

Glucagon-like peptide 1 in the pathophysiology and pharmacotherapy of clinical obesity

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Abstract

Though the pathophysiology of clinical obesity is un-

doubtedly multifaceted, several lines of clinical evidence implicate an important functional role for glucagon-like peptide 1 (GLP-1) signalling. Clinical studies assessing GLP-1 responses in normal weight and obese subjects suggest that weight gain may induce functional deficits in GLP-1 signalling that facilitates maintenance of the obesity phenotype. In addition, genetic studies implicate a possible role for altered GLP-1 signalling as a risk factor towards the development of obesity. As reductions in functional GLP-1 signalling seem to play a role in clinical obesity, the pharmacological replenishment seems a promising target for the medical management of obesity in clinical practice. GLP-1 analogue liraglutide at a high dose (3 mg/d) has shown promising results in achieving and maintaining greater weight loss in obese individuals compared to placebo control, and currently licensed anti-obesity medications. Generally well tolerated, provided that longer-term data in clinical practice supports the currently available evidence of superior short- and long-term weight loss efficacy, GLP-1 analogues provide promise towards achieving the successful, sustainable medical management of obesity that remains as yet, an unmet clinical need.

Key words: Obesity pathophysiology; Glucagon-like peptide 1 analogues; Glucagon-like peptide 1; Clinical obesity

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Core tip: Several lines of clinical evidence implicate an important functional role for glucagon-like peptide 1 (GLP-1) signalling in the pathophysiology of clinical obesity. Here we critically evaluate such findings in way that as yet has been unexplored; using the well established roles of GLP-1 as an incretin and meal to meal satiety signal to go some way toward explaining findings from interventional and observational clinical data that suggest functional deficits of GLP-1 to be a contributor to the obesity phenotype. We also explore

the promise shown by GLP-1 analogues in achieving and maintaining significant weight loss in obese individuals, and use findings to discuss to what extent they too may support a role for GLP-1 in obesity pathophysiology. We conclude by exploring what an association with functional GLP-1 deficit could mean for the clinical management of obesity; conducting cost and risk benefit analyses to evaluate the extent to which GLP-1 analogues may provide a successful and sustainable option for the medical management of obesity that remains as yet, an unmet clinical need.

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INTRODUCTION

Public health and economic impacts of obesity

Obesity is a global epidemic, perhaps the greatest challenge to global and public health of our time. With a doubling in prevalence from 1980 to 2008^[1], 13% of the world's population at present are obese [body mass index (BMI) ≥ 30 kg/m²] and 39% overweight (BMI ≥ 27 kg/m²)^[2]. If recent trends continue, by 2030 up to 57.8% of the world's adult population will be overweight or obese^[3] (Figure 1). The World Health Organisation (WHO) has estimated that 44% of the global diabetes burden, and 23% and 7%-41% of the burdens for ischaemic heart disease and specific cancers respectively can be attributed to being overweight or obese^[4]. Psychosocially, stigma and discrimination toward obese people can have consequences for psychological as well as physical health^[5], with impaired quality-of life^[6] and increased rates of depression^[7] reported in this group. Even modest losses of 5%-10% of total body weight are associated with reduced risk of comorbidities in obese individuals^[8-10]. Therefore, effectively managing rates of obesity is a major goal in public health policy.

In addition to its physical and psychological burdens, obesity and its comorbidities impose disproportionately high healthcare and economic demands at individual and societal levels^[11]. Affecting the wider economy indirectly through increased rates of worker illness absenteeism and resultant losses in productivity, healthcare systems are burdened from direct healthcare related costs; obese individuals on average incurring healthcare related costs 30% greater than their healthy weight peers^[12-16]. A global systematic review has estimated the direct costs of obesity related diseases to account for between 0.7% and 2.8% of a country's total healthcare expenditure^[16]. In the United Kingdom alone, direct costs to the National Health Service (NHS) of treating overweight and obesity, and related co-morbidities were estimated at £5.1 billion in July 2006; representing around 5% of total

NHS spending^[17,18]. A computer based micro-simulation model predicting the direct healthcare related costs of overweight and obesity in the United Kingdom should 2001 prevalence remain constant, has forecasted the NHS spending £15.4 billion and £22.5 billion in 2015 and 2050 respectively^[18,19] on the direct health costs of treating overweight and obesity and related co-morbidities in England alone. An upward trajectory prevented by significant weight loss in those currently obese (Figure 2), findings imply that whilst the prevention of obesity is the strategic imperative, the effective management of those already obese is an immediate priority.

Current management of obesity

Current medical management of obesity involves lifestyle, pharmacological and surgical interventions^[20]. Lifestyle intervention, in the form of dietary, behavioural and exercise counselling, are currently the suggested first line treatment for obesity; however, whilst a recent meta-analysis reports such interventions to show small but significant benefits on weight loss maintenance, weight loss achieved and sustained with lifestyle intervention alone remains suboptimal^[20-24]. In the face of such challenges, a number of pharmaceuticals have been marketed to assist weight management over the years^[25,26] (Table 1). However, adverse effects of some and the transient weight losses associated with others^[27] mean that the pharmacological management of obesity remains suboptimal. The only proven treatment to achieve and maintain weight loss in obesity is bariatric surgery^[28-30]. However, surgical and anaesthetic risks associated with overweight and obese status sees these invasive procedures reserved to those patients classed morbidly obese (BMI ≥ 40 kg/m²) or as a last resort in those failing more conservative management^[20,31,32]. The minimally invasive and efficacious management of obesity therefore, remains an unmet clinical need.

Glucagon-like peptide 1 and the management of human obesity

The ideal management of any illness involves an understanding of its underlying pathophysiology; greater understanding facilitating the development of targeted pharmacotherapies to either replete physiological factors pathologically depleted, or antagonize pathological processes. The pathophysiology of obesity however, remains poorly understood. The WHO has defined the current obesity crisis epidemiologically, as the consequence of an increasing imbalance between energy intake and expenditure^[33]. Physiologically, energy balance is a closely regulated system involving interactions between peripheral endocrine, nutritional and neural signals acting on regulatory central hypothalamic and hedonic brain regions^[34-36]. Clinical obesity has been associated with deregulations in both homeostatic and hedonic controls of energy balance potentially facilitated by impaired glucagon-like peptide 1 (GLP-1) signalling^[35-37] (a role for GLP-1 in the pathophysiology of clinical obesity). Pharmacologically targeting GLP-1

Table 1 Current and previously Food and Drug Administration licenced anti-obesity pharmacotherapeutics

| Drug | Mechanism | Year | Clinical use and limitations | Suspension reason |
|---------------------------------|---------------------------------|------|---|---|
| Currently FDA licenced drugs | | | | |
| Diethylpropion | NA releasing agent | 1959 | FDA approved for short term use (3 mo); not recommended with uncontrolled hypertension or heart disease | - |
| Phentermine | - | 1959 | FDA and EMA approved for long term use; treatment dependent weight loss | - |
| Orlistat (Xenical) | - | 1999 | - | - |
| Orlistat (Alli) | Pancreatic lipase inhibitor | 2007 | - | - |
| Phentermine-topiramate (Qysmia) | - | - | Approved for long term use; treatment dependent weight loss | - |
| Lorcaserin (Belviq) | 5HT _{2c} -R antagonist | 2012 | FDA approved for long term use, recommended in those with cardiovascular disease; treatment dependent weight loss | - |
| Liraglutide (Saxenda) | GLP-1 analogue | 2014 | FDA and EMA (2015) approved | - |
| Previously FDA licenced drugs | | | | |
| Dinitrophenol | Unknown | 1938 | - | Dermatitis, neuropathy, agranulocytosis, visual impairment, death |
| Aminorex | Unknown | 1968 | - | Chronic pulmonary hypertension |
| Amphetamines | Monoamine reuptake inhibitor | 1971 | - | Addiction, hypertension, myocardial toxicity |
| Fenfluramine | Serotonin reuptake inhibitor | 1997 | - | Valvular heart disease |
| Phenylpropanolamine | NA-R and DA-R agonist | 2000 | - | Haemorrhagic stroke |
| Rimonabant | CB ₁ R antagonist | 2009 | - | Psychiatric disorders, depression, suicidal ideation |
| Sibutramine | Serotonin-NA reuptake inhibitor | 2010 | - | Risk of major cardiovascular events |

The pancreatic lipase inhibitor Orlistat and GLP-1 analogue liraglutide are the only currently UK licenced anti-obesity agents). 5HT_{2c}: Serotonin receptor; NA: Noradrenaline; DA: Dopamine; CB₁R: Cannabinoid receptor; R: Receptor; FDA: Food and Drug Administration; EMA: European Medical Association.

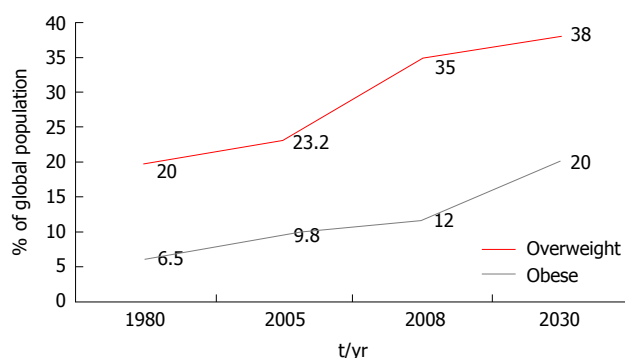


Figure 1 Global overweight and obesity trends and projections. If recent trends continue unabated, by 2030, 38% and 20% of the world's adult population are projected to be overweight or obese respectively^[8].

therefore, may go some way towards achieving the successful and sustainable medical management of clinical obesity that as yet remains to be achieved.

GLP-1 is a 31 amino acid polypeptide primarily synthesized by the enteroendocrine L cells of the terminal ileum. Amongst its pleiotropic central and peripheral effects, GLP-1 acts as a potent incretin first clinically used in the medical management of overweight or obese individuals with type 2 diabetes mellitus (T2DM)^[38]. The repeatedly demonstrated ability of GLP-1 analogues to induce weight loss in this cohort^[39,40] prompted phase

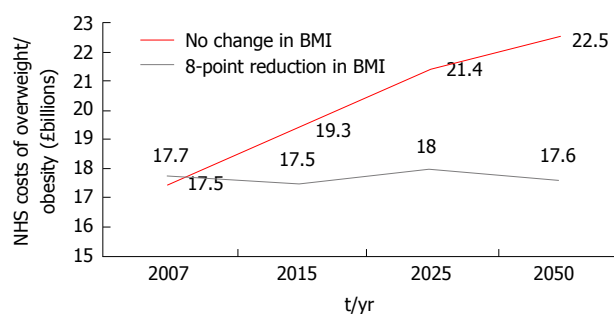


Figure 2 Projected trends in National Health Service costs from a micro-simulation model. A computer based micro-simulation model^[18] predicted the direct healthcare related costs of overweight and obesity in the United Kingdom at five time points from 2001 (2001, 2007, 2015, 2025 and 2050) should prevalence of overweight and obesity remain constant (red) or if an average of an 8-point BMI reduction was achieved in all those obese in 2001 (grey). BMI: Body mass index; NHS: National Health Service.

III trials studying the weight loss efficacy of the GLP-1 analogue liraglutide (3 mg; trade name Saxenda) vs placebo^[41] and the pancreatic lipase inhibitor orlistat^[42,43] (the only anti-obesity drug licensed in the United Kingdom) in non-diabetic overweight and obese adults. The greater weight loss efficacy achieved and maintained by GLP-1 analogues prompting the Food and Drug Administration (FDA) in 2014 to approve Saxenda as the first GLP-1 analogue for use as a weight loss aid in obese

adults and overweight adults with at least one weight related co-morbidity^[44]. March 2015 saw the European Medical Association (EMA) grant marketing authorization for 3 mg liraglutide under the FDA approved criteria in all 28 European Union (EU) states^[45]. However, launching in April 2015 in the United States at a cost of over \$1000 per patient a month, cost-benefit is of greater issue in EU nations such as the United Kingdom where health care is primarily socially funded; undoubtedly contributing to the uncertainty of launch plans in the United Kingdom at present^[46]. Clinical evidence however implicates a role for functional impairments in GLP-1 signalling in the pathophysiology of obesity, GLP-1 agonism therefore may be the first truly targeted therapeutic in the medical management of clinical obesity. Therefore, with its superior clinical efficacy to currently United Kingdom licensed therapies benefiting patients through greater achieved and maintained weight loss and the economy through the potential to reduce long-term financial burdens of obesity, the cost-benefit spectrum may therefore be swayed, favouring the use of GLP-1 analogues in the medical management of obesity in the United Kingdom^[46].

THE HOMEOSTATIC AND HEDONIC CONTROL OF ENERGY BALANCE

Physiologically, energy balance is a closely regulated system involving interactions between peripheral endocrine, nutritional and neural signals acting on regulatory central hypothalamic^[34] and hedonic^[35,36] brain regions. Where previously the neurocircuits mediating the homeostatic and hedonistic control of energy balance were considered distinct entities, it has now emerged that considerable cross talk exists with implications for the pathophysiology of clinical obesity.

Peripheral afferents

Peripheral signals involved in energy homeostasis are often stratified as long or short acting. Long acting signals provide information about available energy stores, and in response, the brain makes corrective adjustments to food intake and energy expenditure to maintain body weight^[47]. The white adipocyte hormone leptin^[48] and pancreatic hormone insulin are the two major afferents governing long-term energy balance and act primarily as anorexigens. Food intake and energy expenditure in the short term are modulated by a wide variety of situational and meal-related factors, among the most important are short-term gut derived hormones such as GLP-1 that act to signal acute energy status. Originally thought to exert their effects on energy balance through modulating homeostatic hypothalamic circuits, both long and short term afferents may also modulate the hedonic drive toward food consumption, though these pathways remain less extensively studied^[49] (Figure 3).

Central controllers

The homeostatic control of food intake: The hypothalamic

arcuate nucleus (ARC) is believed to play a crucial role in the homeostatic control of energy balance. At a cellular level, the ARC contains two distinct neural populations exerting antagonistic effects on food intake; a medially located orexigenic (appetite stimulating) population consisting of neurons co-expressing Agouti related peptide (AgRP) and neuropeptide Y and a laterally located anorexigenic (appetite suppressing) population consisting of neurons co-expressing pro-opiomelanocortin (POMC) and cocaine and amphetamine related transcript (CART)^[55-58]. Both neural subsets project to melanocortin 4 receptor (MC4R) positive neurons located in intra- and extra-hypothalamic sites. POMC is cleaved to produce α -MSH an agonist of MC4R whereas AgRP acts an inverse agonist^[59-61]. The ARC may exert its effects on energy homeostasis by direct cortical projections or indirectly *via* second order neurons in adjacent hypothalamic nuclei of which the paraventricular nucleus (PVN) is believed to be play a crucial role^[62,63]. GLP-1 receptors (GLP1-Rs) have been localized pre-clinically in the ARC and PVN^[50,51] and stimulation of these receptors reduce food intake to induce weight loss in rodents. Targeting the homeostatic controls of energy balance may therefore be the means by which GLP-1 agonism achieves its weight loss effects in the clinic, suggesting an underlying deregulation in GLP-1 signalling contributing to the multifactorial pathophysiology of human obesity.

The hedonic control of food intake: Despite a robust homeostatic system governing energy balance, feeding and meal termination are also influenced by hedonic, reward-related factors such as palatability and the perceived rewards associated with meal consumption. The drive to pursue such pleasurable experiences largely mediated by the mesolimbic rewards system originating from dopaminergic neurons in ventral tegmental area (VTA) that terminate on neurons in the nucleus accumbens. Though the relationship between peripheral afferents signalling acute and long term energy status and central hedonic control centres are less well defined, GLP-1Rs have been located in the dopaminergic neurons of the VTA^[64] where activation inhibits neural firing, potentially reducing hedonic drives toward food consumption. Interestingly, where the homeostatic control of energy balance modulates food intake to regulate the amount of body fat an individual maintains^[65], in obesity, despite an overall positive energy balance, hyperphagia is the norm. Where previously, the neurocircuits mediating the homeostatic and hedonistic control of energy balance were considered distinct entities, it has now emerged that considerable cross talk exists and central GLP-1 signalling has been implicated as a mediator of such interactions (detailed in a number of excellent reviews^[36,37,54]). A skew toward hedonic and away from homeostatic controls of energy balance may explain the pathological hyperphagia seen in obesity; restoring the balance between homeostatic and hedonic drives towards food consumption may therefore be the means by which GLP-1 agonism achieves its sustained

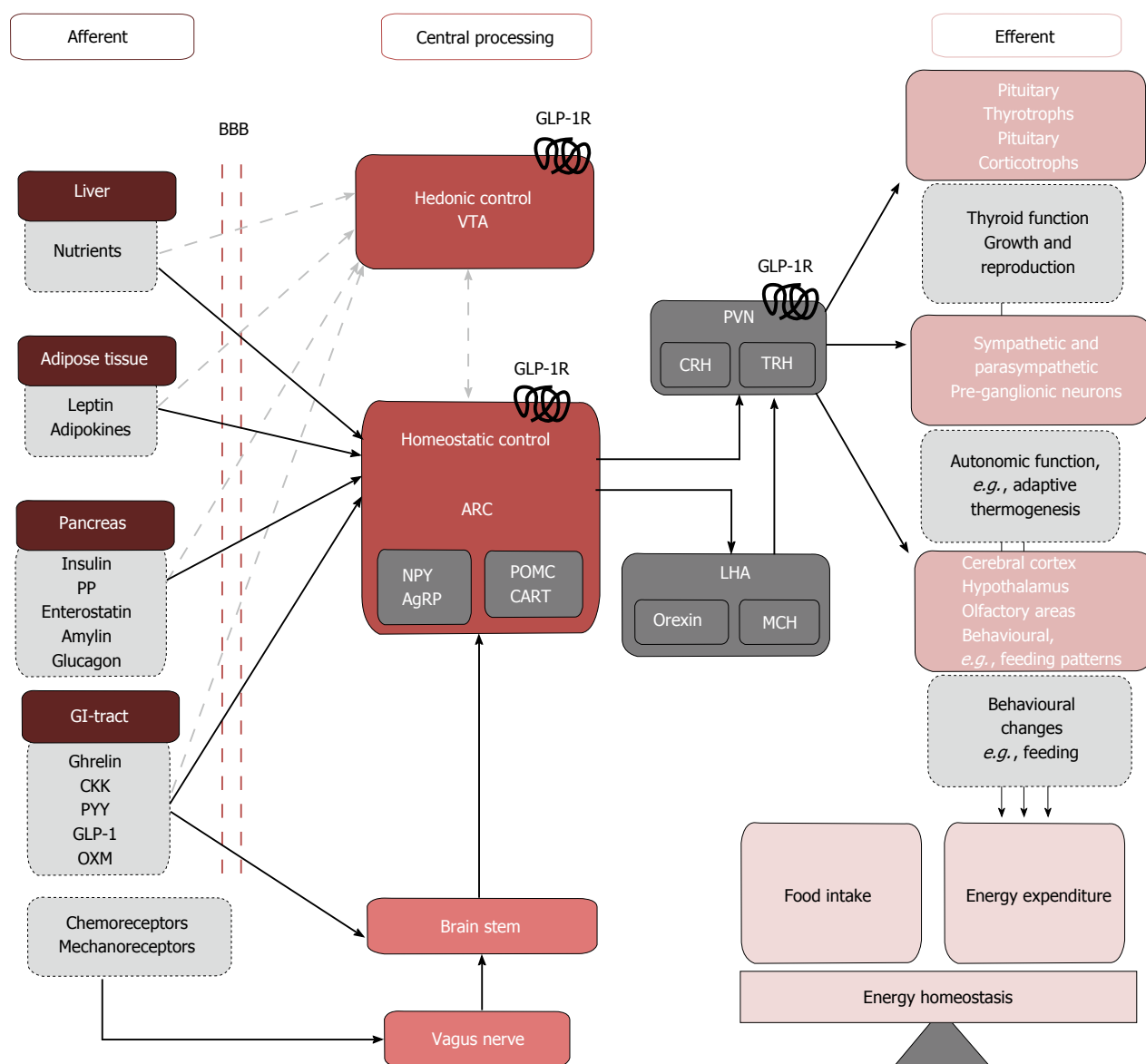


Figure 3 The hedonic and homeostatic controls of energy balance. Peripheral signals from the Liver, adipose tissue pancreas, GI-tract cross the BBB to directly signal to neurons of the ARC of the hypothalamus. GI-tract enteroendocrine hormones and chemo- and mechanoreceptor neural afferents can also indirectly activate the ARC via the vagus nerve and brainstem. The net output of the ARC neurons is relayed to second order intrahypothalamic neurons in the PVN, and LHA that express the MC4R. GLP-1Rs have been localized pre-clinically in the ARC and PVN^[50,51], stimulation of these receptors inducing reductions in food intake and weight loss potentially through efferent pathways that involve the activation of TRH and CRH expressing neurons and pre-ganglionic sympathetic and parasympathetic neurons. Feeding and meal termination are also influenced by hedonic, reward-related factors centrally processed in the VTA. Though the interactions between peripheral nutrient signals and rewards neurocircuitry are not extensively defined (grey dashed arrows) GLP-1Rs have been localized pre-clinically in the VTA^[52]. Previously considered as separate entities, severe cross-interactions exist between central homeostatic and hedonic control centres^[53]. This communication may be mediated by central GLP-1 signalling^[36,37,54]. GI-tract: Gastrointestinal tract; BBB: Blood-brain barrier; ARC: Arcuate nucleus; PVN: Paraventricular nucleus; LHA: Lateral hypothalamic area; MC4R: Melanocortin 4 receptor; TRH: Thyrotrophin releasing hormone; CRH: Corticotrophin releasing hormone; VTA: Ventral tegmental area; PP: Pancreatic polypeptide; CCK: Cholecystokinin; PYY: Polypeptide-YY; OXM: Oxymodulin.

weight loss effects in the clinic, suggesting an underlying deregulation in GLP-1 signalling contributing to the multifactorial pathophysiology of human obesity.

GLP-1

Synthesis, secretion and degradation

GLP-1 is a 31 amino acid polypeptide derived from post-translational processing of the native 160 amino acid peptide proglucagon by the enzyme prohormone convertase 1 (PC1/3). Peripheral proglucagon gene

expression has been localized to the enteroendocrine L cells and pancreatic α -cells whilst centrally, proglucagon expressing neurons have been localized to brainstem regions such as the nucleus of the solitary tract (NTS)^[66-68]. Tissue specific post-translational processing liberates different pro-glucagon derived peptides^[69] depending on subtype of PC enzyme present. Figure 4 details the different post-translational products following PC1/3 and 2 cleavage.

GLP-1 is primarily synthesized by PC1/3 activity in the intestinal L cells^[75]; open-type epithelial cells

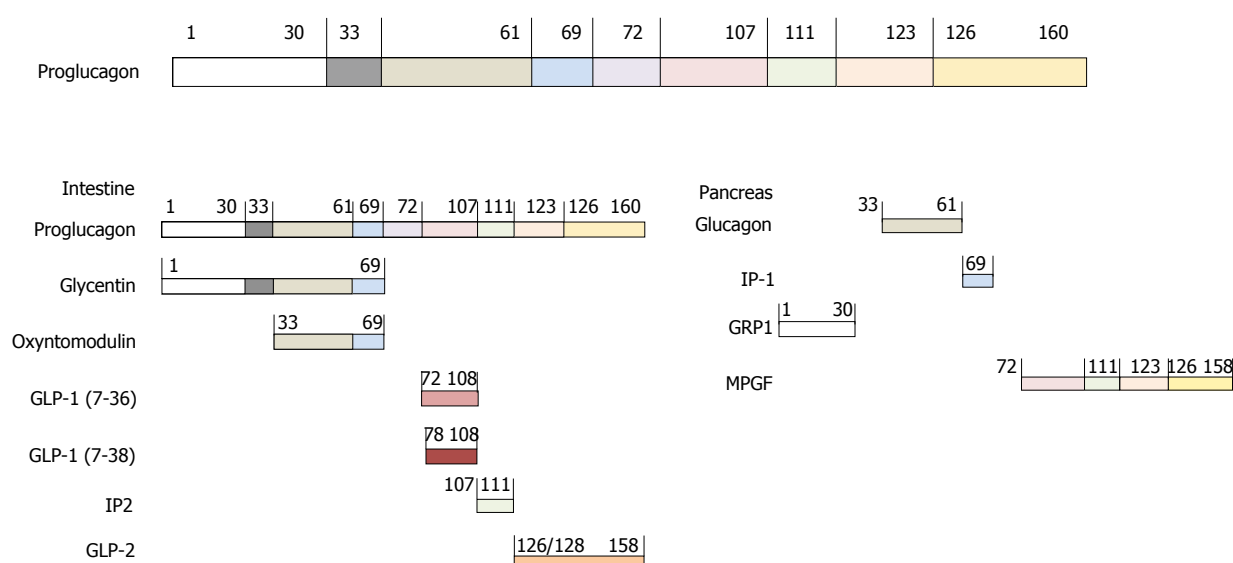


Figure 4 Post-translational tissue specific processing of proglucagon^[70-72] The 160 amino acid pro-glucagon gene (GCG) encoded on chromosome 2 undergoes tissue specific post-translational cleavage by prohormone convertase (PC) 1/3 and PC2 in central and peripheral sites. This figure shows the major cleavage products of the GCG with numbers indicating the amino acids between which the hormone product lies and at which the PC enzymes act. In the pancreas, PC2 dominates and liberates glucagon. In the intestine PC 1/3 activity dominates and produces GLP-1, of note, the other products of proglucagon cleavage by PC1/3 are produced in a 1:1 ratio with GLP-1^[73,74]. The PC responsible for cleaving GCG in the central nervous system is not well established; both PC1/3 and PC2 may play a role. GLP: Glucagon-like peptide; GRP1: Gastrin-releasing peptide 1; IP2: Intervening peptide 1/2.

most densely located in the ileum and colon^[76-78]. Long apical processes that extend toward the intestinal lumen^[77] allow direct nutrient sensing by L cells, of which glucose has been implicated as the most potent GLP-1 secretagogue in both healthy and T2DM humans^[79]. Being in close proximity to neurons of the enteric nervous system and the intestinal microvasculature^[80,81], L cells also receive neural and hormonal signals that act as indirect nutrient sensors. Following synthesis, GLP-1 is secreted from the L-cells *via* secretory granules located in the basolateral membrane. GLP-1 secretion in response to nutrient sensing is biphasic; an initial rapid rise occurring within 10-15 min post-prandial, followed by a second longer phase peaking at 30-60 min^[82]. The early phase of GLP-secretion has traditionally been attributed to signals from the parasympathetic vagal nerve and neurotransmitters such as gastrin-releasing peptide (GRP) and acetylcholine. However, more recently, GLP-1 secreting cells that show direct secretory responses to nutrient stimulation have been localised in significant numbers in the proximal small intestine implicating a role for this albeit sparser population of proximal GLP-1 releasing cells in the rapid postprandial rises of plasma GLP-1^[83-85]. The second phase is mediated *via* direct nutrient contact with subsequent membrane depolarization or activation of second messenger systems mediating GLP-1 release. Figure 5 depicts the major nutrient, neural and hormonal secretagogues of GLP-1.

Secreted GLP-1 is rapidly degraded at its N-terminal residue by the ubiquitously expressed enzyme dipeptidyl peptidase IV (DPPV) to yield residues GLP-1 (9-36 amide) and GLP-1 9-37^[88,89]. The majority of GLP-1 degradation is attributed to membrane-bound DPPV in the hepatic portal system resulting in an extremely short half-life (about 2 min)^[81,90]. As such, only about 10%-15%

of GLP1 secreted from intestinal L cells reaches peripheral downstream targets. The amount of GLP-1 reaching potential central targets involved in energy balance is unknown. As parenteral administration of GLP-1 avoids the physiological first-pass effect of hepatic DPPV, the supraphysiological plasma concentrations achieved by subcutaneous (SC) administration may explain the weight loss efficacy achieved by 3 mg liraglutide in obese and overweight patients in the clinic. Findings also go some way to suggest either a reduction in secretion of, or sensitivity to, physiological GLP-1 secretion as a contributor to the multifactorial pathophysiology of human obesity.

Central and peripheral effects of GLP-1

GLP-1 exerts its effects by intracellular signalling pathways activated after binding to the G-protein coupled receptor GLP-1R^[91]. The extensive central and peripheral expression of the GLP-R reflects the pleiotropic physiological roles of GLP-1 that are summarised in Figure 6 and extensively reviewed elsewhere^[70,86]. From this point onward the review will focus on exploring the evidence surrounding a role for physiological GLP-1 signalling in the regulation of energy balance and deregulations of this signalling as one contributor to the multifactorial pathophysiology of clinical obesity.

GLP-1 AND THE REGULATION OF ENERGY BALANCE

Evidence: Effects of GLP-1 administration on food intake and energy expenditure in man

Numerous clinical studies have examined the relationship between acute physiological and supraphysiological

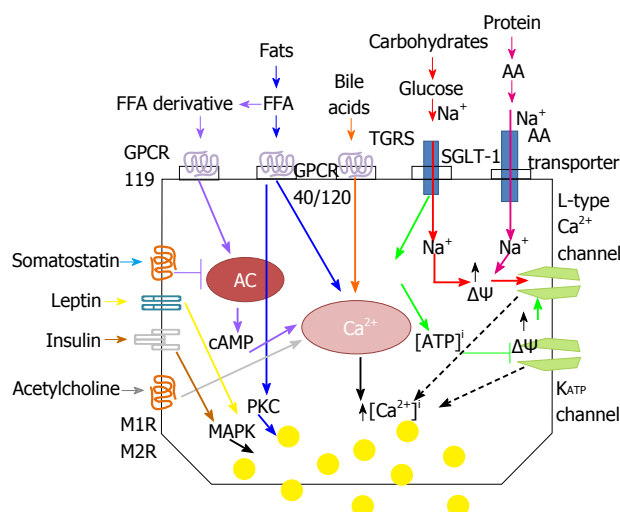


Figure 5 Mechanisms of glucagon-like peptide 1 release from enteroendocrine L cell. Glucagon-like peptide 1 (GLP-1) release from L-cells is regulated by direct nutrient sensing *via* receptors and channels on apical processes or indirectly *via* neuro-hormonal mechanisms^[70,71,86,87]. A: Nutrient signals. Carbohydrates: Glucose derived from carbohydrate metabolism is the most potent stimuli for GLP-1 secretion. Glucose can trigger GLP-1 release by two mechanisms: (1) the sodium-glucose cotransporter-1 (SGLT-1) couples the transport of glucose with Na⁺ ions. Na⁺ influx leads to membrane depolarization ($\Delta\Psi$) (red arrows); and (2) glucose metabolism generates adenosine triphosphate (ATP). Elevated intracellular ATP concentrations [ATP]ⁱ close KATP channels and leads to membrane depolarization ($\Delta\Psi$) (green arrows). Both routes to membrane depolarisation increase intracellular Ca levels ([Ca²⁺]ⁱ) by opening L-type Ca channels. Elevated [Ca²⁺]ⁱ triggers the exocytosis of GLP-1 secretory granules located at the basolateral surface of the enteroendocrine L cell (dashed lines). Fats: Fats are potent stimuli for GLP-1 secretion. Free fatty acids (FFA) (blue arrows) interact with G-protein coupled receptors (GPCRs) that trigger Ca²⁺ release from internal stores and also activate protein kinase C (PKC). FFA derivatives (purple arrows) interact with GPCRs that activate second messenger systems involving adenylate cyclase (AC) and cyclic AMP (cAMP) which increases [Ca²⁺]ⁱ. Bile acids (orange arrows) and short chained fatty acids (not shown) also increase [Ca²⁺]ⁱ by GPCR interactions. Proteins: Protein is a weak stimulator of GLP-1 release when compared with sugars and lipids. Amino acids (AA) derived from protein breakdown are transported intracellularly with Na⁺ *via* Na⁺ dependent AA transporters. Na⁺ influx causes membrane depolarization and elevated [Ca²⁺]ⁱ with resultant GLP-1 exocytosis (pink arrows); B: Hormonal signals. Somatostatin inhibits GLP-1 release by blocking AC activation (light blue arrows). The peripheral adiposity signals leptin (yellow arrows) and insulin (brown arrows) are thought to stimulate GLP-1 release *via* activation of mitogen-activated protein kinase (MAPK) signalling pathway; C: Neural signals. Acetylcholine binding to muscarinic receptors (M1R, M2R) elevates [Ca²⁺]ⁱ stimulating GLP-1 release (grey arrows). GRP is thought to stimulate GLP-1 release in association with the activation of mitogen activated protein kinase kinase (MAPKK) and subsequent phosphorylation and activation of MAPK (not shown).

doses of GLP-1 with measurements of food intake and feelings of hunger and satiety in healthy normal weight and obese adults with and without T2DM^[92-99]. The main findings of these studies have been summarized in Figure 7. Though individual studies are conflicting, a meta-analysis reports that acute GLP-1 infusion induces a mean 11.7% decrease in food intake when compared with saline control in man^[100]. Interestingly, whilst supra-physiological doses of GLP-1 reduces appetite and food intake in both lean and obese subjects, physiological GLP-1 doses reduces appetite and food intake in only lean subjects^[93,94,97,99]. Findings go some way to suggest

a role for resistance to physiological GLP-1 signalling as a factor contributing to obesity pathophysiology. Interestingly, whilst physiological GLP-1 infusions in obese subjects induce appetite reductions^[92,95] similar to those observed in their lean peers, this is not translated into a reduction in food intake, suggesting pathological alterations of GLP-1 signalling in obesity that reinforce feeding despite a reduced physiological drive to food intake. One mechanism that this may be achieved is through a pathological skew toward hedonic and away from homeostatic controls of energy balance in obesity, potentially mediated by deregulated central GLP-1 signalling (a role for GLP-1 in the pathophysiology of clinical obesity).

Whilst evidence from clinical interventional studies suggests that physiological GLP-1 contributes to negative energy balance by decreasing food intake. The effects of GLP-1 on energy expenditure are less clear. Fasting plasma GLP-1 concentrations have been positively associated with increased rates of energy expenditure in man^[101]. Clinical evidence regarding the effects of acute GLP-1 administration on energy expenditure however is conflicting. Physiological infusions of GLP-1 have been reported to reduce energy expenditure in lean and non-diabetic obese patients^[95,102] associated with reduced carbohydrate metabolism. Others, however, have observed that supraphysiological infusions of GLP-1 increase energy expenditure in lean individuals in an insulin dependent manner^[103].

Interpretations: Implications for the clinic

Evidence from clinical interventional studies suggests that acute post-meal rises in GLP-1 contribute to negative energy balance primarily through an anorexigenic effect. The long-acting GLP-1 analogue liraglutide (3 mg) has recently been approved as a once daily bolus SC injection for the medical management of obesity. The sustained anorectic effect of a long term agonist combined with supra-physiological dosing perhaps the mechanism of the clinical weight loss efficacy achieved by liraglutide 3 mg. Unfortunately, to date, clinical studies assessing the comparative efficacy of acute vs continuous GLP-1 administration on appetite reduction and weight loss remain scarce. Näslund *et al.*^[104] compared the effects of 4 doses of acute GLP-1 infused 30 min prior to meals [prandial subcutaneous infusion (PSI)] to an equivalent dose of continuous SC GLP-1 infusion (CSI) on food intake and weight loss in non diabetic obese patients. Though both acute and continuous GLP-1 infusion produced significant reductions in food intake when compared to placebo ($P = 0.02$ PSI and CSI), a statistically significant weight loss compared to placebo was only observed following PSI. With respect to the clinic, findings suggest that lowered dose; more frequent GLP-1 administration may prove more efficacious in inducing weight loss in obese patients. Nevertheless, in view of the negative impact of SC drug administration on patient adherence and the potential biases associated with the

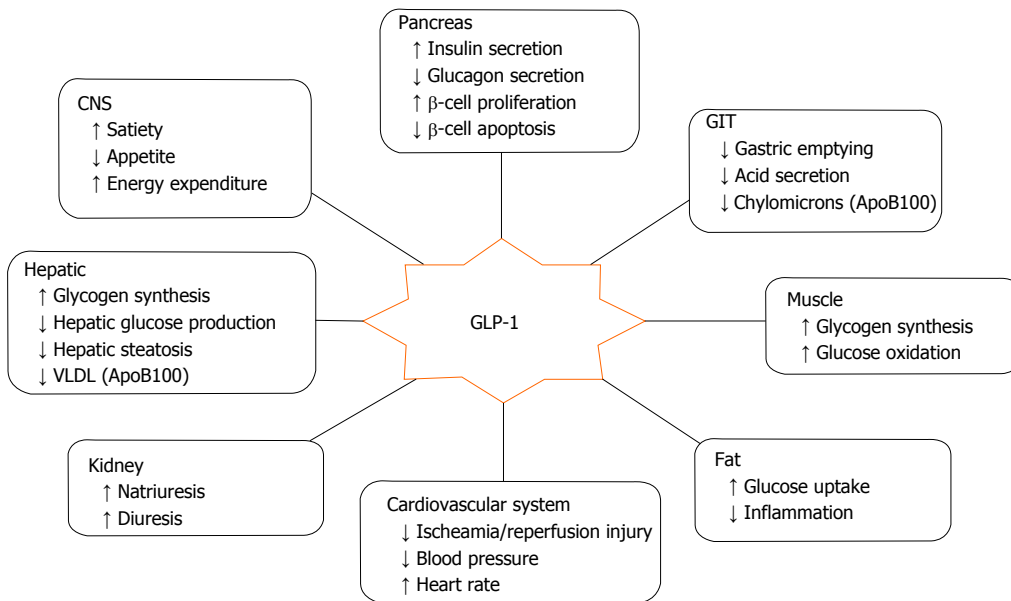


Figure 6 Central and peripheral effects of glucagon-like peptide 1. *Ex vivo* and *in vivo* studies in rodents, and observational and interventional studies in man have allowed the characterization of numerous central and peripheral effects of GLP-1. Peripheral effects of GLP-1 may be classed broadly as pancreatic or extra-pancreatic. Pancreatic effects of GLP-1 act to promote insulin secretion (incretin effect). Extra-pancreatic effects of GLP-1 include: (1) regulation of energy metabolism and nutrient storage (liver, muscle and fat); (2) efficient nutrient handling (stomach and GIT); and (3) others: Cardiovascular repair, blood pressure control, diuresis^[86]. VLDL: Very low-density lipoproteins; GLP-1: Glucagon-like peptide 1; GIT: Gastrointestinal tract; CNS: Central nervous system.

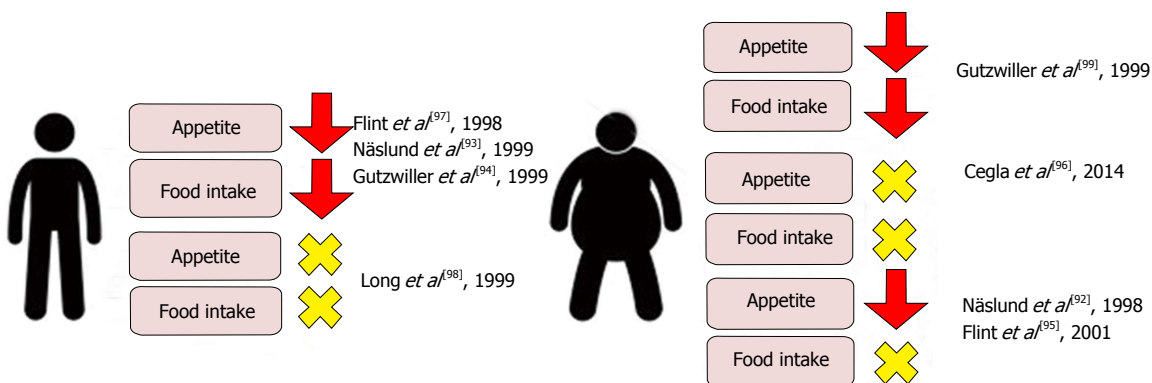


Figure 7 Effects on Visual Analogue Scale assessed appetite scores and ad libitum food intake in lean and obese subjects following physiological and supraphysiological infusions of glucagon-like peptide 1. Though individual studies report conflicting data, a meta-analysis of clinical studies evaluating the acute effects of GLP-1 infusion on food intake reports a mean 11.7% decrease when compared with saline control^[100]. GLP-1: Glucagon-like peptide 1.

significantly greater peak plasma GLP-1 concentrations achieved following PSI compared to CSI (269.4 pmol vs 88.7 pmol) once daily bolus administration at present, seems to be the most clinically efficacious means of therapeutic GLP-1 analogue delivery.

Interpretations: Potential effectors of GLP-1s negative energy balance effects

Clinical and pre-clinical evidence suggests that targeting peripherally and centrally located GLP-1Rs may exert the anorectic effects of physiological GLP-1 signalling.

Peripheral effectors: Histological studies in man have shown GLP-1Rs to be expressed in cells of the gastric mucosa and in pancreatic islet cells^[105,106]. Pre-clinically, stimulation of gastric and pancreatic GLP-1Rs are associated with reductions in food intake that

occurs alongside activation of hedonic and homeostatic brain regions^[47,63,86]. Findings suggest physiological GLP-1 signalling may induce its anorectic effects in man by indirectly activating central controllers of appetite through gastric and pancreatic receptors.

Gastric mechanoreceptors are activated by gastric distension following acute nutrient intake, and gastric mechanoreceptor signalling plays an important role as a meal-to-meal satiety signal, activating the NTS which in turn modulates neural activity in both the ARC the VTA^[107] (the homeostatic and hedonic control of energy balance). By relaying to the NTS, mechanoreceptor induced anorectic effects may therefore be exerted through modulation of both homeostatic and hedonic appetite control. The amount of gastric distension in response to a given meal is negatively associated with the rate of gastric emptying; delayed gastric emptying

positively associated with increased satiety and fullness in both healthy and obese patients^[108-112]. GLP-1 has been found to delay gastric emptying in healthy lean, obese and T2DM subjects, and histological studies in man have shown that GLP-1Rs are expressed in gastric mucosa^[92,105,113-116]. Post-prandial GLP-1 secretion may therefore exert its anorectic effect through activating GLP-1Rs in gastric mucosa, which in turn increase mechanoreceptor firing and signalling to the NTS. Though the neurotransmitters involved in relaying signals from the NTS to homeostatic and hedonic appetite controls remain to be defined, physiological gastric distension in rodents has been shown to up-regulate *GLP-1* gene expression in the NTS associated with central proglucagon processing^[117], implicating a role for centrally synthesised GLP-1.

In the fasted state, the stomach is empty and so gastric motility is reduced to basal levels. That reductions in appetite after GLP-1 administration have been observed in fasting human subjects^[99], suggests that mechanisms other than delaying gastric motility contribute to the physiological anorectic effect of GLP-1. The glucoregulatory hormone insulin, traditionally viewed as an anorectic signal involved in the regulation of long-term energy balance^[47,63], displays both basal and acute meal-related secretion^[118]. With acute insulin administration associated with reduced *ad libitum* food intake in healthy lean individuals^[119], findings implicate a role for insulin as an anorexigen involved in the regulation of short term energy balance. Insulin receptors are widely expressed in the ARC and VTA^[120-122], thus modulation of both homeostatic and hedonic appetite control may be the means by which insulin exerts its anorectic effects on short-term energy balance.

The most extensively studied of GLP-1's physiological roles is as a positive modulator of insulin secretion from pancreatic β -cells^[123] (evidence: Effects of GLP-1 administration on food intake and energy expenditure in man). Whilst GLP-1 has been shown to increase energy expenditure in healthy lean individuals in an insulin dependent manner^[103], no clinical evidence to date exists exploring the role of insulin as a mediator of GLP-1 anorexigenic signalling. Studies assessing the effects of GLP-1 interactions with the orexigen ghrelin however, suggest that this may indeed be the case. Ghrelin receptors have been localised preclinically in *Agrp/NpY* neurons of the ARC and dopaminergic neurons of the VTA^[124,125], with activation of neurons in either brain region producing orexigenic effects. GLP-1 infusion in healthy lean humans is associated with significant suppression of postprandial rises in ghrelin^[126]; the decline in orexigenic signalling a potential indirect mediator of GLP-1's anorexigenic effect. Interestingly, the reductions in ghrelin concentration observed with GLP-1 infusion inversely correlate with coinciding rises in insulin concentration and elsewhere, insulin infusion has been shown to display a reciprocal relationship with ghrelin secretion in man^[127]. Together, findings suggest that

GLP-1's anorectic effects may be mediated secondary to its incretin effect that in turn suppresses ghrelin release, thus orexigenic signalling.

Central controllers: Histological and *in vivo* studies in rodents have shown that GLP-1Rs are expressed in anorexigenic POMC/CART neurons of the ARC and in dopaminergic neurons of the VTA^[59,61,18,128] where they stimulate and inhibit neural firing respectively. Preclinical studies have shown that the stimulation of the POMC/ARC neurons of the hypothalamus and inhibition of the dopaminergic neurons of the VTA reduce food intake. Findings suggest that GLP-1 may exert its negative energy balance effects in man through direct activation of central GLP-1 receptors in the ARC and VTA; activating the anorexigenic homeostatic and inhibiting the hedonic hyperphagic drives to food intake. With the development of neuroimaging techniques, *in vivo* clinical studies substantiate the effects of GLP-1 on brain regions involved in the homeostatic and hedonic controls of energy balance. Whether these effects are mediated by direct central GLP-1R activation or indirectly *via* peripherally located GLP-1Rs however, remain to be defined.

Using fluorodeoxyglucose positron emission tomography Alvarez *et al.*^[129] demonstrate that GLP-1 infusion in lean individuals reduces glucose metabolism in the hypothalamus and brainstem. With patients fasted during the study and with no changes in peripheral hormone profiles observed, the effects of gastric mechanoreceptor activation or other hormonal influences respectively on observed effects are negated. Elsewhere, correlations between PET assessed increases in hypothalamic blood flow and physiological post-prandial rises in serum GLP-1 have been observed^[130]. Both findings may represent altered neural activity in brain regions associated with homeostatic energy balance secondary to direct or indirect GLP-1/GLP-1R signalling. The effects of this alteration in central neural activity on food intake and appetite however, have not been explored. Using functional magnetic resonance imaging (fMRI), De Silva *et al.*^[131] demonstrate that GLP-1 infusion in lean individuals attenuates neuronal activity in 6 brain regions involved in rewards processing and hedonic feeding accompanied with reductions in food intake. Though neither parameter reached statistical significance vs placebo, results support the idea that central GLP-1 signalling may at least in part exert its negative energy balance effects through modulations in hedonic appetite control centres, potentially by reducing the hedonic value associated with food and food-driven motivation.

Clinical evidence exists to suggest that the SNS modulates energy expenditure through increased thermogenesis assessed *in vivo* as muscle sympathetic nerve activity (MSNA)^[132,133]; increased MSNA positively associated with increased short and longer term energy expenditure in otherwise healthy human subjects^[134,135]. Peripheral GLP-1 infusion has been shown to significantly

Table 2 Obesity and endocrine phenotypes in probands with *PCSK1* gene deletion monogenic obesity

| Ref. | Jackson <i>et al</i> ^[144] , 1997 | Jackson <i>et al</i> ^[143] , 2003 | Farooqi <i>et al</i> ^[148] , 2007 | Frank <i>et al</i> ^[145] , 2013 | Parker <i>et al</i> ^[147] , 2013 | Bandsma <i>et al</i> ^[146] , 2013 |
|-------------------------------------|---|---|---|---|--|---|
| Obesity phenotype | | | | | | |
| Hyperphagic, early-onset | Yes | Yes | Yes | Yes | Yes | Yes |
| Endocrine phenotype | | | | | | |
| Abnormal glucose metabolism | Yes | Yes | | Yes | Yes | Yes |
| Hypogonadotrophic hypogonadism | Yes | | | Yes | Yes | |
| Hypocortisolaemia | Yes | Yes | | Yes | Yes | |
| Hypothyroidism | | | Yes | Yes | Yes | |
| Central diabetes insipidus | | | | | Yes | |
| Others | | | | | | |
| Early onset malabsorptive diarrhoea | Yes | Yes | Yes | Yes | Yes | Yes |

Proband details: Jackson *et al*^[144] (1997) - a 40-year-old Caucasian woman; Jackson *et al*^[143] (2003) - female Caucasian infant, non consanguineous; Farooqi *et al*^[148] (2007) - 6 North African boy, consanguineous; Frank *et al*^[145] (2013) - male infant; Parker *et al*^[147] (2013) - 13 children aged 3 to 17; Bandsma *et al*^[146] (2013) - 2 children age 2 and 7 Arab, consanguineous, 2 children aged 1 and 10, African, non-consanguineous.

increase MSNA in healthy human controls^[136] and suggest that GLP-1 signalling may produce its negative energy balance effects not only through anorexigenic signalling, but also by increasing energy output.

A ROLE FOR GLP-1 IN THE PATHOPHYSIOLOGY OF CLINICAL OBESITY

Genetics

Genetic analyses in man suggest clinical obesity is associated with a lack of functional GLP-1 signalling that may contribute to the development of the obesity phenotype.

Monogenic human obesity: Monogenic human obesity is a rare form of clinical obesity that shows Mendelian patterns of inheritance; the obesity phenotype attributed to the loss or gain of function in a single gene^[137]. Two broad classes of Mendelian human obesity exist; syndromic obesity encompasses about 30 Mendelian disorders wherein obesity co-presents alongside characteristic physical and developmental anomalies. Though causative genes have been identified, the mechanisms through which the genetic mutations induce obesity are not completely understood in all cases^[138]. Non-syndromic obesity is characterized by a severe, early onset hyperphagic obesity attributed to loss of function mutations in 1 of 11 genes^[139-141]. Interestingly, 8 of these genes have physiological roles in the central control of energy balance^[142]. One such gene is PCSK1 encoding the enzyme PC1/3 involved in the proteolytic processing of proglucagon, to yield, amongst other peptides, GLP-1 (GLP-1). Six studies to date document the relationship between autosomal recessive, compound heterozygous or homozygous^[143-148] mutations in PCSK1 in 21 probands associated with reduced or absent function of PC1/3. Table 2 details the phenotypes of probands, all of whom presented with an early onset hyperphagic obesity and malabsorptive diarrhoea with varying, though extensively

overlapping endocrine phenotypes.

Though the cause of the obesity and endocrine phenotypes associated with PCSK1 mutation are unknown, they may well be attributed to the loss of PC1/3 pro-hormone processing function. Signs of impaired intestinal^[146] pro-glucagon processing have been described in probands with PC1/3 deficiency and may contribute to the development of the obesity phenotype secondary to reduced GLP-1 synthesis. Disappointingly, only 2 of 6 studies detailing the phenotypes PCSK1 mutant probands assess post-prandial GLP-1 secretory responses and report conflicting results; whilst an oral glucose load (OGTT) yields significantly reduced GLP-1 response in three child probands compared to age matched controls, post-prandial responses in a 40-year-old proband match those of healthy age-matched controls. One interpretation of such findings may be that whilst other PCs may compensate for lacking PC1/3 to allow for GLP-1 synthesis in response to mixed nutrient secretagogues, PC1/3 is necessary and essential for GLP-1 synthesis in response to its most potent secretagogue, glucose. An alternative interpretation comes from observations that GLP-1 secretion following OGTT in the 3 child probands studied by Bandsma *et al*^[146] seem to show an age dependent impairment improving with increasing age. Following follows reports by Parker *et al*^[147] who observed that the pattern of endocrinopathy in probands with PCSK1 mutant monogenic obesity change with age, perhaps GLP-1 secretion too may show an age-dependent alteration, potentially compensated for over time. One way to test this hypothesis would be to histologically examine the enteroendocrine expression of GLP-1 in adult PCSK1-mutant probands; enteroendocrine expression of GLP-1 is significantly reduced compared to control in children with PCSK1 monogenic obesity^[146], if indeed the normal post-prandial GLP-1 responses seen in adulthood are a reflection of the activation of redundant PC activity in intestinal cells up regulation of enteroendocrine GLP-1 expression would be observed. Though the cause of the hyperphagic obesity in PCSK1 mutant human monogenic obesity remains ill defined,

monogenic obesity implicates a role for deregulated GLP-1 signalling in the development of the obesity phenotype.

Polygenic obesity and Genome Wide Association

Studies: Monogenic obesity is a rare form of clinical obesity, accounting for less than 1% of total cases of obesity worldwide. The obesity epidemic of the past 10-50 years has been largely attributed to environmental and societal changes facilitating a positive energy balance; "the obesogenic environment"^[149,150]. However evidence from adoption, twin and family studies suggest the genetic contribution to BMI ranges between 60% and 84%^[151]. As such, the current obesity epidemic may be defined as the interaction between a genetic predisposition and the "obesogenic environment"^[149,150,152-154]. Genome wide association studies have identified 119 independent gene loci implicated as risk factors toward "common" obesity^[155,156], as such today's obesity epidemic may be referred to as a polygenic obesity. One such susceptibility gene is PCSK1 encoding the enzyme PC1/3 involved in the proteolytic processing of proglucagon, to yield, amongst other peptides, GLP-1.

Single-nucleotide polymorphisms (SNPs) at three independent *PCSK1* loci have been consistently linked to an increased risk of obesity^[157-161]. Though it is unclear how these minor alleles predispose to obesity, *in vitro* studies suggest that the encoded PC1/3 variants may not be as enzymatically active or physiologically available as the common form, potentially resulting in a partial PC1/3 deficiency. Decreased GLP-1 synthesis secondary to reduced proglucagon processing by PC1/3 in enteroendocrine L cells may therefore be the mechanism by which identified PCSK1 SNPs confer an increased risk toward the obesity phenotype.

Intestinal neuroendocrine gene expression:

Neuroendocrine signals from the gut play an important role in the physiological control of energy balance. Findings from a recent study by Ritze *et al.*^[162] studying the gene expression of several proteins in the intestinal neuroendocrine network go some way to suggest intestinal GLP-1 expression and/or function may be altered in obesity. Though GLP-1 was not directly tested in the study, the anorectic neuropeptide PYY shown to co-localise and be co-secreted with GLP-1 in enteroendocrine cells^[163] was tested. Taking PYY levels as proxy measures of GLP-1, Ritze *et al.*^[162] report significant correlations between GLP-1 with the GLP-1R in non-obese subjects (suggesting physiological ligand-receptor signalling), a correlation lost in obese subjects and replaced by correlations with the orexigen ghrelin ($P < 0.01$). Ritze *et al.*^[162] also observed correlations between the long-term satiety signal leptin and GLP-1R in obese subjects not seen in their lean counterparts.

A recent *in vitro* study on human L cells has shown that ghrelin is a positive modulator of GLP-1 release^[164]. Ghrelin levels have also been reported to be reduced in humans with obesity^[165,166]. The correlations between

intestinal PYY (GLP-1) and ghrelin reported in obese subjects suggests that ghrelin decreases in obesity coincide with decreased GLP-1 levels, the latter potentially antagonising the anorexigenic effects of the former and may explain the difficulty to attain and maintain weight loss observed by many obese patients. Intestinal GLP-1 signalling has been suggested to promote small-intestinal motility in humans^[167] and preclinically, central administration of leptin has been shown to increase the satiating effect of GLP-1, possibly through enhancing GLP-1R signalling. Correlations between the leptin and GLP-1R in obese subjects may therefore reflect a leptin-mediated enhancement of intestinal GLP-1/GLP-1R increasing intestinal motility to promote increased gastric emptying and reduced gastric mechanoreceptor activation in response to a given meal; the resultant decrease in anorexigenic signalling potentially explaining the persistent hyperphagia seen in obesity despite an overall positive energy balance.

Clinical studies in polygenic obesity

Interventional and observational clinical evidence suggests that malfunctioning of GLP-1 contributes to the development and/or maintenance of the obesity phenotype, rationalizing the use of GLP-1 analogues as novel therapeutic agents in the medical management of obesity.

Post meal and oral glucose GLP-1 secretory responses:

A number of clinical studies have assessed the effect of physiological GLP-1 secretion responses in obese and lean subjects following an oral 75 g glucose load (OGTT) or post-prandial following a balanced meal. Where an OGTT consistently demonstrates a reduced GLP-1 secretion in obese subjects compared to their lean control post-prandial GLP-1 responses are conflicting; some observing significant reductions and others no change^[168-178] in obese subjects when compared to their lean counterparts (Figure 8). That oral glucose, the most powerful GLP-1 secretagogue consistently demonstrates reduced GLP-1 responses in obese subjects may suggest that the impaired GLP-1 response observed are secondary to a reduced L-cell glucose sensing capacity in obesity. Support for such a postulate comes from findings by Ranganath *et al.*^[170] who demonstrate that whilst GLP-1 secretion to an oral fat load remains intact, GLP-1 secretion in response to an oral carbohydrate load is decreased in obesity. However, reports by Adam *et al.*^[168] that demonstrate reductions in GLP-1 response in obesity to a balance meal with retained responses to an oral carbohydrate load challenge such an interpretation. Interestingly however, in their observational study, Adam *et al.*^[168] also demonstrate that whilst carbohydrates stimulate post-prandial GLP-1 release similarly in obese and non-obese subjects, these rises are positively correlated with increased satiety only in lean subjects and put forward an alternate hypothesis that rather than impaired GLP-1 secretion, downstream receptor resistance may be the root of GLP-1 dyshomeostasis in

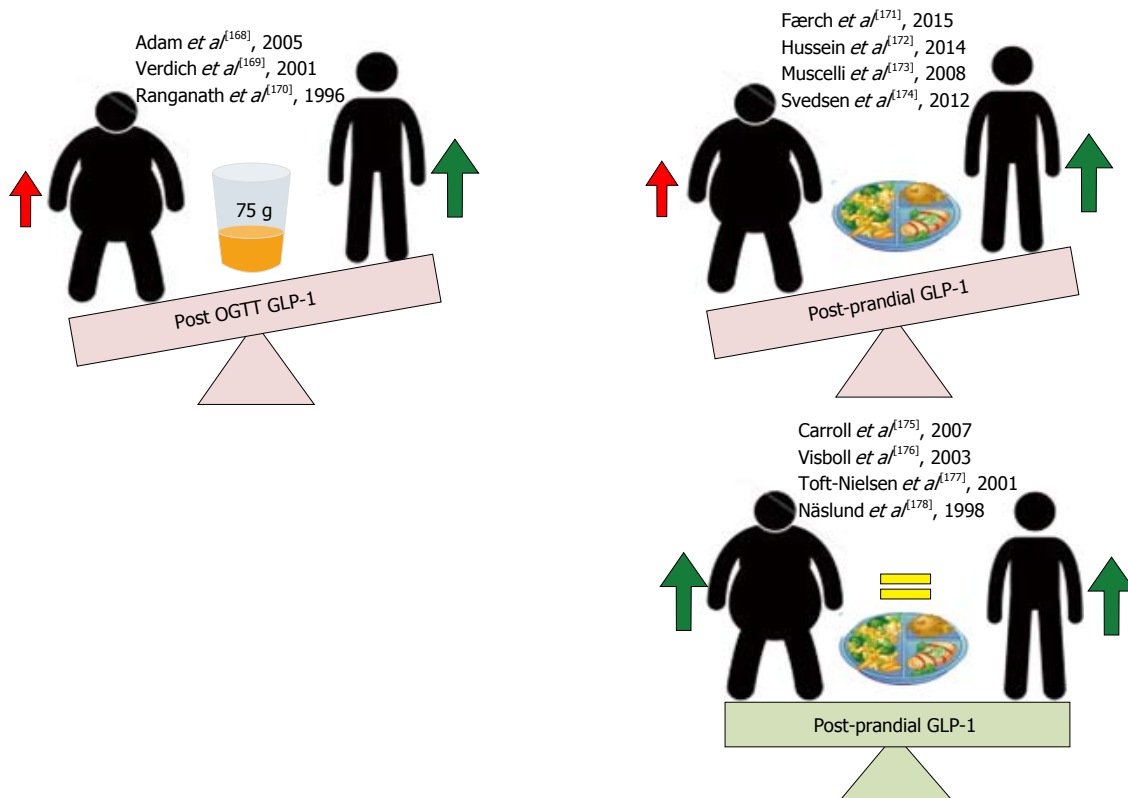


Figure 8 Effects of obesity on glucagon-like peptide 1 responses post oral glucose load and post-prandial. Obese subjects consistently demonstrate reduced glucagon-like peptide 1 (GLP-1) secretory responses following a 75-g oral glucose load compared to lean controls. Post-prandial GLP-1 secretory responses in obese subjects are conflicting, with some studies observing significant reductions and others observing no change^[168-178] when compared to lean controls.

obesity. That deranged GLP-1 signalling is observed only in obese subjects suggests that obesity induces changes in functional GLP-1 signalling that through resultant reductions of signalling at central and peripherally located receptors (GLP-1) may facilitate the maintenance of the obesity phenotype. Pharmacologically targeting GLP-1 to restore physiological signalling may therefore be an efficacious method to prevent the propagation of, and potentially reverse weight gain in obesity.

Evidence from clinical studies suggests that weight gain induces alterations in functional GLP-1 signalling that facilitates and propagates the obesity phenotype. Though the mechanisms of reduced functional post-prandial GLP-1 signalling in obesity remain to be defined, clinical evidence implicates a role for interactions between GLP-1 and the long-term satiety signals insulin and leptin, and short-term orexigen ghrelin. The most extensively studied of post-prandial GLP-1's physiological roles is as a positive modulator of pancreatic β -cell insulin secretion^[123]. Hyperinsulinaemia is positively associated increased BMI in individuals with normal glucose tolerance and increased BMI and increasing glucose intolerance have been shown to independently and additively impair GLP-1 secretion^[171-173,175,179]. The chronic hyperinsulinaemia positively associated with increasing levels of obesity therefore, may acting as a negative feedback signal to inhibit physiological post-prandial GLP-1 release observed in obese subjects when compared with healthy lean control^[171-173]. The long term

adiposity signal leptin acts as a satiety signal governing long term energy balance and clinically, increased BMI has been shown to be positively correlated with fasted leptin, however obese subjects are thought to be resistant to leptin's effects^[180,181]. *In vitro* studies of human intestinal L-cells have shown that leptin acts a GLP-1 secretagogue and go some way to suggest that the leptin resistance associated with obesity may account for the decreased post-prandial GLP-1 secretion observed in obese humans^[168-170,182]. Ghrelin is the only orexigenic gut derived hormone^[183]; released pre-prandial, ghrelin promotes meal initiation and increases food intake, and complex reciprocal interactions exist between GLP-1 and ghrelin that have implications for obesity pathophysiology. Preclinically, physiological ghrelin signalling has been shown to enhance post-prandial GLP-1 release^[164], clinical obesity has however been associated with reductions in fasting ghrelin levels that may contribute to the reduced post-prandial GLP-1 release observed^[168-170]. Conversely, clinical data exists to suggest that suppression of late post-prandial rises in ghrelin is one mechanism by which GLP-1 exerts its anorexigenic effect^[126]; reduced post-prandial GLP-1 secretion in obesity potentially explaining the attenuated decreases of post-prandial serum ghrelin observed in this cohort^[168-170,184,185] (Figure 9).

Together, evidence exists to suggest that the hyperinsulinaemia, leptin resistance and impaired ghrelin secretion occurring secondary to obesity cause functional deficits in GLP-1 signalling; the resultant reductions in

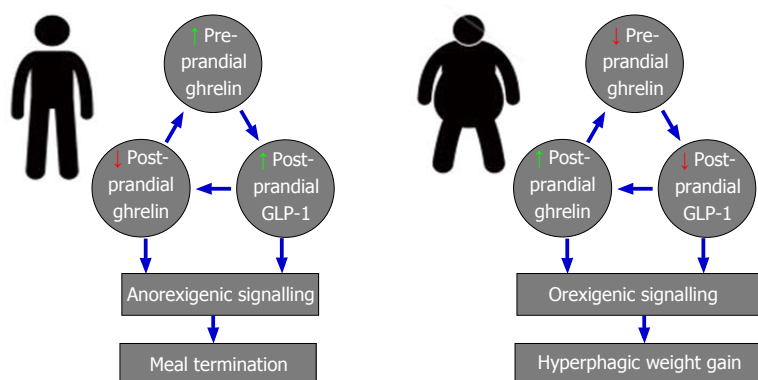


Figure 9 Physiological and pathophysiological interactions between orexigenic ghrelin and anorexigenic glucagon-like peptide 1 signalling in lean and obese individuals. GLP-1: Glucagon-like peptide 1.

GLP-1 mediated anorexigenic signalling facilitating post-meal hyperphagia, weight gain and thus perhaps the obesity phenotype. Pharmacologically targeting GLP-1 to restore homeostatic signalling may therefore be an efficacious method to prevent the propagation of, and potentially reverse the weight gain in obesity.

GLP-1 secretion post RYGB: Weight losses following bariatric surgery, pharmacotherapy or diet and lifestyle modification are all associated with decreases in circulating leptin and improved insulin sensitivity. The resultant reductions in anorexigenic signalling potentially facilitating weight gain and may explain the difficulty obese subjects have in attaining and maintaining weight loss. Bariatric surgery remains the most effective treatment modality for morbid obesity, with a meta-analysis reporting the Roux-en-y gastric bypass (RYGB) to produce a greater and more sustained weight loss than currently available pharmacotherapeutics, diet and lifestyle interventions or other bariatric options. Prospective studies assessing the effects of RYGB on post-prandial GLP-1 responses in non-diabetic obese patients consistently report statistically significant increases in post-prandial GLP-1 when compared to the pre-operative state, following equivalent weight losses with GB^[186-193] and when compared with healthy lean control^[188] (Figure 10). This post-operative supraphysiological GLP-1 secretory response therefore may explain the greater short- and long-term weight loss efficacy achieved with this treatment modality.

Evidence from clinical studies implicate the supra-physiological^[188] post-prandial GLP-1 responses achieved following RYGB in the superior weight loss efficacy of this treatment modality. Though the mechanisms by which RYGB may induce increases in GLP-1 secretion remain poorly understood, clinical studies implicate a role for altered gut mechanics and L cell resensitisation.

That increases in post-prandial GLP-1 responses following RYGB are observed as early as 3 d post-operatively^[190] suggest physical changes associated with RYGB, rather than gene-mediated up-regulations GLP-1 synthesis play a role in the increased GLP-1 secretory

responses observed. Where both RYGB and GB induce weight loss through volume restriction, the former also redirects nutrient flow from the upper stomach directly into the distal jejunum. The exaggerated GLP-1 response following RYGB likely secondary to the increased glucose load delivered to the distal small intestine where L-cells are more densely populated. Such a concept is supported by the observed reductions in foregut and increases in hindgut hormones following RYGB and the hyperplasia of GLP-1 containing ileal cells in biopsy samples of obese humans after bypass^[194-196].

RYGB induces a weight loss greater time-for-time and reaches a plateau more successfully maintained when compared with weight loss following GB^[186-189]. Post-prandial GLP-1 responses following RYGB are also significantly greater than those following GB (that show no change from pre-operative levels^[186,190,191]) however this response does not plateau but instead shows a tendency to increase with time past surgery. A relationship between the exponentially increasing post-prandial GLP-1 response and greater weight loss maintenance achieved post-RYGB may be explained by findings observed Kellum *et al.*^[189] who report that at 1 year post RYGB, alongside significantly greater achieved and maintained weight loss when compared to GB, GLP-1 responses were significantly increased in response to a carbohydrate meal in subjects post RYGB; a response positively associated with amount of weight lost. With derangements in L-cell carbohydrate sensing implicated in the pathophysiology of human obesity (see 5.1.1B, 5.2.1B), and with no alterations in response to a protein-fat meal observed following weight loss with RYGB and no altered response to either meal following weight loss with GB, findings suggest that weight loss following RYGB may be associated with a restoration of L cell sensitivity to the most potent GLP-1 secretagogue; a resensitisation that may occur proportionately to the amount of weight lost, the feed forward effect of weight loss on increased GLP-1 secretion resulting in supraphysiological GLP-1 signalling with the potential to antagonize the increased orexigenic drives of decreased leptin and insulin signalling associated with weight loss.

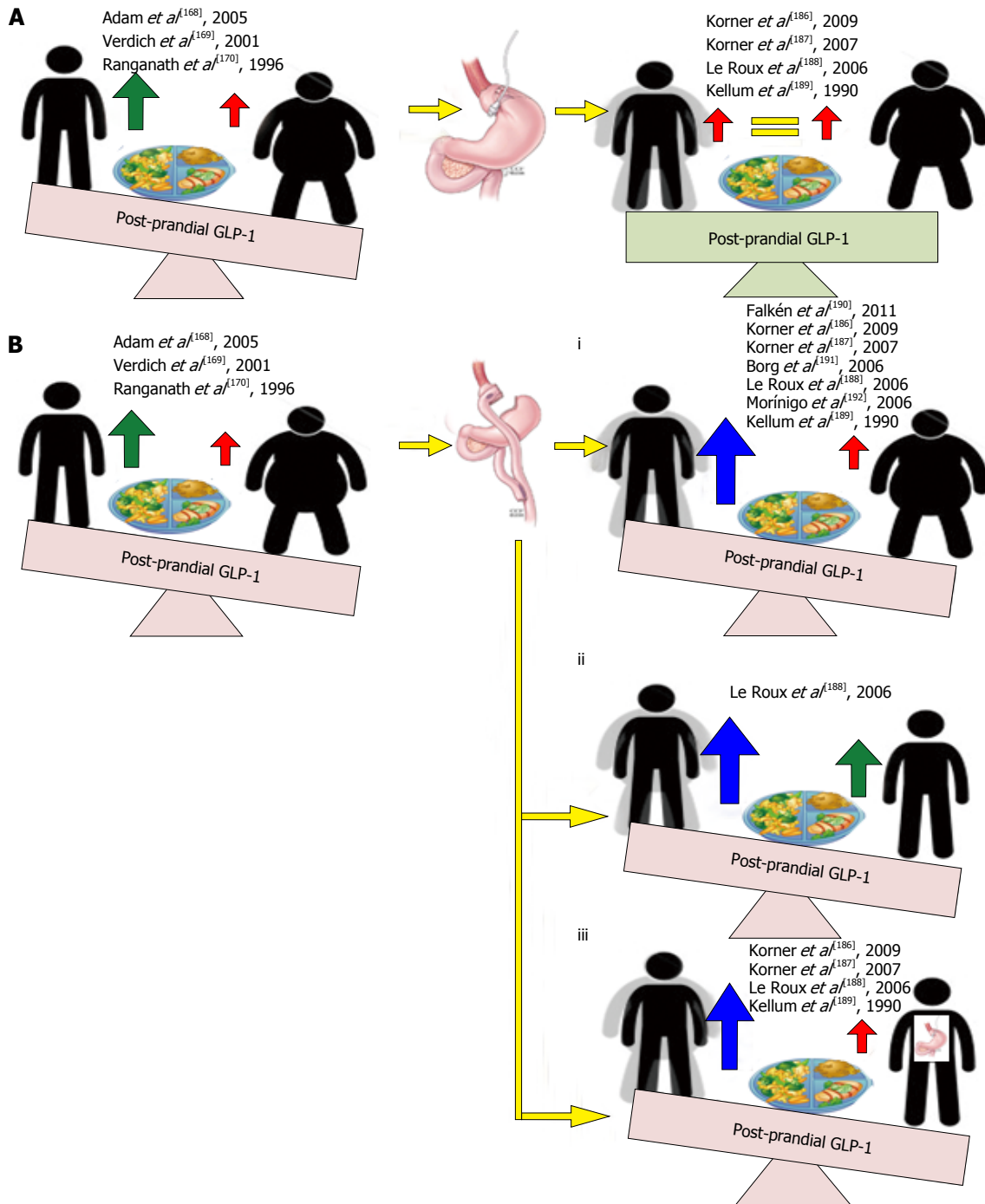


Figure 10 Effects of weight loss induced by gastric banding and Roux-en-Y gastric bypass on post-prandial glucagon-like peptide 1 secretion. Weight loss following gastric banding induces no changes in post-prandial glucagon-like peptide 1 (GLP-1) levels from pre-operative levels (A). All 7 studies assessing the effects of post-prandial GLP-1 secretion following weight loss with RYGB show significantly increased responses compared with pre-surgery responses and healthy obese controls (Bi), healthy lean controls (Bii) and following weight losses following gastric banding (Biii).

Such a concept may explain the long-term weight loss efficacy associated with RYGB.

Together, evidence exists to suggest that the supraphysiological^[188] upregulation in GLP-1 signalling seen following RYGB contributes to the superior short and long term weight loss efficacy observed with this treatment modality. Not only do findings go some way to suggest a role for impaired GLP-1 signalling in the pathophysiology of human obesity, findings support the potential for pharmacological mimicry of this supraphysiological GLP-1

secretion as a minimally invasive, thus risk reducing and cost-effective alternative of achieving and maintaining similarly significant weight loss in obese subjects in the clinic.

Functional neuroimaging and self-assessments of appetite: fMRI studies have provided evidence *in vivo* to suggest that central nervous system responses in brain regions involved in rewards processing are altered in obese individuals; reduced brain activity in response to the

consumption of, and increased activity in response to the anticipation of palatable food consistently observed when compared with healthy lean controls^[197-199]. Interestingly, GLP-1 agonism reverses these functional brain changes to match those of lean control with associated reductions in *ad libitum* food intake^[199], an effect prevented by pre-treatment with a GLP-1 antagonist^[200] (Figure 11). Together, findings suggests that obesity induced decreases in functional GLP-1 signalling contribute to altered rewards processing in obesity to facilitate hyperphagic weight gain despite an overall positive energy balance.

Further support for a role for GLP-1 and altered rewards processing in obesity pathophysiology comes from self-assessments of appetite. Subjectively assessed emotional eating scores have been defined as hedonic markers of appetite that display strong positive associations with the degree of human obesity, and, in obese subjects, relate to the extent to which GLP-1 receptor activation in brain regions involved in rewards processing are reduced^[201-203]. Together, findings suggests that obesity induced decreases in functional GLP-1 signalling creates a feed-forward loop of hyperphagic weight gain despite an overall positive energy balance, an effect perhaps secondary to a GLP-1 deficit mediated skew toward hedonic and away from homeostatic controls of food intake. Together, findings from fMRI and subjective appetite assessment scores implicate obesity-associated reductions in functional GLP-1/GLP-1R signalling in the pathophysiology of hyperphagic weight gain in obesity. As such, findings support the role of the GLP-1R as a novel therapeutic target in the medical management of obesity, providing rationale for the use of liraglutide 3 mg in the pharmacotherapy of obesity in the clinic.

A ROLE FOR GLP-1 IN THE PHARMACOTHERAPY OF CLINICAL OBESITY

The balance between drug efficacy and cost determines the selection of a pharmacological agent for use in the medical management of any disease; greater understanding of underlying disease pathophysiology facilitating the development of targeted therapeutics with the potential for greater efficacy. Several lines of clinical evidence implicate a role for altered GLP-1 function in the pathophysiology of human obesity and a number of recent clinical trials have validated the clinical efficacy of long-term once daily SC 3 mg liraglutide (Saxenda) as an adjunct to calorie-restriction and exercise counselling in obese and overweight individuals with at least one weight related comorbidity. Significant improvements in clinical outcome measures such as body weight, anthropometric and cardiometabolic parameters, and indices of glucose tolerance have been observed and recently reviewed elsewhere^[204]. Though March 2015 saw the EMA grant marketing authorization for 3 mg liraglutide as a weight-management agent in all 28 EU states^[45], cost-benefit of funding treatment on the NHS undoubtedly contributes

to the uncertainty of launch plans in the United Kingdom at present^[46].

Weight loss efficacy of GLP-1 analogues

Evidence: One phase II (NCT00422058)^[43], and a number of phase III multi-national double-blinded randomized control trials conducted in non-diabetic obese adults (NCT00480909)^[42], overweight adults with at least one weight related co-morbidity (SCALE Obesity and Pre-diabetes, and SCALE Maintenance^[205,206]), non-diabetic obese adults with obstructive sleep apnoea (OSA) (SCALE OSA^[41]) and obese adults with T2DM (SCALE diabetes^[207]) have established the efficacy of once daily 3 mg SC liraglutide as an adjunct to an energy-deficient low-calorie diet and physical activity counselling for weight management in this cohort. Results from the first study; a 20-wk phase II trial in non-diabetic obese subjects showed that weight loss with liraglutide is dose-dependent up to 3.0 mg once daily^[42,206]. Significantly more liraglutide 3 mg/d recipients than placebo or orlistat recipients achieved a 5% or 10% reduction of body weight at 20 wk. In a 2-year phase III extension of the same study^[42], double-blind treatment (liraglutide 1.2-3 mg/d) was continued until week 52, after which all liraglutide (< 2.4 mg/d) and placebo recipients were switched to liraglutide 2.4 mg, then 3.0 mg (week 70-96) based on 20-wk and 1-year results respectively (Figure 12) that indicated this was the optimal dosage. At 2 years, mean bodyweight reductions in those randomized to liraglutide were significantly greater than pancreatic lipase inhibitor orlistat, the only alternative licenced weight loss agent in the United Kingdom. Results from the SCALE maintenance and SCALE obesity and prediabetes^[205,206] trials report similarly significant reductions in bodyweight in subjects randomized to 3 mg liraglutide when compared with placebo at 56 wk ($P < 0.0001$) alongside increased 5% and 10% responder rates. Findings are supported by results of the 32 wk SCALE Sleep Apnoea trial^[41] in obese non-diabetic subjects with moderate to severe OSA and in the 56-68 wk SCALE Diabetes^[207] trial in obese subjects with T2DM (Figure 13). With even modest losses of 5%-10% of total body weight associated with reduced risk of comorbidities in obese individuals^[8-10], findings provide rationale for the licensing and funding of 3 mg liraglutide as an adjunct to lifestyle alteration as the first line anti-obesity pharmaceutical agent for weight management in obese and comorbid overweight adults in the United Kingdom.

Interpretations - obesity pathophysiology:

Excessive consumption of palatable food can trigger neuroadaptive responses in brain reward circuits similar to that of alcohol and drugs of abuse^[208] and clinical studies provide evidence to suggest that human obesity is associated with altered rewards processing mediated in part by altered GLP-1 function that may render the hyperphagia of obesity the manifestation of a "food addiction". Whilst 3 mg liraglutide has been shown to induce weight loss in man by reductions appetite pre-

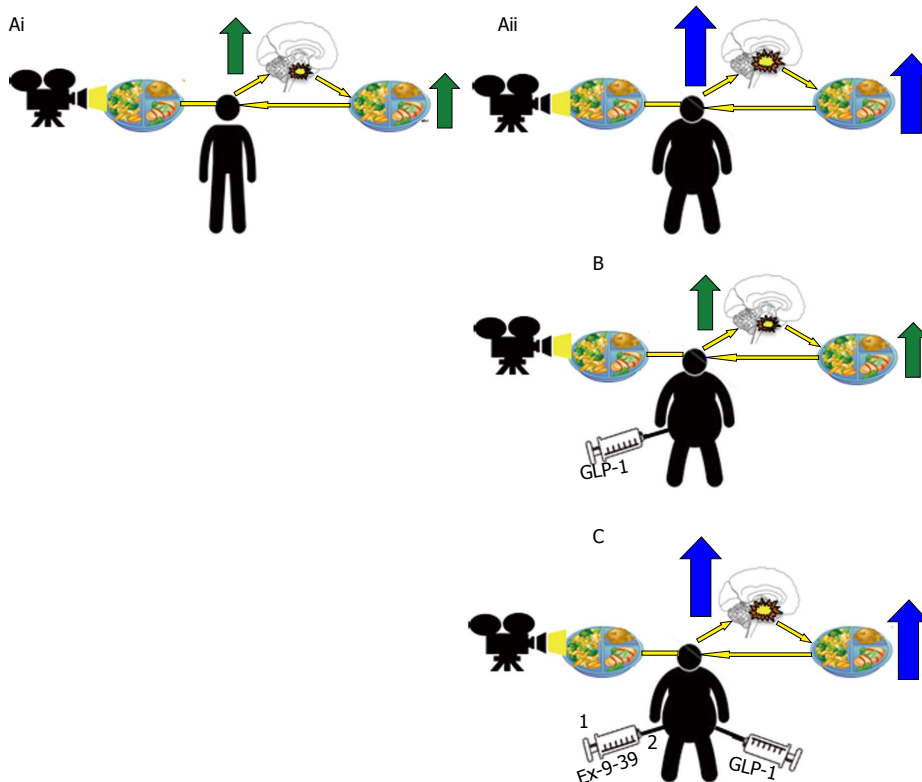


Figure 11 Altered central nervous system responses in brain regions involved in rewards in obese subjects is reversed upon glucagon-like peptide 1 receptor activation. Central nervous system activity in regions involved in rewards processing show increased responses in obese subjects when exposed to food related images (Aii) associated with increased ad libitum food consumption when compared to healthy lean control (Ai). A response reversed upon administration of a GLP-1 analogue with concomitant reductions in ad libitum food intake (B), this effect antagonized by pre-treatment with GLP-1 antagonist Extendin 9-39 (EX9-39) (C). GLP-1: Glucagon-like peptide 1.

clinically, liraglutide attenuates the reinforcing properties of alcohol *in vivo*^[209,210]. As such, perhaps GLP-1 agonism may attenuate produce its weight loss effects in part, by attenuating the negative reinforcement of hyperphagia in obesity. Interestingly, though all aforementioned trials^[41-43,205-207] advise participants to restrict food consumption throughout the treatment period, adherence rates are not reported. If indeed GLP-1 agonism induces its weight loss effects by modulating food related rewards that potentially reverses the negative reinforcement of hyperphagia in obesity, an increased adherence to caloric restriction would be expected. It would be interesting to see if this were the case.

Interpretations - cost-benefit of 3 mg liraglutide as an anti-obesity agent on the NHS: Follow-up period (FUP) assessments in the SCALE Maintenance, and SCALE Diabetes^[205-207] trials suggest that weight loss with 3 mg liraglutide is treatment dependent; weight gains in excess to those seen in placebo control and subjects re-randomized to treatment observed in liraglutide treated participants upon treatment cessation (Figure 12).

Though reductions in bodyweight have been shown to significantly improve health outcomes and thereby reduce healthcare costs long term^[211], in 2013, 24.9% of the United Kingdom adult population were classed obese and 90% of the £2.7 million T2DM adults in the United Kingdom were overweight. Following FDA and

EMA approval criteria, all these individuals are potential candidates for treatment with liraglutide 3 mg. Costing in excess of \$1000 per patient a month, and with prevalence of obesity and overweight predicted to rise (introduction), prolonged treatment seems unsustainable. A potential solution comes from longitudinal observations from Astrup *et al*^[43] who observed that subjects randomized to liraglutide 3 mg achieve maximal rates of weight loss in the initial 0-20 wk treatment period with a tendency toward weight gain beyond 36 wk^[42,43]. Findings suggest that whilst initially treatment with a GLP-1 analogue may compensate for functional deficits in obesity, treatment beyond 20 wk may be associated with the development of treatment resistance, most apparent 36 wk from initiation (Figure 14). Based on this, perhaps treatment with liraglutide 3 mg should be prescribed for 20 to a maximum of 36 wk alongside behavioural therapies promoting lifestyle changes and developing strategies to combat the addiction driven hyperphagia implicated in obesity pathophysiology (GLP-1 secretion post RYGB); combining behavioural therapies in the initial 20 wk of drug induction where weight loss is most pronounced may act as a positive reinforcer of sustained behavioural change facilitating continuation of these behaviours. This approach, integrating the psychosocial empowerment associated with patient self-management of chronic illness, alongside cost benefits associated with limited in-treatment period seems an

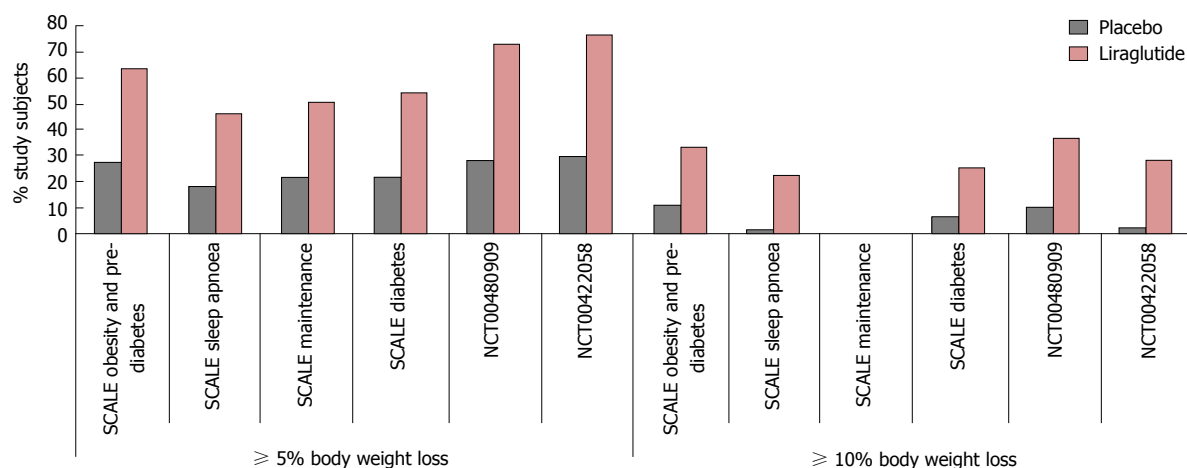


Figure 12 Significantly greater 5% and 10% weight loss achieved following 3 mg subcutaneous liraglutide compared to placebo and orlistat. Five percent and 10% responder rates in NCT00480909 reported at 1 year (see text).

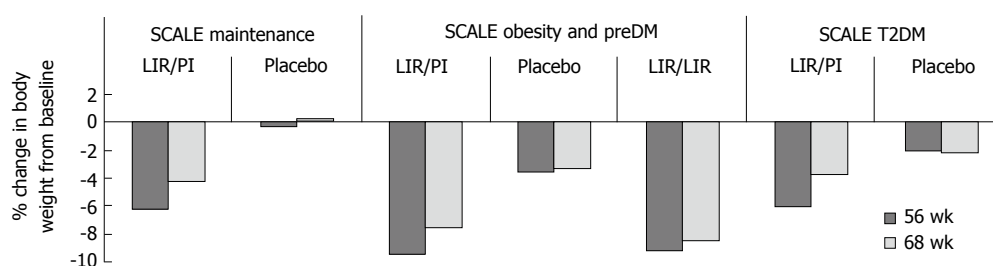


Figure 13 Body weight changes with liraglutide are treatment dependent. Following the 56-wk treatment period a 12-wk follow-up (FUP) was conducted in SCALE maintenance, SCALE obesity and pre-diabetes and SCALE diabetes trials. Twelve weeks FUP was an off-treatment period in SCALE Maintenance and SCALE diabetes. In SCALE Obesity and pre-diabetes FUP period involved a re-randomisation to either 3 mg liraglutide (LIR/LIR) or placebo (LIR/PI) and though weight gain occurred in all three groups weight gain was significantly higher following cessation of liraglutide. T2DM: Type 2 diabetes mellitus.

attractive one, especially if sustainable long-term weight losses with resultant reductions in the socioeconomic impacts of weight-related comorbidities can be achieved.

Glucose tolerance

Evidence: Clinical studies in obese subjects with pre-diabetes consistently demonstrate a greater reversion to normal glycaemic control following treatment with liraglutide 3 mg coinciding reduced T2DM incidence^[42,206,212].

Interpretations - obesity pathophysiology: Being overweight or obese is the main modifiable risk factor for T2DM and increasing BMI is positively associated with hyperinsulinaemia even in those with normal glycaemic control^[175,179,213] suggesting a common pathophysiology to both conditions. That increased BMI and impaired glucose tolerance have been shown to independently and additively impair GLP-1 secretory responses following an OGTT^[171-173] suggests that this common pathophysiology may lie in a functional deficit of GLP-1. Support for the existence of a common pathophysiology between obesity and T2DM comes from observations that treatment with the insulin sensitizer metformin (currently the first line pharmacotherapeutic agent in the management of T2DM) upregulates GLP-1 secretory response following

an OGTT, the restoration of physiological anorexigenic and incretin effects perhaps explaining the weight loss, and insulin sensitising properties of the drug seen in the clinic respectively^[214,215].

Interpretations: Cost-benefit of 3 mg liraglutide as an anti-obesity agent on the NHS: Being overweight or obese is the main modifiable risk factor for T2DM^[213] and T2DM is one of the major indirect financial burdens of obesity and overweight. Treating T2DM and its complications alone current costs the NHS £8.8 billion a year with indirect costs estimated at £13 billion^[216]. With the incidence of obesity projected to rise (introduction), so too can be expected the incidence of T2DM, the management of which therefore, may become unsustainable on the NHS. Though costly, treatment with liraglutide 3 mg is associated with reductions in the rate of development of T2DM in overweight and obese subjects^[42,206,212] and goes some way to suggest that treatment may reduce both direct burdens of obesity and overweight and the large indirect burden posed by new incidences of T2DM. However, weight loss in itself is associated with an improvement in glycaemic control. It may be argued therefore, that true cost-benefit of funding liraglutide 3 mg on the rationale of T2DM prevention in overweight and obese

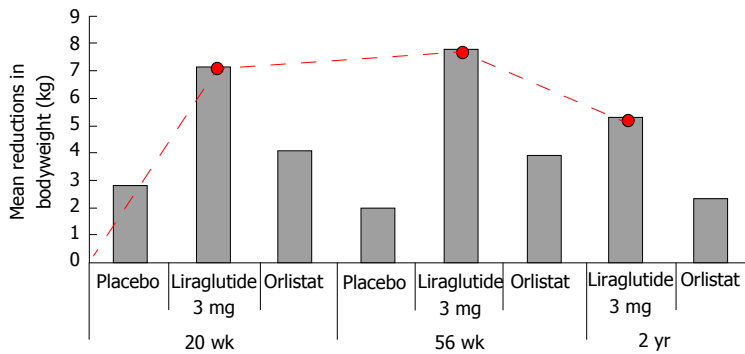


Figure 14 Liraglutide 3 mg shows greater, dose dependent, reductions in body weight compared to placebo and orlistat with maximal effect between 0-20 wk of treatment. Red line dotted trace shows patterns of weight loss from baseline in those subjects treated with 3 mg liraglutide. Greatest rate of weight loss was observed between 0-20 wk, reducing from 20-36 with a tendency toward weight gain from 36 wk and beyond.

subjects exists only if the improved glucose tolerance achieved following a given weight loss with liraglutide 3 mg exceeds those attained following other, arguably cheaper treatment modalities. Calculating correlation coefficients between percentage weight lost and percentage changes in glucose tolerance in non-diabetic obese subjects randomized to liraglutide 3 mg compared to those administered orlistat or placebo^[41-43,205,206] in aforementioned phase III trials may be one way in which this could be assessed. Figure 15 interprets the possible findings of such a test.

If indeed pharmacological GLP-1 agonism improves glucose tolerance independent of weight lost, the potential curb in prevalence, thus socio-economic burden of T2DM achieved with treatment provides a second rationale for the licensing and funding of liraglutide 3 mg as an adjunct to lifestyle alteration as the first line anti-obesity agent for weight management in obese and co-morbid overweight individuals in the United Kingdom.

Adverse drug events

Evidence - in-treatment tolerability: Whilst evidence exists to suggest GLP-1 agonism may be a targeted agent with long term cost-benefit for use in the medical management of obesity, tolerability and safety are important considerations in determining the choice of any pharmaceutical, especially in the management of chronic disease. The safety and efficacy of liraglutide 3 mg has been evaluated in 5 phase III double-blinded placebo controlled trials comprising 3384 overweight or obese subjects receiving liraglutide 3 mg and 1941 placebo controls for a treatment periods of 32, 52 and 56 wk^[42,42,205-207]. In a pooled analysis of the 5 aforementioned trials, liraglutide 3 mg in obese and overweight subjects was generally well tolerated, with most adverse drug events gastrointestinal in nature, transient and of mild to moderate intensity^[42,43,205-207]. However, 9.8% of liraglutide and 4.3% of placebo recipients discontinued treatment because of an adverse event^[217]. Figure 16 details adverse reactions occurring with a higher incidence to placebo with an incidence of $\geq 10\%$ in liraglutide 3 mg recipients, stratified by system. Of interest, 0.6% of subjects receiving liraglutide

3 mg experienced increases in mean heart rate (an average baseline increase of 2.5 beats/min) compared to 0.1% of placebo recipients^[218]. Potentially a manifestation of GLP-1 induced increases in SNS activity (potential effectors of GLP-1s negative energy balance effects: Central controllers) contributing to GLP-1 induced weight loss *via* increases energy expenditure, elsewhere tachycardia associated with 3 mg liraglutide treatment in non-diabetic obese subjects yields no associated increases in 24 h energy expenditure^[209]. Thus, whilst the clinical significance of this finding remains to be determined, observations may warrant more intense monitoring in patients with pre-existing cardiovascular disease.

Interpretations - long term risk-benefit of liraglutide 3 mg as an anti-obesity agent on the NHS:

Though generally well tolerated in the acute setting, safety concerns have been raised regarding the potential risk of pancreatitis and pancreatic and thyroid cancer with long-term use of GLP-1 analogues^[219,220]. Confirmed cases of acute pancreatitis and papillary thyroid carcinoma were reported in 0.3% of liraglutide 3 mg treated compared to 0.2% of placebo treated participants, however the relative rarity of events means the relationship between treatment with disease incidence and severity remains to be defined. Ongoing clinical experience and thorough post-marketing surveillance should help clarify any such associations and also identify other potential adverse drug events. To this end, episodes of acute renal failure and medullary thyroid carcinoma (not observed during in-treatment and FUP period assessments^[42,43,205-207]) have been reported in the post-marketing period, though again, insufficient data exists to establish or exclude a causal relationship. Figure 17 details other potentially serious medical conditions observed in during in-treatment and FUP assessments^[42,43,205-207].

Though potentially associated with serious long-term adverse effects, the rarity of incidence and lack of causal relationship mean that current knowledge supports benefit over risk, supporting the licensing and funding of liraglutide 3 mg as the first line anti-obesity pharmaceutical agent for weight management in obese and overweight adults with at-least one weight related

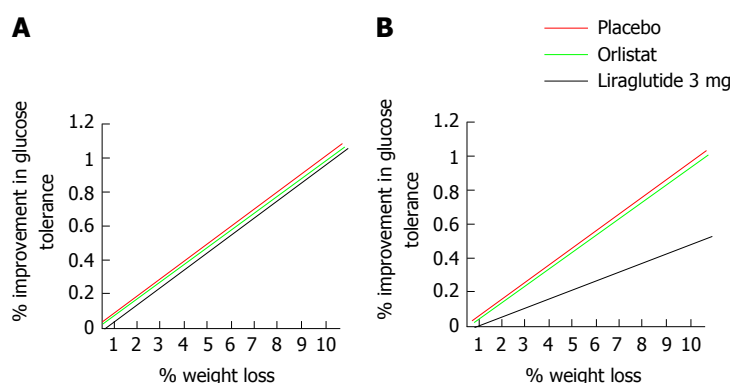


Figure 15 Theoretic model to assess glucose tolerance as a factor of weight. Liraglutide 3 mg produces increased weight loss and increased improvements in glucose control compared to both placebo and control in non-diabetic obese and overweight subjects^[41-43,205,206]. If the greater glucose sensitivity seen following treatment with liraglutide 3 mg is secondary to the greater weight loss achieved, the relationship between a given weight reduction and the percentage improvement in glucose tolerance should be the same in all treatment groups (A). If however, the relationship between a given weight loss and change in glucose tolerance is less strong (B) following treatment with liraglutide, findings would suggest that mechanisms beyond weight loss contribute to the greater improvements of glucose tolerance seen following GLP-1 agonism. One mechanism may be *via* activation of GLP-1R in the pancreas, where endogenous GLP-1 signalling has a well established incretin effect. GLP-1: Glucagon-like peptide 1.

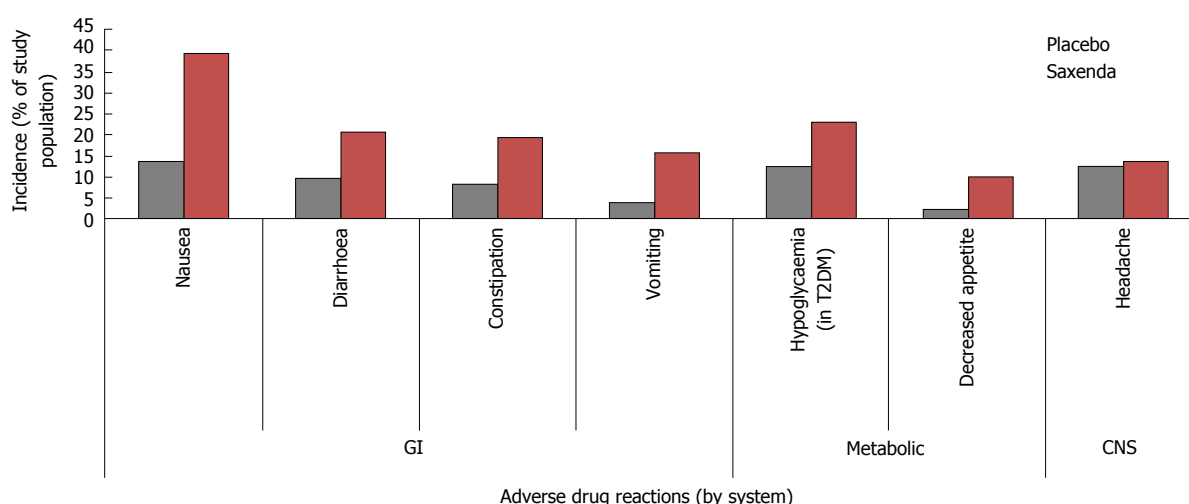


Figure 16 Adverse drug reactions reported in $\geq 10\%$ of liraglutide 3 mg recipients with a higher incidence than placebo stratified by system. GI: Dyspepsia, abdominal pain, dry mouth, gastritis, gastroesophageal reflux disease, flatulence, eructation and abdominal distension were also more prevalent in liraglutide treated participants but occurred with incidence $\leq 10\%$, not shown; 6.2% with Saxenda vs 0.8% with placebo discontinued treatment as a result of gastrointestinal adverse reactions; CNS: Dizziness, malaise and fatigue occurred were more also prevalent in liraglutide treated participants but occurred with incidence $\leq 10\%$, not shown; Metabolic: Liraglutide reduces blood glucose and thus, there is a potential for hypoglycaemia to occur. In the SCALE diabetes trial severe hypoglycemia occurred in 3 (0.7%) of 422 Saxenda-treated patients and in none of the 212 placebo-treated patients. In clinical trials involving patients without T2DM^[42,43,205,206] no systematic reporting of hypoglycemia occurred but spontaneously reported symptomatic episodes potentially hypoglycemic in cause were reported by 1.6% (46/2962) of liraglutide 3 mg and 1.1% of (19/1729) placebo treated non diabetic patients. T2DM: Type 2 diabetes mellitus; GI: Gastrointestinal; CNS: Central nervous system.

co-morbidity in the United Kingdom.

CONCLUSION

Obesity is a global epidemic, perhaps the greatest challenge to global and public health of our time. Whilst public health initiatives should continue to focus on curbing the projected upward trends in the incidence of obesity and overweight, effective management of those individuals already obese remains an important and as yet unmet clinical need. The current medical management of obesity in the United Kingdom is suboptimal, with the only treatment modality with proven long-term

efficacy being bariatric surgery. Both risky and costly, this treatment option is not viable for the widespread management of obesity, and remains reserved for extreme cases. The ideal medical management of any illness utilizes a targeted pharmacotherapy that either repletes physiological factors pathologically depleted, or antagonizes pathological processes, the development of such an agent requiring an understanding of the pathophysiology underpinning a disease. Though the pathophysiology of clinical obesity is undoubtedly multifaceted, several lines of clinical evidence implicate a role for functional impairments in GLP-1 signalling. Whilst genetic studies implicate a role for primary altered GLP-1

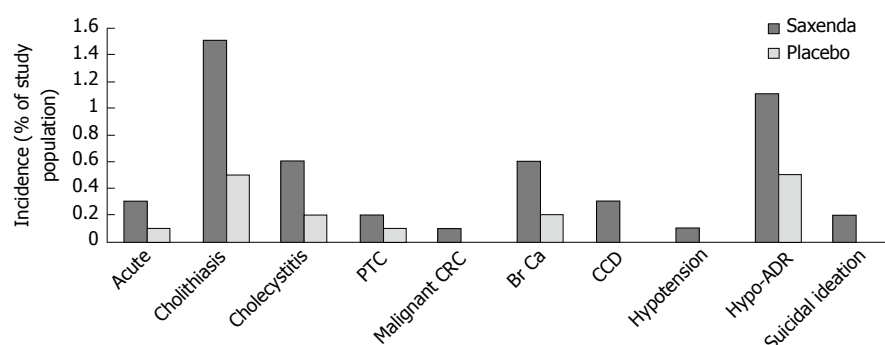


Figure 17 Reported incidences of serious medical conditions from pooled analyses of 5 double-blinded placebo controlled trials studying the safety and efficacy of 3 mg liraglutide (Saxenda) in 3384 overweight or obese subjects receiving liraglutide and 1941 placebo controls. Hypotension associated adverse reactions (Hypo-ADR) refer to hypotension, orthostatic hypotension, circulatory collapse, and decreased blood pressure). One of the six (0.2%) liraglutide treated subjects reporting suicidal ideations attempted suicide. PTC: Papillary thyroid carcinoma; CRC: Colorectal carcinoma; Br Ca: Breast cancer; CCD: Cardiac conduction disorders.

signalling as a risk factor towards development of the obesity phenotype, clinical studies assessing physiological GLP-1 responses in normal weight and obese subjects suggest weight gain may induce functional deficits in GLP-1 that facilitates maintenance of the obesity phenotype. Whatever the relationship, cause or effect, reductions in functional GLP-1 signalling seems to play a role in clinical obesity, as such, the pharmacological replenishment of this functional deficit seems a promising target for the medical management of obesity in the clinic. Indeed, the GLP-1 analogue liraglutide 3 mg has shown promising results in achieving and maintaining greater weight loss in obese individuals when compared to control or currently licensed anti-obesity medication. Though results from extended phase III and phase IV studies report the development of potentially fatal adverse drug events in those randomized to or prescribed liraglutide 3 mg respectively, the scarcity of incidence and lack of causal relationship sees such potential risks overshadowed by the proven superior weight loss efficacy of treatment. Cost-benefit, however, may pose a barrier toward viable NHS funding, though this may be overcome by strategic treatment delivery; combining short-term liraglutide 3 mg treatment (≤ 36 wk) with behavioural therapies targeted toward promoting healthy lifestyle changes. With drug induced weight loss potentially reinforcing adherence to long-term lifestyle changes, if successful, shortened in-treatment period alongside decreases in direct and indirect socioeconomic burdens of obesity and overweight secondary to achievement and maintenance of significant weight loss associates a long-term cost-benefit to funding treatment. Such a concept supports the use of liraglutide 3 mg as the first line anti-obesity agent on the NHS when conservative lifestyle management alone has failed in achieving clinically significant weight loss in comorbid overweight or obese adults.

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