doi: 10.1111/j.1467-789X.2011.00860.x

Obesity Treatment

Obesity – an indication for GLP-1 treatment? Obesity pathophysiology and GLP-1 treatment potential

S. S. Torekov[1], S. Madsbad[2] and J. J. Holst[1]

[1]Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; [2]Department of Endocrinology, Hvidovre University Hospital, Hvidovre, Denmark

Received 9 August 2010; revised 4 November 2010; accepted 22 December 2010

Address for correspondence: SS Torekov, Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, 2200 Copenhagen, Denmark.
E-mail: torekov@sund.ku.dk

Summary

Obesity is common and associated with a high rate of morbidity and mortality; therefore, treatment is of great interest. At present, bariatric surgery is the only truly successful treatment of severe obesity. Mimicking one of the effects of bariatric surgery, namely the increased secretion of glucagon-like peptide (GLP)-1, by artificially increasing the levels of GLP-1 might prove successful as obesity treatment. Recent studies have shown that GLP-1 is a physiological regulator of appetite and food intake. The effect on food intake and satiety is preserved in obese subjects and GLP-1 may therefore have a therapeutic potential. The GLP-1 analogues result in a moderate average weight loss, which is clinically relevant in relation to reducing the risk of type 2 diabetes and cardiovascular disease. Inspired by the hormone profile after gastric bypass, a future strategy in obesity drug development could be to combine several hormones, and thereby produce a superior appetite suppressing hormone profile that may result in a weight loss exceeding that seen in single-agent trials. In conclusion, with the GLP-1 analogues combining a moderate weight loss with beneficial effects on metabolic and cardiovascular risk factors, it seems that we are on the right track for future treatment of obesity.

Keywords: GLP-1 analogues, obesity, obesity treatment.

obesity reviews (2011) **12**, 593–601

Introduction

Obesity is a common disorder, and in many western countries and the USA more than half of the populations are overweight or obese. The prevalence is increasing dramatically, and the number of obese individuals worldwide is now projected to reach as many as 1.1 billion by 2030 (1). As obesity is associated with a high rate of morbidity and mortality, and thereby accounts for a large part of the public health care expenses (2), there is a great interest in treatment of obesity. At present, bariatric surgery, including gastric bypass surgery is the only truly successful treatment of severe obesity. Nevertheless, due to cost, shortage of bariatric surgeons, side effects and complications, gastric bypass surgery is not an option for treatment of common obesity at the population level. Instead, mimicking one of the effects of bariatric surgery, namely the increased secretion of glucagon-like peptide (GLP)-1 (3), by artificially increasing the levels of GLP-1 might prove successful as obesity treatment.

GLP-1

Glucagon-like-peptide-1 is encoded by the glucagon gene (*GCG*) which also encodes oxyntomodulin, glucagon and GLP-2. GLP-1 is synthesized in L-cells of the small intestine and is released post-prandially in proportion to the caloric intake, and especially carbohydrate and fat seem to be effective stimuli for GLP-1 secretion (4). Native GLP-1 has a short elimination half-life of 1–2 min due to dipeptidyl

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IPR2025-01346

peptidase-4 (DPP-4)-mediated degradation. GLP-1 is known as an incretin hormone potentiating glucose-induced insulin secretion. GLP-1 also inhibits appetite and food intake in animals and humans (5–7), and recent studies involving the GLP-1 receptor antagonist exendin 9–39 have shown that GLP-1 is a physiological regulator of appetite and food intake (8,9). These anorectic actions may be mediated through both central and peripheral mechanisms.

Central actions of GLP-1 on food intake

After the discovery of GLP-1 expression in the brain (10,11) it was relevant to investigate the possible central actions of the peptide. Early studies indicated an effect on appetite and food intake (12), and subsequent more detailed studies confirmed these effects after intracerebroventricular administration of low doses of the peptide (9,13). The proglucagon-producing neurones of the brain stem may represent a link in a system whereby enteroceptive stress, but possibly also food ingestion transmit satiety signals to the brain (14,15). Thus, the GLP-1-producing neurones are activated (show *c-fos* expression) upon distension of the stomach (16). GLP-1 receptors are expressed in many regions of the brain and in particular in the arcuate nucleus and other hypothalamic regions involved in the regulation of food intake (Fig. 1) (17). Destruction of the arcuate nucleus with perinatal monosodium glutamate abolishes the inhibitory effect of intracerebroventricularly administered GLP-1 on food intake and appetite, but not the effect of peripherally administered GLP-1 (18). This indicates that the arcuate nucleus is essential for the central, but not for the peripheral actions of GLP-1. As processing of proglucagon in the brain stem neurones leads to the formation of GLP-1 as well as GLP-2 and oxyntomodulin, all of which have been reported to inhibit food intake after intracerebroventricular administration (19,20), it is possible that the impact on food intake of activation of these neurones is underestimated when only a single transmitter is studied.

How does peripheral GLP-1 reduce weight?

The mechanism whereby peripherally administered GLP-1 inhibits food intake is not clear. It may not be related to the effect on gastric motility and emptying, because appetite reduction can be elicited also in fasting human subjects (21), and because the effects of GLP-1 analogues on gastric emptying in rats wanes with time, in contrast to the appetite inhibiting effect (22). In rats, it has been shown that interaction with sensory afferent neurones of the vagus nerves in the gastrointestinal tract is involved (23). Another possibility is that peripherally administered GLP-1 can access the brain via leaks in the blood-brain barrier such as the subfornical organ and the area postrema, as demonstrated to occur in rats (24) (Fig. 2). In agreement with this,

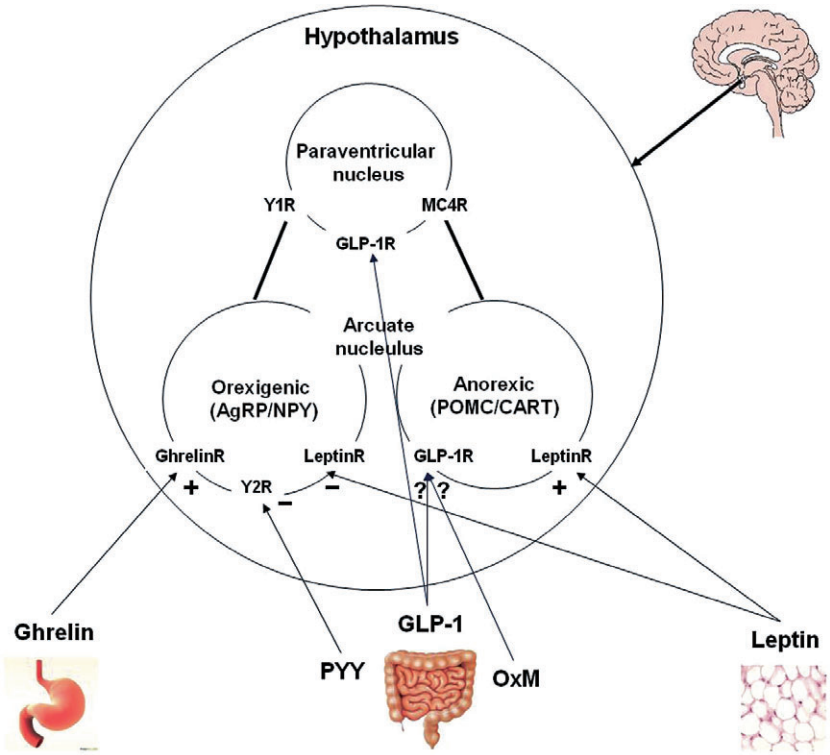

Figure 1 Hypothalamic regulation of food intake. The arcuate nucleus contains two sets of neurones: the neuropeptide Y (NPY)/agouti-related peptide (AgRP) orexigenic neurones which promote food intake; and the proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) anorexigenic neurones which inhibit appetite. Ghrelin, secreted mainly from the gut, activates the ghrelin receptor present on NPY/AgRP neurones leading to activation of the orexigenic pathway. Leptin secreted from adipose tissue activates the anorexigenic pathway through activation of the melanocortin 4 receptor (MC4R) located on paraventricular neurones (PVN). Peptide YY (PYY), glucagon-like peptide (GLP)-1 and oxyntomodulin (OxM) are all mainly secreted from L-cells in the distal gastrointestinal tract in proportion to food intake and they inhibit appetite. Plus indicates stimulation, whereas minus indicates repression of the pathway. Question mark indicates that the precise activation pathway is yet unknown.

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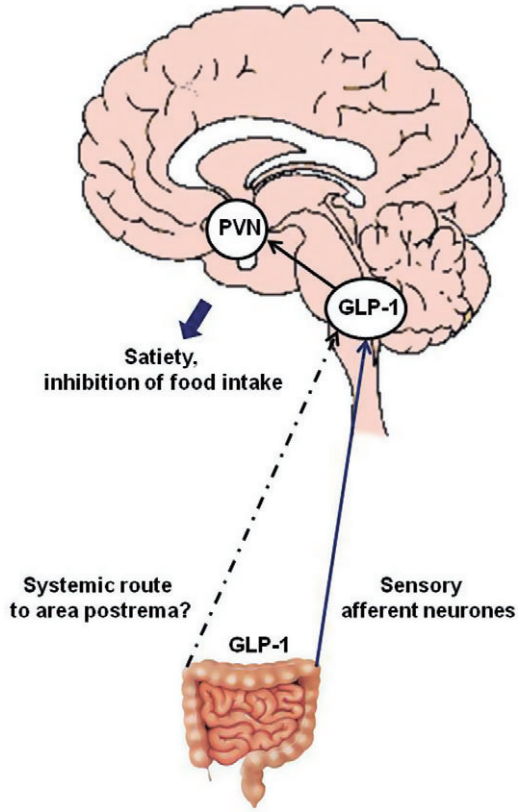

Figure 2 How does peripheral glucagon-like peptide (GLP)-1 reduce weight? The ingestion of food promotes the release of GLP-1 from the intestine, which activates vagal afferents. Cells within the nucleus of the solitary tract (NTS), possibly including GLP-1-producing neurones, respond to this vagal afferent activity. Systemic GLP-1 may also access the brain via leaks in the blood-brain barrier such as the subfornical organ and the area postrema, as demonstrated to occur in rats. In the brain, release of GLP-1 within the NTS and from projections of GLP-1 neurones to the paraventricular neurones (PVN) leads to GLP-1-R activation which promotes satiety and anorexia, potentially with subsequent weight loss.

infusions of GLP-1 in the systemic circulation have been demonstrated to inhibit food intake in rats, independent of the preservation or absence of vagal sensory afferents (23). It has also been claimed that regulatory peptides from the periphery may access the arcuate nucleus perhaps via diffusion from the median eminence (15) although the actions of GLP-1 in the arcuate nucleus now seem to be associated with insulin secretion rather than appetite regulation (25). Studies with large molecular size GLP-1 receptor agonists (albumin-conjugated GLP-1 receptor agonists) in both humans and mice show that even though these large proteins cannot cross the blood-brain barrier, they inhibit feeding (26,27). This demonstrates that at least some effect of GLP-1 may not be exerted directly through the central nervous system, but possibly through the neurones afferents of the vagus nerve with cell bodies in the nodose ganglion (28). In rats it has been shown that peripherally administered GLP-1 activates vagal afferents. This effect was blocked by a GLP-1 receptor antagonist, exendin (9–38) amide, suggesting that GLP-1 receptors on vagal afferent nerves mediate sensory input from the gastrointestinal tract or pancreas (29). Another study with a large molecular weight GLP-1 receptor agonist in rodents show that neurones found in the area postrema are important for transmitting the satiety signal of GLP-1 from the periphery to the central autonomic regulatory system (30). The authors argue that GLP-1 receptors that influence food intake are likely located in the periphery or in an area of the brain that is exposed to circulation (30).

Recent studies in rats have demonstrated that infusions of the orexigenic peptide, ghrelin, may dampen the effects of GLP-1 on gastric emptying and food intake, and the authors suggested that the stimulating effect of ghrelin on food intake might derive at least in part from its ability to attenuate the effects of GLP-1 (and Peptide YY [PYY]) on gastric emptying and food intake (31). Rats with transplanted glucagonomas that secrete large amounts of glucagon and GLP-1 develop severe anorexia and die of starvation (32), presumably due to the combined overproduction of GLP-1 and glucagon. It should be noted that GLP-1 receptor knockout mice do not become obese (33), but this may reflect the redundancy of the appetite-regulating mechanisms rather than ineffectiveness of the signal. In fact, the efficacy of the appetite-reducing effect was convincingly demonstrated not only in clinical studies but also in studies involving life-long administration of the GLP-1 analogue, exendin 4, to rats. The treated animals survived longer than controls, an effect that was thought to result from decreased food intake and hence a significantly lower body weight (34).

GLP-1 and obesity pathophysiology

A role for GLP-1 in the development of obesity was suggested partly because of the apparently physiological effects of the hormones on appetite and food intake (8,35), and partly because of the reports that GLP-1 secretion may be reduced in obesity. Thus in 1983, it was demonstrated that the diurnal L-cell secretion (measured as enteroglucagon secretion) was dramatically decreased in morbid obesity (36), and in a subsequent study, again in morbidly obese subjects, there was no measurable increase in post-prandial GLP-1 secretion (37). However, after a jejuno-ileal bypass operation meal responses were restored to normal values. This should not be interpreted to suggest that the weight loss restored L-cell sensitivity to meal stimulation because it is known that abnormal exposure of the distal gut to unabsorbed nutrients as occurs after jejuno-ilal bypass as well as gastric bypass operations results in exaggerated L-cell secretion (38). However, obese subjects showing decreased post-prandial GLP-1 responses compared with lean

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controls, did exhibit improved secretion after weight loss (39). The mechanism whereby obesity lowers GLP-1 secretion is not known, but the insulin resistance that accompanies weight gain also results in impaired GLP-1 secretion (40). It has been suggested that particularly the L-cell responsiveness to carbohydrates is affected (41), and that circulating fatty acids could be responsible (42). However, in a large study in both diabetic and non-diabetic subjects, in whom body mass index (BMI) again emerged as a significant negative factor for meal-induced GLP-1 secretion, free fatty acid levels did not appear to influence the responses upon multiple regression analysis (43). Another study shows that incretin action expressed as insulin secretion is inversely related to both glucose tolerance and BMI in an independent, additive manner (44). Thus, it seems that glucose tolerance and obesity impair the incretin effect independently of one another. In that same study, also GLP-1 secretion was negatively related to both BMI and glucose intolerance (44). Interestingly, new results suggest that the weight neutral/weight reducing type 2 diabetes drug *metformin* causes up-regulation of GLP-1 receptor expression as well as proglucagon-gene expression (45) and enhances GLP-1 secretion (46) as shown in both rodents and humans (47).

Further support for an important role of GLP-1 (and PYY) in the regulation of appetite and food intake comes from studies of GLP-1 secretion after gastric bypass surgery. In these individuals, the secretion of GLP-1 (and PYY) is greatly elevated post-prandially and is believed to result in reduced appetite and food intake and hence weight loss (3,48–50). It is of interest that the operations also cause a dramatic improvement in glucose tolerance that occurs very early post-operatively, before a major weight loss has been achieved (51). Again, it is thought that the exaggerated GLP-1 secretion may be responsible, via its effects on insulin and glucagon secretion (52).

GLP-1 as an obesity drug?

Several studies have shown that peripheral infusions of GLP-1 significantly and dose-dependently enhance satiety and reduce food intake in normal subjects (7,35). The effect on food intake and satiety is preserved in obese subjects (6) as well as in obese subjects with type 2 diabetes (53,54). This indicates that GLP-1 may not only be a physiological regulator of food intake but may also have a therapeutic potential.

Exenatide

The first commercially available, stable GLP-1 receptor agonist was exendin-4 (*exenatide*, Byetta; Amylin/Eli Lilly, Amylin Pharmaceuticals, Inc., San Diego, California, US) which is a potent GLP-1R agonist isolated from the saliva of a lizard that is resistant to DPP-4-mediated degradation (55,56). Phase III trials of short-acting *exenatide* have shown that subcutaneous injections given twice daily (*exenatide* BID) to people with type 2 diabetes for 30 weeks is associated with 1.6–2.8 kg weight loss compared with placebo treatment (57–59). In a subgroup of patients (368 out of 1446 patients), a gradual and almost linear weight loss of 5 kg was observed during 3-year follow-up (60). A long-acting version of *exenatide* suitable for once-weekly dosing is in clinical development (61,62). In a direct comparison in type 2 diabetes patients, the weight loss was 4 kg after 30-week treatment with *exenatide* once weekly compared with 3.8 kg in the *exenatide* BID group (61). After 1 year, where all patients had been treated with *exenatide* once weekly from week 30, the weight loss was 4.1 to 4.5 kg (63). Nausea was seen in 26% of the patients on *exenatide* once weekly and in 35% of the patients on *exenatide* BID, decreasing with duration of treatment (61). It has been demonstrated that weight loss during *exenatide* treatment is not a consequence of nausea (58,64). Furthermore, a recent series of studies with *exenatide* once weekly showed less nausea (14%) than treatment with *exenatide* BID (35%) (65).

In a small-scale, open-label study conducted in obese, non-diabetic women with polycystic ovary syndrome, *exenatide* BID and *metformin* in combination resulted in a weight loss of 3 kg and had a beneficial effect on menstrual cyclicity and insulin sensitivity. The weight loss effect was more marked with combination treatment than treatment with either *exenatide* or *metformin* alone (66). Recently, the effect of *exenatide* BID on body weight and glucose tolerance was assessed in 152 obese (BMI 39.6 kg m^{-2}) with normal glucose tolerance or impaired fasting glucose tolerance. *Exenatide*-treated subjects lost 5.1 kg from baseline vs. 1.6 kg with placebo in 24 weeks. Pre-diabetes normalized in 77% with *exenatide* compared with 56% with placebo-treated subjects (67). Interestingly, in a very recent study, an 8.8% weight loss was induced by a very low-calorie diet in obese subjects with early diabetes, and a weight-maintaining diet was then combined with placebo or *exenatide* BID for 6 months. Those on *exenatide* maintained their bodyweight, whereas the placebo groups regained weight (68). This indicates that GLP-1 analogues, like *exenatide*, successfully help maintaining a significant weight loss, perhaps by resetting the 'set point' after weight loss and/or by combating the forces activated to attain it.

Liraglutide

A stable GLP-1 analogue, *liraglutide* (Victoza; Novo Nordisk A/S, Bagsværd, Denmark) received a license for use in the treatment of type 2 diabetes in 2009. *Liraglutide* has 97% structural homology to human GLP-1. *Liraglutide* has a long half-life of about 13 h and can be

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administered once a day by subcutaneous injection. The long half-life is due to albumin binding, which results from the addition of a palmitoyl group coupled to lysine at position 26 (69). In a series of phase III studies, in patients with type 2 diabetes, *liraglutide* was shown to improve glycaemic control in association with a dose-dependent weight loss (70–74). Therefore, *liraglutide* could be an attractive treatment option not only for type 2 diabetes but also for obesity. The underlying mechanisms that mediate the effects of weight reduction of liraglutide are most probably a combination of effects on the gastrointestinal tract and the brain. In minipigs, *liraglutide* reduces feeding frequency and meal size causing weight loss (75).

In the six LEAD (Liraglutide Effect and Action in Diabetes) studies, the weight loss after 30-week to 52-week treatment with *liraglutide* was 2–3 kg more than placebo treatment (71–74,76,77). The body weight was constant after 20-week to 24-week treatment and the weight loss was sustained over 52 weeks (73). The weight loss increased with increasing BMI, thus the patients who were the most overweight experienced the greatest weight loss. About 25% of the patients did not lose weight, while the mean weight loss in the quartile with the greatest weight loss was 7 kg (71–74,76,77). The weight loss occurred in the ratio 2:1 between fat : lean tissue, and the relative weight loss was relatively greater in visceral fat compared with peripheral fat tissue (78). Also hepatic steatosis was reduced during treatment with liraglutide (78). Waist circumference is an even stronger predictor of development of cardiovascular disease and type 2 diabetes, compared to BMI (79). Interestingly, in a meta-analysis of the LEAD 1–6 phase III trials, the weight loss obtained with *liraglutide* in type 2 diabetes patients was more strongly linked to waist circumference than to BMI (80). A recent study comparing the effect of *exenatide* BID and *liraglutide* 1.8 mg daily in type 2 diabetes patients treated for 26 weeks showed that the drugs have similar effect on weight loss (3.2 kg for *liraglutide* and 2.9 kg for *exenatide*), but that nausea was less frequent and persistent in the *liraglutide* group (70).

Recently, the effect on bodyweight of *liraglutide* (at doses up to 3.0 mg per day), in combination with an energy-deficient, low-fat diet and physical activity counselling, was assessed in a group of non-diabetic obese individuals. *Liraglutide* was compared with *orlistat* (inhibits pancreatic lipase causing fat malabsorption) in a double-blind, placebo-controlled 20-week trial with 564 obese non-diabetic individuals (81). Treatment with *liraglutide* led to a sustained dose-dependent weight loss that was significantly greater than that with placebo or *orlistat*. Mean weight loss with *liraglutide* 3.0 mg was 7.2 kg (4.4 kg greater than with placebo). Weight loss was accompanied by reductions in waist circumference, systolic and diastolic blood pressure, and frequency of both metabolic syndrome and pre-diabetes. A third of the subjects had impaired glucose tolerance and in 90% of these, glucose tolerance was normalized during *liraglutide* treatment, whereas *orlistat* had no substantial effect on either metabolic syndrome or pre-diabetes parameters (81). In a post hoc analysis the efficacy of *liraglutide* was similar in obese individuals with metabolic syndrome and those without (82). One-year data from this study showed a progressive weight loss and a mean weight loss after 1 year with 3.0 mg *liraglutide* of 7.8 kg (5.8 kg greater than with placebo). In the quartile of greatest weight loss, subjects given 3.0 mg *liraglutide* had a mean weight loss of 18 kg compared with 9 kg with placebo and all subjects on that dose responded with a weight loss (83). *Liraglutide* was generally well tolerated. Nausea and vomiting were more frequent with *liraglutide* than with *orlistat*, and although these events were mostly transient and of mild intensity, it has been suggested that part of the weight loss associated with *liraglutide* is a consequence of nausea and vomiting (84). However, in post hoc analysis, the dose-dependent weight loss produced by increasing doses of liraglutide was maintained both for patients with and without nausea and vomiting (82). Hence nausea cannot be a major contributor to the weight loss produced by GLP-1.

Albiglutide

Albiglutide (GlaxoSmithKline, Middlesex, United Kingdom) is a human GLP-1 receptor agonist consisting of two copies of the 30-amino acid sequence of a DPP-4-resistant human GLP-1 analogue (as a tandem repeat) fused to serum human albumin (85). Resistance to DPP-4 cleavage is obtained by a single substitution (Ala to Gly) at the cleavage site of the GLP-1 molecule (85,86). Plasma half-life is about 5 days, enabling once-weekly dosing. In a study with 356 type 2 diabetic subjects the weight loss after 16 weeks was 1.1–1.7 kg with the highest *albiglutide* doses (30 mg weekly, 50 mg biweekly or 100 mg monthly) compared with 2.4 kg in the *exenatide* BID-treated groups and 0.7 kg in the placebo group (27).

Taspoglutide

Taspoglutide is a human GLP-1 analogue with 93% homology with the native hormone currently in phase III trials by Hoffmann-La Roche. *Taspoglutide* contains two α-aminoisobutyric acid substitutions replacing Ala8 and Gly35 of hGLP-1 (7–35) NH2 (87). *Taspoglutide* is fully resistant to DPP-4 degradation (87). *Taspoglutide* reduced bodyweight in a dose-dependent manner throughout a 24-week treatment in type 2 diabetes patients with 2.6 kg compared with 0.5 kg with placebo (88). Recent studies with *taspoglutide* show a rather high frequency of gastrointestinal side effects and dropout rates (14% with *taspoglutide* 20 mg weekly compared with 1% with placebo

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(88). Furthermore, hypersensitivity reactions have been noted in a few patients (press release: http://www.roche.com/investors/ir_update/inv-update-2010-06-18b.htm), so the development program is currently on halt.

Discussion

Almost no one can maintain significant weight loss after dieting (89) and as the absolute number of obese individuals is projected to reach more than one billion obese in near future (1), with subsequent huge impacts on the public healthcare expenses (2) serious interventions are needed to supplement lifestyle changes. In this context, the GLP-1 analogues seem promising as they not only reduce body weight but also have positive effects on hypertension, pre-diabetes, the metabolic syndrome and non-alcoholic steatohepatitis (78,81), thereby decreasing obesity associated health risk factors. One obstacle is the subcutaneous application of the GLP-1 analogues, although in a recent study the weight loss was valued more than the discomfort of injection (90). Another issue is that the GLP-1 analogues, as exemplified by *liraglutide*, only resulted in a moderate average weight loss of ~6 kg during 1 year in non-diabetic, obese individuals, although superior to that of the single currently approved weight loss agent, *orlistat*. Nevertheless, a subgroup of patients corresponding to about 25% of the population will respond with a weight loss of more than 10% of the body weight. In the Diabetes Prevention Program, non-diabetic subjects with elevated fasting plasma glucose or impaired glucose tolerance, a weight loss of 5 kg reduced the risk of manifest diabetes by 61% during 2.8-year follow-up, and a 10 kg weight loss reduced the risk by 83% (91). Therefore, the weight loss obtained by GLP-1 analogues is clinically relevant in relation to reducing the risk of developing type 2 diabetes. Furthermore, the moderate weight loss obtained with the GLP-1 analogues is associated with a significant reduction in the obesity-associated cardiovascular risk factors. Therefore, this moderate weight loss may also reduce pharmaceutical and medical cost significantly in relation to treatment of complications (92,93). The homeostatic responses to weight perturbation are pleiotropic and include coordinated changes in behaviour and physiological systems controlling energy expenditure and appetite. The responses are integrated in a manner that opposes weight loss. Therefore, amplification of a single component, e.g. GLP-1, would be expected to have only a moderate impact on weight. The recognition that several gastrointestinal hormones, released in response to nutritional stimuli are important regulators of appetite (PYY, oxyntomodulin, GLP-1 and decreased secretion of ghrelin), offers a strategy for the development of more effective anti-obesity agents. Inspired by the hormone profile observed after gastric bypass, a future strategy in drug development for treatment of obesity could involved a combination of hormones, e.g. GLP-1, PYY, and/or oxyntomodulin to produce a superior appetite suppressing hormone profile that may result in a weight loss far exceeding that seen in single-agent trials (94). Using several hormones in low doses and incorporating lifestyle interventions might maximize the clinical effect while minimizing the side effects. A similar strategy has been useful in the treatment of hypertension and pain. In conclusion, with the GLP-1 analogues combining a moderate weight loss with beneficial effects on metabolic and cardiovascular risk factors, it seems that we are on the right track for future treatment of obesity.

Conflict of Interest Statement

Jens Juul Holst is consultant for Novo Nordisk.

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