Published in final edited form as:
Rev Endocr Metab Disord. 2011 September ; 12(3): 187–195. doi:10.1007/s11154-011-9170-8.

Is the GLP-1 system a viable therapeutic target for weight reduction?

Jenny Tong and **Darleen A. Sandoval**
Division of Endocrinology, Department of Medicine, University of Cincinnati, 2170 E. Galbraith Rd, Cincinnati, OH 45237, USA

Jenny Tong: Jenny.tong@uc.edu; Darleen A. Sandoval: Darleen.sandoval@uc.edu

Abstract

Incretin hormones are intestinally derived peptides that are known to augment glucose-stimulated insulin secretion and suppress glucagon levels. Incretin mimetics are attractive adjunctive therapy for type 2 diabetes due to its efficacy on reducing hyperglycemia with a minimal risk of hypoglycemia. In contrast to most available hypoglycemia agents that cause weight gain, incretin mimetics are associated with moderate weight loss. In this review, we focused our discussion on the actions of glucagon-like peptide 1 (GLP-1) in the brain regulation of energy expenditure and food intake. Furthermore, we reviewed the data from preclinical and clinical studies in humans and discussed the actions of GLP-1, GLP-1 analogs, dipeptidyl pepidase 4 (DPP-4) inhibitors on body weight regulation as well as mechanism by which these effects may occur. The gastrointestinal side effects common to GLP-1 based therapeutics such as nausea hamper its wide spread use. Here, we discussed theoretical possibilities for maximizing weight loss and minimizing nausea with of incretin-based therapy.

Keywords

Incretin; Energy balance; Body weight regulation; Rodent; Human

1 Introduction

Over 50 years ago, it was discovered that insulin secretion in response to a glucose load was greater with oral vs. intravenous glucose administration [1]. The authors hypothesized that this was due to hormones secreted from the gut that stimulated insulin release in response to nutrient exposure. We now know that gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) are two such incretins. However, the predominant role of GIP seems to be related to increased adipogenesis, likely through direct actions on adipocytes [2], while GLP-1 has been found to be a very important regulator of glucose homeostasis. In fact, long acting GLP-1 derivatives and pharmaceuticals aimed at increasing circulating GLP-1 by inhibiting the cleavage enzymes (dipeptidyl pepidase 4 [DPP-4]) have been found to be effective treatments for type 2 diabetes mellitus (Table 1). While majority of the diabetes therapies cause weight gain [3, 4], GLP-1-based therapies are associated with weight loss that is actually comparable to the handful of FDA-approved drugs available to treat obesity [5]. One of the side effects of GLP-1 analogs is that they cause nausea in many patients [5]. This review will focus on the potential contribution of GLP-1 on regulation of energy

Correspondence to: Jenny Tong, Jenny.tong@uc.edu.

homeostasis. We will discuss the CNS regional effects GLP-1 and how this could be exploited to optimize weight loss and minimize nausea.

2 The GLP-1 system

In response to a meal, GLP-1 is secreted into the circulation by enteroendocrine L-cells located predominantly in the mucosa of the distal intestinal tract [6, 7]. Only one GLP-1 receptor (GLP-1r), initially cloned from pancreatic islets, has been described. The receptor is also found within the CNS, heart, and lung. In general, GLP-1 is thought to be a brain-gut peptide that acts as a hormone and neurotransmitter mediating several distinct processes related to nutrient metabolism, including glucose metabolism and regulation of food intake.

3 Review of clinical data on GLP-1 and energy homeostasis

3.1 Regulation of energy homeostasis

Energy intake and energy expenditure are two essential elements for body weight regulation. Data on the effect of GLP-1 on energy expenditure in humans is limited. Higher fasting GLP-1 levels were found to be correlated with higher resting energy expenditure and fat oxidation [8]. GLP-1 infusion resulting in a four-fold increase in plasma GLP-1 and increased energy expenditure in healthy individuals [9]. However, this effect was abolished when insulin level was kept constant during a pancreatic clamp suggesting that the effect on energy expenditure was indirect. In another study, a similar dose of GLP-1 infusion lowered diet induced thermogenesis by 47% due to reduced carbohydrate oxidation but did not alter fat oxidation [10]. In contrast, treatment of a low dose (0.6 mg daily) of the long-acting GLP-1 analog liraglutide for 8 weeks had no effect on 24 h energy expenditure [11]. The combination of exenatide treatment and lifestyle modification induced greater weight loss and glucose lowering but showed similar decreases in caloric intake and increase in exercise-derived energy expenditure as compared to placebo in overweight or obese individuals with type 2 diabetes [12]. Taken together, exogenous GLP-1 or GLP-1 analogs do not seem to have a consistent or significant effect on energy expenditure in humans.

3.2 Regulation of food intake

The vast amount of literature examining GLP-1 based therapies has focused on the effect of GLP-1 on food intake. Exogenous administration of GLP-1 to humans, raising plasma levels to pharmacologic ranges, has an acute and negative effect on energy intake in humans. In a randomized, blinded, placebo-controlled crossover study, short-term intravenous (IV) infusion of GLP-1(7–36 amide) that increases plasma concentration of total GLP-1 to pharmacological levels (60–90 pmol/L) in healthy normal-weight males enhanced satiety and fullness as well as reduced spontaneous food intake by 12% as compared with placebo [13]. Similar effects of GLP-1 on hunger ratings, satiety and energy consumption were also reported in obese subjects [14] and subjects with type 2 diabetes [15]. The anorexic effect of GLP-1 was also demonstrated in healthy individuals given GLP-1 to achieve plasma concentrations closer to those seen postprandially [16], in which graded GLP-1 infusions caused a dose dependent reduction in caloric intake. In a meta-analysis on 9 published and unpublished studies that included 115 subjects, the average energy intake reduction was 12% during varying rates and durations of GLP-1 infusion [17]. In this analysis, the GLP-1 infusion rate was the only independent predictor of reduced energy intake. However, the negative effects of GLP-1 on satiety and food intake have not been universally observed [18, 19]. Proof of concept for the feasibility of using native GLP-1 for therapeutic purpose was obtained from a 6-week study of patients with type 2 diabetes [20]. GLP-1 delivered via continuous subcutaneous infusion, in addition to benefitting glucose homeostasis, significantly decreased weight by 1.9 kg. Taken together, these data suggest that pharmacological administration of GLP-1 can lead to reductions in food intake, but it

remains whether the physiological changes that occur with GLP-1 during a meal in humans actually contributes to reductions in food intake. Regardless, these pharmacological effects are proving to be beneficial in patients with type 2 diabetes. Whether it is a viable option for weight loss in obese, non-diabetic patients remains to be determined.

3.3 GLP-1 based therapies and regulation of food intake

3.3.1 Long-acting GLP-1r agonists

Exenatide: Exendin-4 is a 39 amino acid peptide extracted from the venom of the Gila monster (*Heloderma suspectum*) with a structural homology of 53% with mammalian GLP-1 and a high affinity for GLP-1 receptors [21]. The glycine residue at position 2 of the peptide confers resistance to DPP-4 degradation. Twice daily administration of subcutaneous injection of exenatide, a synthetic exendin-4 derivative, has been shown to improve glucose control with concomitant weight loss ranging 1.5–3 kg over 30 weeks [22–24]. A 52-week open-label, uncontrolled extension of the 30-week exendin-4 treatment led to a total weight loss of 4–5 kg [25]. In another study, a 5.3 kg weight loss was achieved after 3-year treatment with 10 μg twice daily exendin-4 administration [26, 27]. Importantly, this weight loss is due to reductions in fat mass as one-year exenatide treatment led to significant reduction in body weight (6%), waist circumference, total body and trunk fat mass in addition to increased adiponectin [28]. Mild to moderate gastrointestinal (GI) side effects such as nausea, vomiting or diarrhea was reported in all trials but few subjects discontinued therapy during the trial period.

The requirement that current peptide GLP-1r agonists be given by injection has led to the development of new compounds with daily or weekly effectiveness. A long acting release formula (LAR) of exenatide and albuminexendin-4 conjugates that are partly DPP-4 resistant, have beneficial effects on glycemic control and body weight in rodents and humans, making them attractive alternatives for the treatment of type 2 diabetes [29]. In a phase II randomized control trial, exenatide LAR administered at 0.8 and 2.0 mg once weekly for 15 weeks significantly improved glucose control as compared to placebo, and at the higher dose there was comparable weight loss to previous studies using shorter acting exenatide. Mild nausea was the most frequent adverse event.

Liraglutide: Another long-acting GLP-1r agonist currently available in the clinic is liraglutide, a fatty acid acylated GLP-1 molecule that exhibits a prolonged pharmacokinetic profile after a single injection due to the non-covalent bound with albumin [30]. Liraglutide mimics all of the actions of native GLP-1 and effectively lowers blood glucose in human subjects with type 2 diabetes [31]. The circulating half-life of liraglutide is 10–14 h as compared to 60–90 min with exenatide after a single subcutaneous injection [32, 33].

The efficacy of liraglutide on glucose lowering and body weight as well as body composition changes was evaluated in the phase 3, double-blind, randomized controlled Liraglutide Effect and Action in Diabetes (LEAD) trials. After 26 or 52 weeks of 1.2–1.8 mg liraglutide once daily treatment, weight reduction of 2–2.5 kg was observed with liraglutide monotherapy (LEAD-3) [34], 0.2 kg in combination treatment with sulphonyluea (SU) (LEAD-1) [35], 1.8–2.8 kg in combination with metformin (LEAD-2) [36], 1–2 kg when added to metformin and thiazolidinediones (TZD) (LEAD-4) [37], and 1.8 kg combined with metformin and SU (LEAD-5) [38]. The higher dose of liraglutide led to larger amount of weight loss in these studies suggesting a dose dependency. Interestingly, participants who had nausea for more than 7 days also had a tendency to lose more weight compared to those who did not have nausea days in LEAD-3 [34]; this is similar to findings reported from a recent study with exenatide-LAR (Duration trial) [29]. The effectiveness of weight loss with liraglutide (1.8 mg, once daily) and exenatide (10 μg, twice daily) was

similar when compared in a head-to-head trial (LEAD-6) [39]. Varying combination treatment produces similar degree of weight loss in most trials (LEAD 2–6) [34, 36–39] except for the SU combination where greater weight loss was achieved with exenatide (LEAD-1) [35]. However, this result needs to be interpreted with caution due to the lower baseline body weight in the liraglutide treated group than the exenatide treated group.

The effectiveness of liraglutide in the treatment of obesity was assessed in a randomized, double-blind, placebo-controlled 20-week trial where 564 obese individuals with fasting plasma glucose of less than 7 mmol/L and BMI ranging 30–40 kg/m^2 were randomized to receive one of the four doses of liraglutide (1.2–3.0 mg daily) or placebo or orlistat (120 mg daily) [40]. Treatment with liraglutide, in addition to an energy-deficit diet and exercise program, led to a dose-dependent weight loss that was significantly greater than that with placebo (all doses) and orlistat (vs. liraglutide 2.4 and 3.0 mg only). The mean weight loss with liraglutide 3.0 mg was 7.2 kg over 20 weeks. Nausea and vomiting were again more common in the liraglutide treated group but mostly transient and of mild or moderate intensity.

The reduction of weight with liraglutide was found to be primarily from reduction in fat mass rather than lean tissue mass. Body composition changes related to liraglutide therapy were evaluated by using dual-energy X-ray absorptiometry and computed tomography in LEAD-2 and LEAD-3 trials [41]. Both visceral and subcutaneous adipose tissue were significantly reduced by liraglutide treatment alone (LEAD-3) or in combination with metformin (LEAD-2). In addition, liraglutide 1.8 mg increased the liver-to-spleen attenuation ratio, possibly indicating reduced hepatic steatosis. Absolute total lean body tissue mass was also reduced in all liraglutide treatment arms in a dose-dependent manner. However, these reductions were not significantly different from the placebo control group. Together with the findings from the exenatide treatment study discussed previously [28], GLP-1 analogues induce weight loss and fat mass reduction. In addition, body weight reduction due to liraglutide treatment was also associated with a reduction in lean mass as commonly observed in subjects undergoing a weight loss intervention.

3.3.2 Increasing circulating endogenous GLP-1—The previous literature suggested that raising circulating levels of GLP-1 with exogenous administration could inhibit food intake. Another way to increase circulating GLP-1 is to inhibit the cleavage enzyme, DPP-4. In fact, DPP-4 inhibitors that raise endogenous concentrations of active GLP-1 [42] and have been shown to be effective in lowering fasting and postprandial glucose concentrations [43]. In contrast to GLP-1 based therapy, DPP-4 inhibitors have been shown to be weight neutral [5]. Thirteen randomized controlled trials evaluating the effects of DPP-4 inhibitors on HbA1c and weight loss prior to May 2007 were summarized in this meta-analysis and systematic review by Amori et al. [5]. Overall, there was a small increase in weight with DPP-4 inhibitors compared with placebo (weighted mean difference, 0.5 kg; 95% CI, 0.3–0.7 kg). In non-inferiority trials, sitagliptin produced more weight loss than glipizide (between-treatment difference, −2.5 kg; 95% CI, −3.1, −2.0) [44] while vildagliptin had a favored weight profile compared with thiazolidinediones (TZDs) (−1.7 kg; 95% CI, −2.2 to −1.2 kg) [45, 46] but not compared with metformin [47]. The new member of the FDA approved DPP-4 inhibitors saxagliptin has shown similarly minimal effect on weight as the other members [48]. In contrast to GLP-1r agonists, DPP-4 inhibitors have not shown to have significant effect on body composition at least in rodents [49, 50]. It is still important to note that while these methods of increasing circulating GLP-1 may not cause weight loss, they do not cause the significant weight gain seen with other antidiabetic medications such as insulin and some insulin sensitizers. The respective side effects of DPP-4 inhibitors were summarized in the systematic review by Amori et al. [5].

3.4 Summary of clinical findings

While we still have much to learn regarding the physiological role of GLP-1 in body weight regulation in humans, it is clear that the long acting GLP-1r agonists are effective at lowering body weight through a reduction in food intake vs. increasing energy expenditure. The mechanism for this remains unknown. Data from the LEAD-3 trial [34] suggested greater incidence of nausea was associated with greater weight loss. This leads us to the question of whether nausea is the *cause* of the weight loss. We now turn to a review of basic science literature on the role of GLP-1 in body weight regulation and will explore further the potential role of GLP-1-induced nausea in the reduction of food intake.

3.5 Mechanisms for GLP-1-induced weight loss

GLP-1 is also made within a discrete population of neurons the found in the nucleus of the solitary tract (NTS) [6, 51, 52]. These GLP-1 neurons within the NTS have rich axonal innervation to the hypothalamus [52, 53]. Third ventricular (i3vt) administration of GLP-1, increases c-fos immunoreactivity, a marker for neuronal activation, in various areas of the brain known for regulating energy balance including the paraventricular (PVN) and arcuate (ARC) nucleus of the hypothalamus [54]. Further support for a role for GLP-1 in energy homeostasis is that neuronal expression of preproglucagon within the hindbrain is decreased with fasting in mice [55].

3.5.1 Mechanisms for GLP-1-induced changes in energy expenditure—If GLP-1 regulates energy expenditure, it could be through sympathetic activation. Acute GLP-1 or long-acting GLP-1 agonist administration has been shown to increase sympathetic outflow to regulate heart rate, and blood pressure [56], and lipolysis white adipose tissue [57] via central mechanisms. While this suggests that GLP-1 systemically increases sympathetic activity and thus increases in energy expenditure, the animal literature regarding the role of GLP-1 on energy expenditure conflicts. As stated above, human data shows minimal effect of GLP-1 on energy expenditure [9, 11]. In mice, the effect may depend upon diet since 1 week of ICV administration of GLP-1 prevented the decrease in energy expenditure seen with caloric restriction in lean mice [57]. Further, acute (1 week) central blockade of endogenous GLP-1r had no affect on food intake but increased body weight with a tendency for a decreased energy expenditure in C57/Bl6 mice fed a chow diet [57] while more chronic (1 month) central blockade increased energy expenditure in high fat fed C57/Bl6 mice [58]. It is unknown whether it is the timing (1 week vs. 1 month) vs. the diet (chow vs. high fat) or some other factor that leads to these discordant results. Regardless, it seems that if central GLP-1 action is beneficial for treatment of obesity, increased in energy expenditure does not make a major contribution to the negative energy balance.

3.5.2 Mechanisms for GLP-1-induced anorexia—While GLP-1 may have only minimal effects on energy expenditure, at least in obesity, it is clear that CNS GLP-1 affects the other side of the energy balance equation by decreasing food intake [59–63]. The anorectic action of GLP-1 is short-lived, reducing food intake typically only within the first few hours of the onset of the dark cycle (when rats typically eat most) [59–63]. Unlike the effects on energy expenditure, central GLP-1 administration works equally well to reduce food intake in lean vs. obese animals [60].

GLP-1 administered directly into the lateral [64], 3rd and 4th ventricles [59, 64], the paraventricular nucleus and hindbrain [65] reduces food intake. Interestingly, GLP-1 given directly into the arcuate nucleus (ARC) of the hypothalamus, a key nuclei regulating energy balance, has little effect on food intake [66].

The regional effects of GLP-1 to reduce food intake suggest that GLP-1 acts on a variety of neuronal populations to activate anorectic circuits. The GLP-1r is colocalized with POMC (anorectic neurons) but not NPY (orexigenic neurons) neurons within the ARC [66], However, the role of these cells to mediate the feeding effects of GLP-1 are not direct since administration of peptide to this brain region does not change food intake. While there are data suggesting NPY [67–69] may block GLP-1 anorectic action, neither AgRP [70], nor administration of SHU9119, a melanocortin receptor antagonist, at a dose that blocked the anorectic effects of leptin [71], blocked the anorectic effects of GLP-1. However, it remains possible that these neurons play a role in other CNS effects of GLP-1.

Recent data suggest a link between leptin and GLP-1 in reducing food intake. When sub-threshold doses of GLP-1 and leptin are given together, they potently inhibit food intake suggesting an additive effect of the two drugs [72]. Interestingly, prolonged fasting blunted the anorexic effects of both GLP-1 and exendin-4 (a long acting GLP-1 agonist), an effect that was overcome with a concomitant infusion of leptin. In addition, fasting downregulates hindbrain expression of preproglucagon and this is prevented with leptin infusion during the fast [73]. Whether these effects of leptin are direct or indirect remains unclear but do suggest that these peptides interact to regulate satiety.

3.5.3 The interplay between the peripheral and the central glp-1 systems for regulating body weight—The role for peripheral GLP-1 to regulate glucose homeostasis, and the role of the CNS GLP-1r to regulate food intake are thought to be two separate functions of the GLP-1 system. However, there is evidence for interplay of these two systems. Intravenously administered GLP-1 binds to specific areas within the CNS [74]. However, the short residence time in the circulation raises some doubt as to whether GLP-1 can directly activate CNS neurons from the blood stream or after transport into the brain. An alternative to endocrine action of GLP-1 on the CNS is that the secreted peptide engages visceral afferents which, in turn, activate the central GLP-1 system to initiate some of the physiological effects. Support for this possibility is that nodose ganglion nerves contain GLP-1r [75] and intra-portal infusion of GLP-1 increases pancreatic and vagal afferent activity [76, 77]. However, GLP-1 action in the portal vein seems to be more important for glucose homeostasis [78] rather than food intake [79]. Interestingly, recent data show that the anorectic effect of gastric distention, but not duodenal nutrient infusion, is blocked by hindbrain administration of a GLP-1r antagonist [55]. Together these data suggest a model similar to the CNS GLP-1r system, whereby activation of visceral afferent neurons by GLP-1 is heterogeneous whereby activation of the GLP-1r on the gastric vagal afferents have different physiological effects compared to activation of the GLP-1r located on hepatic visceral afferents. Explaining the physiologic basis for this heterogeneity may facilitate the identification of more specific pharmacologic targets for the GLP-1 system aimed at optimizing weight loss. It is possible to imagine that these targets may even be distinct from targets used to treat type 2 diabetes mellitus.

3.5.4 The role of nausea in GLP-1-induced weight loss—Nausea is the one of the most limiting factors for targeting GLP-1 as a therapy for obesity (and its current use as therapy for type 2 diabetes). Data from the LEAD 3 trial [34] showed an association between increased nausea and increased weight loss in type 2 diabetic patients. This would lead one to speculate that nausea may be a mechanism for GLP-1-induced weight loss.

While the effect of these agents on improving glucose homeostasis is similar between GLP-1 analogues and DPP-4 inhibitors, the GI side effects commonly reported with GLP-1 analogue use is absent with DPP-4 inhibitors [5, 48]. Exogenous GLP-1 that produces high circulating hormone levels can delay gastric emptying [80], increases gastric volume [81, 82], increase satiation and induce weight loss in patients with type 2 diabetes [20]. GLP-1r

agonists decrease caloric intake and are associated with increased GI symptoms such as such as nausea and vomiting [22, 24]. DPP-4 inhibitors (e.g. vildagliptin) on the other hand did not alter satiety, gastric volume, or gastric emptying [83, 84]. The modest increase of active GLP-1 level in the postprandial period with DPP-4 inhibition has been proposed as the explanation for the lack of effect on GI motility and the desirable side effect profile associated with this class of medication. However, even when the peak active GLP-1 concentration following meal ingestion is similar to the level produced by exogenous GLP-1 that is known to cause delayed gastric emptying [84, 85], individuals treated with DPP-4 inhibitor did not have increased frequency of GI symptoms [83]. Therefore, the differential effect of GLP-1 analogues and DPP-4 inhibitors on the GI tract cannot be completely explained by the concentration of active GLP-1 levels in the circulation alone.

Another possibility is that exendin-4, a therapeutically potent GLP-1r agonist, may have distinct potency, duration of action, and altered binding to the GLP-1r compared to GLP-1 [86]. While the fact that exendin-4 may be more potent and have a longer duration of action may not be surprising, but the idea that there are differences in the ability of each agonist to bind to the GLP-1r is novel. Interestingly, it seems that this effect is specific to the CNS GLP-1r signaling as central, but not peripheral affects of exendin-4 are resistance to GLP-1r antagonism. Importantly, there may also be a greater capacity to generate visceral illness with exendin-4 vs. GLP-1.

Like the clinical data, the major adverse effect of GLP-1 administration to rodents is the induction of visceral illness. Importantly, the CNS regions responsible for these effects have been identified. Specifically, GLP-1 acts on neurons within the central nucleus of the amygdala to cause a conditioned taste aversion, a robust indicator of visceral illness [16]. Furthermore, administration of a GLP-1r antagonist, blocks visceral illness induced by lithium chloride in rats and mice [87]. It is important to note that when given directly into the PVN and 4th ventricle (which presumably hits the hindbrain neurons), GLP-1 reduces food intake *without* causing visceral illness. The fact that we can dissociate these effects in animal models lead to the plausibility of developing therapeutic strategies that would dissociate the anorectic effects from illness-inducing effects of GLP-1. This has considerable clinical significance since in humans treated with GLP-1r agonists for diabetes the most commonly reported side effect, and the principle factor limiting tolerance, is nausea [5].

4 Summary and conclusions

GLP-1 infusion and both short- and long-acting GLP-1r agonists in humans are associated with weight loss due to decreased food intake rather than changes in energy expenditure, an effect likely mediated by GLP-1 action in the hypothalamus and hindbrain. Conversely, DPP-4 inhibitors that moderately increase active circulating GLP-1 level are weight neutral. A major adverse effect of these GLP-1 analogue therapies is nausea, an effect that is not seen with DPP-4 inhibitors. This difference may be due to differences in receptor potency of the long acting GLP-1 analogues vs. the endogenous peptide. Regardless, GLP-1 appears to act within very specific regions of the CNS to cause visceral illness in rodents, which may be separate from regions mediating its effect on food intake. The ability to dissociate these effects leads to the possibility that therapies could be developed aimed at reducing food intake without nausea.

This unique function of GLP-1 and GLP-1 mimetics on reducing body weight make them attractive therapeutic alternatives to the limited number of weight loss medications available on the market and the weight-enhancing hypoglycemic agents for the treatment of obesity and type 2 diabetes, respectively. However, the common side effect of GLP-1 such as

nausea makes it less desirable. A recent report on the use of glucagon and GLP-1 co-agonist showed potent and sustained effect on inducing satiation and lipolysis in diet induced obese mice [88]. Combination treatment with agents that have synergistic effects on food intake could enhance potency yet eliminate unwanted side effects associated with single-agent therapy. Agents that specifically target the brain regions that are responsible for the GLP-1 action on food intake but not nausea such as the paraventricular nucleus and 4th ventricle may become attractive options. Overall, a better understanding of the satiety effects of GLP-1 is needed and will have an immediate impact on clinical practice.

References

1. McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. Lancet. 1964; 2:20–21. [PubMed: 14149200]
2. Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med. 2002; 8:738–742. [PubMed: 12068290]
3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:854–865. [PubMed: 9742977]
4. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA. 2002; 287:360–372. [PubMed: 11790216]
5. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007; 298:194–206. [PubMed: 17622601]
6. Drucker DJ. Glucagon and the glucagon-like peptides. Pancreas. 1990; 5:484–488. [PubMed: 2199968]
7. Goke R, Fehmann H, Goke B. Glucagon-like peptide-1 (7–36) amide is a new incretin/enterogastrone candidate. J Clin Investig. 1991; 135:135–144.
8. Pannacciulli N, Bunt JC, Koska J, Bogardus C, Krakoff J. Higher fasting plasma concentrations of glucagon-like peptide 1 are associated with higher resting energy expenditure and fat oxidation rates in humans. Am J Clin Nutr. 2006; 84:556–560. [PubMed: 16960169]
9. Shalev A, Holst JJ, Keller U. Effects of glucagon-like peptide 1 (7–36 amide) on whole-body protein metabolism in healthy man. Eur J Clin Investig. 1997; 27:10–16. [PubMed: 9041371]
10. Flint A, Raben A, Rehfeld JF, Holst JJ, Astrup A. The effect of glucagon-like peptide-1 on energy expenditure and substrate metabolism in humans. Int J Obes Relat Metab Disord. 2000; 24:288–298. [PubMed: 10757621]
11. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diab Care. 2004; 27:1915–1921.
12. Apovian CM, Bergenstal RM, Cuddihy RM, Qu Y, Lenox S, Lewis MS, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. Am J Med. 2010; 123(468) e469-417.
13. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998; 101:515–520. [PubMed: 9449682]
14. Naslund E, Gutniak M, Skogar S, Rossner S, Hellstrom PM. Glucagon-like peptide 1 increases the period of postprandial satiety and slows gastric emptying in obese men. Am J Clin Nutr. 1998; 68:525–530. [PubMed: 9734726]
15. Gutzwiller JP, Drewe J, Goke B, Schmidt H, Rohrer B, Lareida J, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol. 1999; 276:R1541–R1544. [PubMed: 10233049]
16. Gutzwiller JP, Goke B, Drewe J, Hildebrand P, Ketterer S, Handschin D, et al. Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut. 1999; 44:81–86. [PubMed: 9862830]
17. Verdich C, Flint A, Gutzwiller JP, Naslund E, Beglinger C, Hellstrom PM, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7–36) amide on ad libitum energy intake in humans. J Clin Endocrinol Metab. 2001; 86:4382–4389. [PubMed: 11549680]

18. Long SJ, Sutton JA, Amaee WB, Giouvanoudi A, Spyrou NM, Rogers PJ, et al. No effect of glucagon-like peptide-1 on short-term satiety and energy intake in man. Br J Nutr. 1999; 81:273–279. [PubMed: 10999014]
19. Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes Relat Metab Disord. 2001; 25:781–792. [PubMed: 11439290]
20. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet. 2002; 359:824–830. [PubMed: 11897280]
21. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. J Biol Chem. 1992; 267:7402–7405. [PubMed: 1313797]
22. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diab Care. 2005; 28:1092–1100.
23. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diab Care. 2004; 27:2628–2635.
24. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diab Care. 2005; 28:1083–1091.
25. Riddle MC, Henry RR, Poon TH, Zhang B, Mac SM, Holcombe JH, et al. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. Diabetes Metab Res Rev. 2006; 22:483–491. [PubMed: 16634116]
26. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin. 2008; 24:275–286. [PubMed: 18053320]
27. Gedulin BR, Smith P, Prickett KS, Tryon M, Barnhill S, Reynolds J, et al. Dose-response for glycaemic and metabolic changes 28 days after single injection of long-acting release exenatide in diabetic fatty Zucker rats. Diabetologia. 2005; 48:1380–1385. [PubMed: 15915337]
28. Bunck MC, Diamant M, Eliasson B, Corner A, Shaginian RM, Heine RJ. Exenatide affected circulating cardiovascular risk biomarkers independently of changes in body composition. Diabetes Care. 2010
29. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diab Care. 2007; 30:1487–1493.
30. Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agerso H, Veldhuis J, et al. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. Diabetes. 2002; 51:424–429. [PubMed: 11812750]
31. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diab Care. 2004; 27:1335–1342.
32. Agerso H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia. 2002; 45:195–202. [PubMed: 11935150]
33. Kolterman OG, Kim DD, Shen L, Ruggles JA, Nielsen LL, Fineman MS, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health-Syst Pharm. 2005; 62:173–181. [PubMed: 15700891]
34. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised,

52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009; 373:473–481. [PubMed: 18819705]

35. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009; 26:268–278. [PubMed: 19317822]
36. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diab Care. 2009; 32:84–90.
37. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diab Care. 2009; 32:1224–1230.
38. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009; 52:2046–2055. [PubMed: 19688338]
39. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; 374:39–47. [PubMed: 19515413]
40. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009; 374:1606–1616. [PubMed: 19853906]
41. Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, During M, et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab. 2009; 11:1163–1172. [PubMed: 19930006]
42. Drucker DJ. Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. Expert Opin Investig Drugs. 2003; 12:87–100.
43. Ahren B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, et al. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. Diab Care. 2002; 25:869–875.
44. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007; 9:194–205. [PubMed: 17300595]
45. Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. Diab Care. 2007; 30:217–223.
46. Rosenstock J, Kim SW, Baron MA, Camisasca RP, Cressier F, Couturier A, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab. 2007; 9:175–185. [PubMed: 17300593]
47. Schweizer A, Couturier A, Foley JE, Dejager S. Comparison between vildagliptin and metformin to sustain reductions in HbA (1c) over 1 year in drug-naive patients with Type 2 diabetes. Diabet Med. 2007; 24:955–961. [PubMed: 17509069]
48. Deacon CF, Holst JJ. Saxagliptin: a new dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. Adv Ther. 2009; 26:488–499. [PubMed: 19444391]
49. Raun K, von Voss P, Gotfredsen CF, Golozoubova V, Rolin B, Knudsen LB. Liraglutide, a long-acting glucagon-like peptide-1 analog, reduces body weight and food intake in obese candy-fed rats, whereas a dipeptidyl peptidase-IV inhibitor, vildagliptin, does not. Diabetes. 2007; 56:8–15. [PubMed: 17192459]

50. Flock G, Baggio LL, Longuet C, Drucker DJ. Incretin receptors for glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide are essential for the sustained metabolic actions of vildagliptin in mice. Diabetes. 2007; 56:3006–3013. [PubMed: 17717280]
51. Jin SL, Han VKM, Simmons JG, Towle AC, Lauder JM, Lund PK. Distribution of glucagonlike peptide 1, glucagon, and glicentin in the rat brain: an immunocytochemical study. J Comp Neurol. 1988:271.
52. Han VK, Hynes MA, Jin C, Towle AC, Lauder JM, Lund PK. Cellular localization of proglucagon/glucagon-like peptide I messenger RNAs in rat brain. J Neurosci Res. 1986; 16:97–107. [PubMed: 2427741]
53. Rinaman L. Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. Brain Res. 2010
54. Van Dijk G, Thiele TE, Donahey JC, Campfield LA, Smith FJ, Burn P, et al. Central infusions of leptin and GLP-1-(7–36) amide differentially stimulate c-FLI in the rat brain. Am J Physiol. 1996; 271:R1096–R1100. [PubMed: 8898006]
55. Hayes MR, Bradley L, Grill HJ. Endogenous hindbrain glucagonlike peptide-1 receptor activation contributes to the control of food intake by mediating gastric satiation signaling. Endocrinology. 2009; 150:2654–2659. [PubMed: 19264875]
56. Yamamoto H, Lee CE, Marcus JN, Williams TD, Overton JM, Lopez ME, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. J Clin Invest. 2002; 110:43–52. [PubMed: 12093887]
57. Nogueiras R, Perez-Tilve D, Veyrat-Durebex C, Morgan DA, Varela L, Haynes WG, et al. Direct control of peripheral lipid deposition by CNS GLP-1 receptor signaling is mediated by the sympathetic nervous system and blunted in diet-induced obesity. J Neurosci. 2009; 29:5916–5925. [PubMed: 19420258]
58. Knauf C, Cani PD, Ait-Belgnaoui A, Benani A, Dray C, Cabou C, et al. Brain glucagon-like peptide 1 signaling controls the onset of high-fat diet-induced insulin resistance and reduces energy expenditure. Endocrinology. 2008; 149:4768–4777. [PubMed: 18556349]
59. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, et al. A role for glucagon-like peptide-1 in the central regulation of feeding [see comments]. Nature. 1996; 379:69–72. [PubMed: 8538742]
60. Donahey JC, van Dijk G, Woods SC, Seeley RJ. Intraventricular GLP-1 reduces short- but not long-term food intake or body weight in lean and obese rats. Brain Res. 1998; 779:75–83. [PubMed: 9473596]
61. Thiele TE, Seeley RJ, D'Alessio D, Eng J, Bernstein IL, Woods SC, et al. Central infusion of glucagon-like peptide-1-(7–36) amide (GLP-1) receptor antagonist attenuates lithium chloride-induced c-Fos induction in rat brainstem. Brain Res. 1998; 801:164–170. [PubMed: 9729361]
62. van Dijk G, Thiele TE, Seeley RJ, Woods SC, Bernstein IL. Glucagon-like peptide-1 and satiety [letter; comment]. Nature. 1997; 385:214. [PubMed: 9000071]
63. Tang-Christensen M, Larsen PJ, Goke R, Fink-Jensen A, Jessop DS, Moller M, et al. Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. Am J Physiol. 1996; 271:R848–R856. [PubMed: 8897973]
64. Kinzig KP, D'Alessio DA, Seeley RJ. The diverse roles of CNS GLP-1 in the control of food intake and the mediation of visceral illness. J Neurosci. 2002; 22:10470–10476. [PubMed: 12451146]
65. McMahon LR, Wellman PJ. Decreased intake of a liquid diet in nonfood-deprived rats following intra-PVN injections of GLP-1 (7–36) amide. Pharmacol Biochem Behav. 1997; 58:673–677. [PubMed: 9329057]
66. Sandoval DA, Bagnol D, Woods SC, D'Alessio DA, Seeley RJ. Arcuate glucagon-like peptide 1 receptors regulate glucose homeostasis but not food intake. Diabetes. 2008; 57:2046–2054. [PubMed: 18487451]
67. Schusdziarra V, Zimmermann JP, Schick RR. Importance of orexigenic counter-regulation for multiple targeted feeding inhibition. Obes Res. 2004; 12:627–632. [PubMed: 15090630]

68. Furuse M, Matsumoto M, Mori R, Sugahara K, Kano K, Hasegawa S. Influence of fasting and neuropeptide Y on the suppressive food intake induced by intracerebroventricular injection of glucagon-like peptide-1 in the neonatal chick. Brain Res. 1997; 764:289–292. [PubMed: 9295227]
69. Tritos NA, Vicent D, Gillette J, Ludwig DS, Flier ES, Maratos-Flier E. Functional interactions between melanin-concentrating hormone, neuropeptide Y, and anorectic neuropeptides in the rat hypothalamus. Diabetes. 1998; 47:1687–1692. [PubMed: 9792536]
70. Edwards CM, Abbott CR, Sunter D, Kim M, Dakin CL, Murphy KG, et al. Cocaine- and amphetamine-regulated transcript, glucagon-like peptide-1 and corticotrophin releasing factor inhibit feeding via agouti-related protein independent pathways in the rat. Brain Res. 2000; 866:128–134. [PubMed: 10825488]
71. Seeley R, Yagaloff K, Fisher S, Burn P, Thiele T, van Dijk G, et al. Melanocortin receptors in leptin effects. Nature. 1997; 390:349. [PubMed: 9389472]
72. Williams DL, Baskin DG, Schwartz MW. Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. Diabetes. 2006; 55:3387–3393. [PubMed: 17130484]
73. Huo L, Gamber KM, Grill HJ, Bjorbaek C. Divergent leptin signaling in proglucagon neurons of the nucleus of the solitary tract in mice and rats. Endocrinology. 2008; 149:492–497. [PubMed: 17974623]
74. Orskov C, Puolsen S, Moller M, Holst JJ. Glucagon-like peptide 1 receptors in the subformical organ and the area postrema are accessible to circulating glucagon-like peptide 1. Diabetes. 1996; 45:832–835. [PubMed: 8635662]
75. Nakagawa A, Satake H, Nakabayashi H, Nishizawa M, Furuya K, Nakano S, et al. Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. Auton Neurosci. 2004; 110:36–43. [PubMed: 14766323]
76. Nakabayashi H, Nishizawa M, Nakagawa A, Takeda R, Niijima A. Vagal hepatopancreatic reflex effect evoked by intraportal appearance of GLP-1. Am J Physiol. 1996; 271:E808–E813. [PubMed: 8944665]
77. Kakei M, Yada T, Nakagawa A, Nakabayashi H. Glucagonlike peptide-1 evokes action potentials and increases cytosolic Ca2+ in rat nodose ganglion neurons. Auton Neurosci. 2002; 102:39–44. [PubMed: 12492134]
78. Vahl TP, Tauchi M, Durler TS, Elfers EE, Fernandes TM, Bitner RD, et al. Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. Endocrinology. 2007; 148:4965–4973. [PubMed: 17584962]
79. Kim DH, D'Alessio DA, Woods SC, Seeley RJ. The effects of GLP-1 infusion in the hepatic portal region on food intake. Regul Pept. 2009; 155:110–114. [PubMed: 19289143]
80. Schirra J, Wank U, Arnold R, Goke B, Katschinski M. Effects of glucagon-like peptide-1(7–36)amide on motility and sensation of the proximal stomach in humans. Gut. 2002; 50:341–348. [PubMed: 11839712]
81. Delgado-Aros S, Kim DY, Burton DD, Thomforde GM, Stephens D, Brinkmann BH, et al. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. Am J Physiol Gastrointest Liver Physiol. 2002; 282:G424–G431. [PubMed: 11841992]
82. Delgado-Aros S, Vella A, Camilleri M, Low PA, Burton DD, Thomforde GM, et al. Effects of glucagon-like peptide-1 and feeding on gastric volumes in diabetes mellitus with cardio-vagal dysfunction. Neurogastroenterol Motil. 2003; 15:435–443. [PubMed: 12846732]
83. Vella A, Bock G, Giesler PD, Burton DB, Serra DB, Saylan ML, et al. The effect of dipeptidyl peptidase-4 inhibition on gastric volume, satiation and enteroendocrine secretion in type 2 diabetes: a double-blind, placebo-controlled crossover study. Clin Endocrinol (Oxf). 2008; 69:737–744. [PubMed: 18331607]
84. Vella A, Bock G, Giesler PD, Burton DB, Serra DB, Saylan ML, et al. Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. Diabetes. 2007; 56:1475–1480. [PubMed: 17303799]
85. Meier JJ, Gallwitz B, Salmen S, Goetze O, Holst JJ, Schmidt WE, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous

glucagonlike peptide 1 in patients with type 2 diabetes. J Clin Endocrinol Metab. 2003; 88:2719–2725. [PubMed: 12788879]

86. Barrera JG, D'Alessio DA, Drucker DJ, Woods SC, Seeley RJ. Differences in the central anorectic effects of GLP-1 and exendin-4 in rats. Diabetes. 2009
87. Lachey JL, D'Alessio DA, Rinaman L, Elmquist JK, Drucker DJ, Seeley RJ. The role of central glucagon-like peptide-1 in mediating the effects of visceral illness: differential effects in rats and mice. Endocrinology. 2005; 146:458–462. [PubMed: 15459118]
88. Day JW, Ottaway N, Patterson JT, Gelfanov V, Smiley D, Gidda J, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol. 2009; 5:749–757. [PubMed: 19597507]

Table 1

Summary of major classes of GLP-1 based therapies for the treatment of type 2 diabetes

Drug	Route of administration	Dose frequency	Effect on body weight	Manufacture
GLP-1 receptor agonists				
Exenatide	Subcutaneous injection	Twice daily	↓	Amylin Pharmaceuticals
Liraglutide	Subcutaneous injection	Once daily	↓	Novo Nordisk
DPP-4 inhibitors				
Sitagliptin	Oral	Once daily	↔↑	Merck & Co.
Saxagliptin	Oral	Once daily	↔↑	AstraZeneca Pharmaceuticals LP/Bristol-Myers Squibb
Vildagliptin	Oral	Once daily	↔	Novartis