghrelin levels have been shown to have a diurnal rhythm coinciding with leptin levels, being highest in the morning and lowest at night. It has been suggested that ghrelin does not appear to be a functional antagonist to leptin (at least for the regulation of long-term body weight) but perhaps signals responses to short-term changes in energy homeostasis such as food deprivation. Given the above, it appears that ghrelin levels influence and are influenced by both diet composition and body weight. A recent review extensively described ghrelin with particular focus on current controversies around its role in energy balance [23].

#### INTERRELATION OF GUT HORMONES, NUTRIMENT SENSE AND NUTRITIONAL STATUS

Gut hormone regulation and their interaction with energy controlling centres in the brain, “*gut-brain interaction*”, play a key role in the regulation of food intake and energy homeostasis. Gut-brain interaction appears to be influenced by different factors Fig. (2). As discussed earlier, both orexigenic and anorexigenic gut peptides have been shown to bind different receptors in the brain that are involved in appetite regulation. Peripheral administration of PYY has been shown to activate c-fos expression in the ARC, a sign

of neuronal activation [44]. Transportation of gut peptides to the brain may occur, either directly through the semi intact blood brain barrier at the site of the ARC or via sympathetic or vagal innervations [55,190].

On the one hand, gut peptides have been shown to influence nutrient movement within the gut, thereby promoting satiety by affecting gut motility and gastric and pancreatic secretions. On the other hand, nutrient sense within the gut [16,98] has been shown to influence the release of gut peptides; a “*gut-gut interaction*”. As mentioned earlier, the number of calories ingested and meal composition [88,98,99], but not gastric distension, influence the release of anorexigenic gut peptides [24]. Hence the feeling of satiety acquired following ingestion of a high fat meal has been attributed to the stimulatory effect of the fat content on PYY3-36 [107,191], GLP-1, and CCK release [60]. A similar mechanism has been suggested for OXM [16]. Reduced calorie intake up to 12-24 h following high calorie meals was attributed to higher and persistent release of PYY3-36 [18]. In contrast, ghrelin has been shown to be suppressed postprandially in proportion to meal caloric content [30].

There is evidence to suggest that gut hormone release and action is inter-dependent. Some gut peptides share structural homology (PYY3-36 and PP), are co-secreted from the same

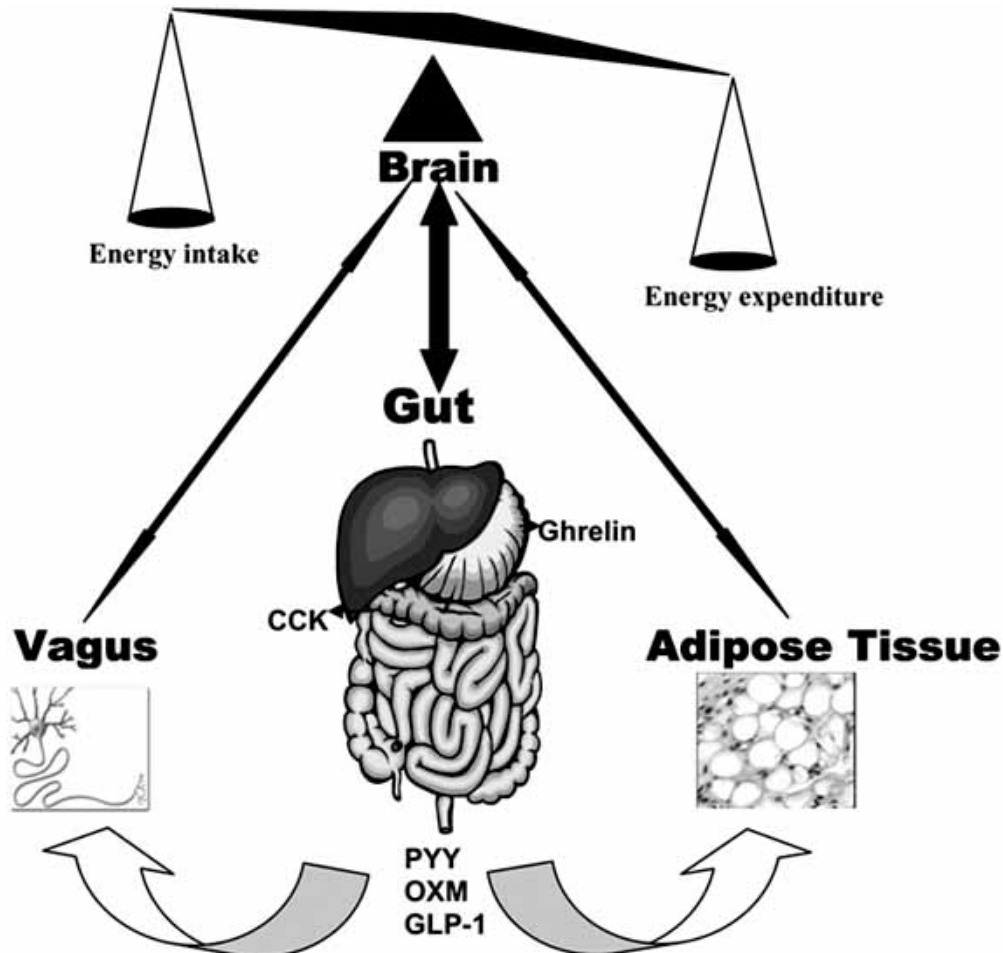


Fig. (2). Gut–gut, brain and adipose interactions.

cell line (PYY3-36, OXM and GLP-1) and have been shown to be products of the same gene (OXM and GLP-1). Though these peptides have been shown to exert their effects through different mechanisms, they all inhibit appetite and promote satiety. CCK is known to induce satiety [60,142], but because of its very short half life in the circulation, other factors have been proposed to maintain prolonged periods of feeling of full. Therefore, it is reasonable to suggest that prolonged satiety and food inhibition might be a function of additive and complementary effects of different peptides. For example, while the increase in ghrelin has been shown to contribute to meal initiation, CCK promotes early satiety that is complemented and maintained by sustained release of PYY3-36 and OXM. The latter two are thought to contribute to meal termination as well as maintenance of the feeling of fullness in between meals [18,72]. It is worth noting that, although GLP-1 has been shown to suppress PYY3-36 [101], the effect is not long lasting because of its short half life in circulation. In turn, this might explain the persistent release of PYY3-36 up to 6 h postprandially. In addition, ghrelin suppression following OXM infusions has been proposed to explain the anorexigenic effects of OXM. Therefore, it is tempting to hypothesize that these gut hormones act in a synchronised way to stop the hunger pangs and produce regulated satiety responses. However, the mechanism is not that simplistic with yet more complex factors being implicated. Gut hormones have been shown to interact with long-term signals from adipose tissue “*gut-adipose interaction*”. GLP-1 improves insulin sensitivity and, therefore, glycaemic control [192-194]. Repeated administration of PYY3-36, in rodents over a period of four weeks, was shown to improve glycaemic control, reduce body weight and visceral fat [58,195]. In humans, altered leptin and adiponectin (markers of adiposity) was shown following repeated subcutaneous injections of OXM in association with reduced body weight [47].

Furthermore, an inverse relationship between BMI and ghrelin [160,178], PYY [18], and GLP-1 levels has been demonstrated [52], though the latter has not been confirmed [196-198]. Insulin resistance has been postulated to play a role in determining this lower level of ghrelin, [199], however, different peptide configurations, receptor defects or L-cell failure may be other contributing factors.

Alterations in gut peptide levels have also been shown following bariatric surgery [47,58,183,184]. This has been suggested to contribute to the maintenance of weight loss in these patients [46,58,183,184]; though, contrary to expectation, reports on the levels of PYY and ghrelin following these surgical operations are inconsistent [58]. While fasting levels of both PYY and ghrelin have been shown to vary postoperatively [58,103], in the long-term (after 35 months following RYGB) an exaggerated rise in PYY3-36 level has been demonstrated in weight-stable patients [46]. Suppression of ghrelin after RYGB may be due to the removal of the gastric fundus, the ghrelin secreting part of the stomach [23]. Other studies have reported inconsistent results at 6 [200], 8 [182] and 12 [58] months post gastric banding. This further supports the important role of gut hormones in the regulation of food intake and energy homeostasis, though more studies are required.

## POTENTIAL ROLE OF GUT HORMONES AS ANTI-OBESITY THERAPEUTIC AGENTS- COMPARISON WITH OTHER AVAILABLE OPTIONS

In order to prevent weight gain and/or promote weight loss in obese individuals, a mechanism should be in place to prevent excess body adiposity. This can be achieved by keeping the balance between energy intake and energy expenditure. Options available to attain this are discussed below:

*Reduction of energy intake* includes eating less or absorbing less. Eating the right food, the right amount, at the right time and in the right proportions has proved difficult in general. Different dietary programs have been invented and have been followed by millions of individuals. Though useful in the short-term, it has been proved difficult to maintain the reduced weight in the long-term. A consequence of which is weight regain (yo yo diet). Absorbing less can only be achieved via drugs/preparations or invasively as in bariatric surgery (discussed below).

*Increased energy expenditure* is another way of preventing weight gain. Attempts to *increase physical activity and exercise* on a regular basis have shown similar results to dieting in the long-term. Current stressful sedentary life style and work environment add limitations to continuity of exercise regimes. Counselling on behavioural changes has also proved ineffective.

Pharmaceutical agents have long been investigated and developed to target obesity without dramatic effects. These include *centrally* acting appetite suppressants, some of which were in use previously but discontinued due to side effects. Currently, three such drugs, sibutramine (Abbott), orlistat (Roche) and rimonabant (Sanofi-Aventis) are licensed. Sibutramine, a serotonergic and noradrenergic reuptake inhibitor, acts centrally to reduce appetite and increase energy expenditure. Though it can now be used long-term in the treatment of obesity, close monitoring of side effects such as, hypertension and tachycardia, is required [10,201,202]. In addition, the NICE guidelines and product information recommend that physicians should re-evaluate patients who have not lost 2kg body weight following daily sibutramine (10 mg for one month), and either increase the dose to 15mg or discontinue therapy. The NICE guidelines also recommend that sibutramine is stopped if less than 5% body weight is lost in the first 3 months of therapy. Therefore in clinical practice, the use of sibutramine is governed by guidelines [201]. In a study conducted recently, a combination of counselling, administration of a therapeutic agent (sibutramine) and a low calorie diet were shown to significantly reduce weight and maintain weight loss [203]. However, the study only lasted for 1 year. Therefore, long-term effects cannot yet be evaluated. Over a 2 year period, orlistat, an intestinal lipase inhibitor which blocks intestinal absorption of dietary fat, resulted in only a 3-4% additional weight loss over diet modification alone. Socially unacceptable side effects have resulted in incompletion in a number of patients [8].

The most recent drug approved is rimonabant, a selective CB1 endocannabinoid receptor antagonist, produced by Sanofi-Aventis. Rimonabant, launched in March 2006,

appears to offer a relatively better prospect over the other agents [12]. In a large multicentre trial over Europe and the USA, rimonabant at a dose of 20mg daily was shown to cause a significant weight loss (>10%), greater loss in waist circumference, HDL cholesterol, triglyceride and insulin resistance over placebo with only mild and transient side effects [12].

Recently, weight loss by promoting increased thermogenesis has been reviewed by Himms-Hagen [204] in their article "Exercise in a pill". No such pill is found yet to be without side effects.

Bariatric surgery has gained popularity in the last decade and is increasingly performed in the management of morbid obesity [205]. Though effective in a small proportion of the population, it is not recommended in overweight patients with a BMI<30 who are still at higher risk of obesity associated co-morbidities [205]. In addition, mortality and risk of the operation is high at 2-5% in the more invasive types of bariatric surgery [14]. A recent study examined early death figures for all U.S. fee-for-service Medicare beneficiaries who underwent bariatric procedures from 1997-2002 [14]. The researchers found that among all patients, the rates of 30-day, 90-day, and 1-year deaths were 2.0%, 2.8%, and 4.6 % respectively. This demonstrates a considerably higher risk of early post-surgical death than what has been reported in previous case series. On the other hand, adjustable gastric banding performed under laparoscopy has been shown to cause a greater weight loss, compared to the currently available pharmacotherapy and life style changes. In a recent randomized trial, laparoscopic gastric banding in patients with mild to moderate obesity who were denied surgery due to guidelines, was shown to cause a greater weight loss, improvement of metabolic syndrome and quality of life, compared to a control group (patients who didn't have surgery) over the 24 months duration of the trial [13]. Though no peri-operative mortality/morbidity was encountered, a small number of the patients required a second laparoscopy for the revision of the band position.

The ideal anti-obesity drug "ENABLES" a balance between energy intake and energy expenditure:

1. **E**vent free Naturally occurring to be devoid of side effects
2. **A**ppetite **B**locking to reduce energy intake
3. **L**ong lasting levels to avoid resistance
4. **p**romote **E**nergy expenditure
5. **S**atiety factor, thereby, reduce energy intake

Gut hormones are ideally placed to fulfil the above criteria. They are naturally released from the GI tract after each meal. As previously mentioned, evidence is accumulating on their appetite inhibitory effects (PYY3-36, OXM, GLP-1 and PP) and satiety promotion. This is accomplished by sending coordinated signals to the hypothalamic nuclei and higher centres in the brain that are involved in the regulation of energy homeostasis (Fig. (2)).

Given the above, the therapeutic roles of gut hormones have lately been under immense investigation. The reduced calorie intake caused by single infusions of PYY3-36 was

promising in both lean and obese subjects [18]. Similar results were also shown on single OXM infusions to humans [72]. Recently, in a double-blind randomized controlled trial, Wynne *et al.* showed that 3 times daily subcutaneous injections of OXM, 30 min before each meal, in 14 obese subjects over 4 weeks resulted in a significant ( $p=0.0106$ ) reduction of weight in the treatment group, compared to 12 age and BMI matched controls [47]. No significant adverse events were reported. Body weight was reduced by  $2.3 \pm 0.4$  kg in the treatment group, compared to  $0.5 \pm 0.5$  kg in the control group. In addition, changes in the levels of adipose hormones in the treatment group were suggested to be consistent with loss of adipose tissue. This may prove a novel and promising anti-obesity therapy.

The therapeutic effects of GLP-1 and incretin mimetics have been well established with the first, Exenatide (Byetta by Amylin Pharmaceuticals), approved by the US FDA early 2006 for use in the management of type 2 diabetics as an adjuvant therapy to metformin/and or sulphonylurea. Exenatide has been shown to bind the GLP-1 receptor and improve glycaemic control. In  $\beta$ -cells it stimulates insulin secretion and in  $\alpha$ -cells normalises the pathologic hypersecretion of glucagon in a glucose-dependent manner. This reduces hepatic glucose production postprandially without causing hypoglycaemia. In a recent study, type 2 diabetic patients were shown to achieve a 1.2% reduction in HbA1c and an average 12.1 lb weight reduction over 18 months therapy with exenatide 10 $\mu$ g daily in combination with metformin and/or sulphonylurea [206]. The most common adverse effect reported was nausea, which was demonstrated in <10% of the patients and appeared to disappear with time. However, it was suggested that exenatide in combination with sulphonylurea, but not metformin, should be used with caution because of risk of hypoglycaemia [206]. This provides promising results regarding the long-term efficacy and safety of the drug, both in terms of diabetes control and weight reduction. The latter has been shown to be associated with further improvements in diabetes control and other components of the metabolic syndrome.

Other studies have directed their efforts towards the prolongation of GLP-1 half life in the circulation. Vidagliptin and sitagliptin, DPP IV inhibitors are in clinical development and are currently explored as novel agents in the treatment of diabetes [207-209]. These are orally administered agents, which is the preferred route over injection, hence resulting in better compliance by the patients. Since DPP IV cleaves PYY1-36 resulting in the release of its active form, PYY3-36, it may provide additive weight regulatory activities over and above the actions of GLP-1. Liraglutide, [210-212] (under development by Novo Nordisk) a long-acting GLP-1 analogue, with a pharmacokinetic profile suitable for once-daily administration, has been shown to improve glycaemic control and weight in type 2 diabetic patients [213].

Various other therapeutic strategies are being explored including  $\beta$ -adrenoceptor agonists, leptin agonists and melanocortin 3 agonists.

Bariatric surgery is increasingly used as a long-term treatment option in morbidly obese patients. Changes in gut

hormone levels (discussed above) are inconsistent in the short-term but the more exaggerated response in the long-term provides evidence and support regarding their potential role in the maintenance of weight loss in those patients.

## CONCLUSION

Obesity causes premature death of about 2 million people a year worldwide and the prevalence is rising. The decision to eat or when to stop eating and/or to increase energy expenditure is central to the dilemma of increased body adiposity. No single and/or combination therapy has yet been fully successful. Counselling on behavioural changes, to eating less and increasing exercise on a regular basis has proved difficult. Even going to the extremes of removing parts of the body with high risk operations has achieved relatively little. Available pharmaceutical drugs are limited and those on the market are struggling to achieve targets in reducing energy intake and increasing energy expenditure without side effects.

Gut hormones are secreted from the GI tract either before or after each meal. They have been shown to influence appetite and gastric motility, thus promoting satiety by sending coordinated signals to the hypothalamus and other higher centres in the brain. Because they occur naturally, they are almost free from undesirable side effects that would result in reduced tolerability and safety. Despite the controversy around the efficacy of some of the peptides, evidence strongly supports their role in appetite regulation. Therefore, they are regarded as potential novel therapeutic agents in obesity treatment. However, further studies are required to explore their efficacy, safety and tolerability, particularly in the long-term. Perhaps studies need to be designed to explore the right configuration of the active molecule and/or molecules in-vivo which are likely to be functioning in consortium in appetite regulation and energy homeostasis.

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