



Incretin Therapies: Effects Beyond Glycemic Control☆☆☆

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ABSTRACT

Impaired insulin secretion plays a major role in the pathogenesis of type 2 diabetes mellitus, and progressive loss of β -cell function is a pathophysiologic hallmark of type 2 diabetes. Recent science has elaborated on the role of the incretin hormones on β -cell function and insulin secretion, as well as the role that incretin-based pharmacotherapies may have on glycemic control and β -cell function, possibly altering the progressive loss of β -cell function and possibly reversing/halting disease progression. However, incretin-based therapies may also have benefits extending beyond glycemic control and insulin secretion. In this review we examine some of those “beyond-glycemic” benefits, including presentation of data on weight reduction, blood pressure lowering, beneficial changes in the lipid profile, and improvements in myocardial and endothelial function. We investigate how those effects may help ameliorate the cardiovascular burden in patients with diabetes.

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The incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are neuroendocrine hormones produced by the gastrointestinal tract in response to nutrient entry and play a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake. These hormones exert their effects through interaction with G-protein-coupled receptors. While the GIP receptor is mainly expressed on pancreatic β -cells, the GLP-1 receptor is more widely expressed throughout the body—in the α - and β -cells in the islets, in other parts of the gastrointestinal tract, in the central and peripheral nervous systems, and in the heart, the kidney, and the lung. Activation of these receptors in rodent and human islet cells leads to glucose-dependent insulin secretion and also to an antiapoptotic effect with enhanced β -cell survival. In addition, activation of the GLP-1 receptor (but not the GIP receptor) leads to inhibition of glucagon secretion, gastric emptying, decreased appetite/increased satiety, and other beneficial effects on the cardiovascular system and the central nervous system (in animal studies).

In patients with type 2 diabetes mellitus, the incretin effect of enhancing insulin secretion is reduced or even absent due to a small, but significant, reduction in meal-stimulated levels of GLP-1 and an attenuation of the insulinotropic effect of GIP (despite near-normal levels). Because GLP-1 action (unlike GIP action) is preserved in patients with type 2 diabetes, therapeutic efforts have been focused on the development of GLP-1 receptor agonists, which would appear to be ideal therapeutic agents for use in patient with type 2 diabetes. A major therapeutic hurdle, however, is that circulating levels of the endogenous incretins decrease rapidly after secretion into the circulation because of enzymatic inactivation, mainly by dipeptidyl peptidase-4 (DPP-4). This has been overcome through the use of incretin mimetics, exenatide and liraglutide, which are GLP-1 receptor agonists resistant to DPP-4 degradation, and the DPP-4 inhibitors (the gliptins), which potentiate the effect of the incretin hormones by competitively inhibiting the enzyme responsible for their degradation.

Elsewhere in this supplement, the authors elaborate on the science of the incretins and the role of incretin therapies in lowering blood glucose and improving glycemia in patients with type 2 diabetes. In this article, we discuss (1) the extraglycemic effects of the incretin therapies and their potential to prevent or reverse progressive loss of β -cell function in patients with type 2 diabetes by means of trophic effects on the pancreatic β -cells; (2) their ability to decrease appetite, leading to weight loss; (3) their beneficial effects on lipids, blood pressure, myocardial contractility, and endothelial function—which collectively have the potential to reduce cardiovascular morbidity and mortality; (4) and finally their neurotrophic and neuroprotective effects (in animal studies only) (Figure 1).

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1. Extraglycemic Effects

1.1. Effects on Islet β -cell Function

It is well established that type 2 diabetes is a progressive disease. In one of the largest studies conducted in patients with diabetes (the UK Prospective Diabetes Study [UKPDS]), glycemic control deteriorated over time in both the active treatment group and the control group independent of the antihyperglycemic agent used [1]. Furthermore, data from the UKPDS (using the homeostasis model assessment) demonstrated that β -cell function at the time of diagnosis in patients with type 2 diabetes had already declined by about 50% [2]. More ominously, concurrent with the worsening of glycemic control, β -cell function also declined progressively through the study. Recent data from human autopsy studies confirm that β -cell mass is decreased in patients with type 2 diabetes [3]. A major defect underlying this decrease is increased β -cell apoptosis, while new islet formation and β -cell replication are normal. Thus, therapeutic agents like the incretin hormones, which in animal and in vitro studies have been shown to inhibit apoptosis and increase β -cell proliferation/islet replication, constitute a novel therapeutic strategy in the management of type 2 diabetes [4]. In the short term, through their β -cell trophic effects, the incretin agents improve β -cell function and glycemia. In the long term, if these β -cell trophic effects are sustained, the potential exists to possibly reverse or stabilize the disease process.

In clinical studies, both the GLP-1 receptor agonists and the DPP-4 inhibitors have been shown to improve β -cell function in humans. The tests used to evaluate β -cell function in these studies include the frequently sampled intravenous glucose tolerance test (FSIVGTT), the hyperglycemic clamp with arginine stimulation technique, and the meal tolerance test with modeling analysis to determine the insulin secretion rate (ISR).

The acute effects of exenatide on β -cell function and first-phase insulin secretion were studied by Fehse and colleagues [5] in subjects with type 2 diabetes and in nondiabetic volunteers. In this study, 13

patients with type 2 diabetes (hemoglobin A_{1c} [HbA_{1c}] ~6.6%) treated with diet, metformin, or acarbose were compared with 12 healthy, weight-matched subjects with normal glucose tolerance. After an intravenous (IV) glucose challenge, the nondiabetic control subjects had a brisk first-phase insulin secretion that was significantly diminished in the subjects with type 2 diabetes. When the subjects with diabetes were pretreated with IV exenatide for 180 minutes, they had an insulin-secretory pattern similar to healthy subjects in both first (0 to 10 minutes) and second (10 to 180 minutes) phases after glucose challenge. The most common adverse event with exenatide was moderate nausea. The authors concluded that acute short-term exposure to exenatide can restore the insulin-secretory pattern in response to acute rises in glucose concentrations in patients with diabetes, who, in the absence of exenatide, do not display any significant first phase of insulin secretion. Similar results were obtained by Chang and colleagues [6] using liraglutide (7.5 μ g/kg) in a randomized, double-blind, placebo-controlled, crossover study in 10 subjects with type 2 diabetes. In this study, β -cell sensitivity was assessed by a graded glucose infusion protocol. ISRs were estimated by deconvolution of C-peptide levels and findings were compared with those in 10 nondiabetic volunteers during the same glucose infusion protocol. In subjects with type 2 diabetes, liraglutide, in comparison with placebo, significantly increased insulin and C-peptide levels, the ISR area under the curve, and the slope of ISR versus plasma glucose, with values similar to those of nondiabetic control subjects. Thus, in this study, liraglutide (7.5 μ g/kg) restored β -cell responsiveness to physiologic hyperglycemia in subjects with type 2 diabetes [6].

In contrast to the above studies, which demonstrated the acute β -cell effects of a GLP-1 receptor agonist, Vilsbøll and coworkers [7] studied the longer-term effects of GLP-1 agonism on β -cell function with liraglutide. They randomized 39 patients with type 2 diabetes (HbA_{1c} ~ 8.5%) to treatment with liraglutide 0.65, 1.25, or 1.9 mg/day or placebo for 14 weeks. First- and second-phase insulin release were measured by means of the insulin-modified FSIVGTT and arginine-stimulated insulin secretion was measured during a hyperglycemic clamp (360 mg/dL). After 14 weeks, the HbA_{1c} in the liraglutide

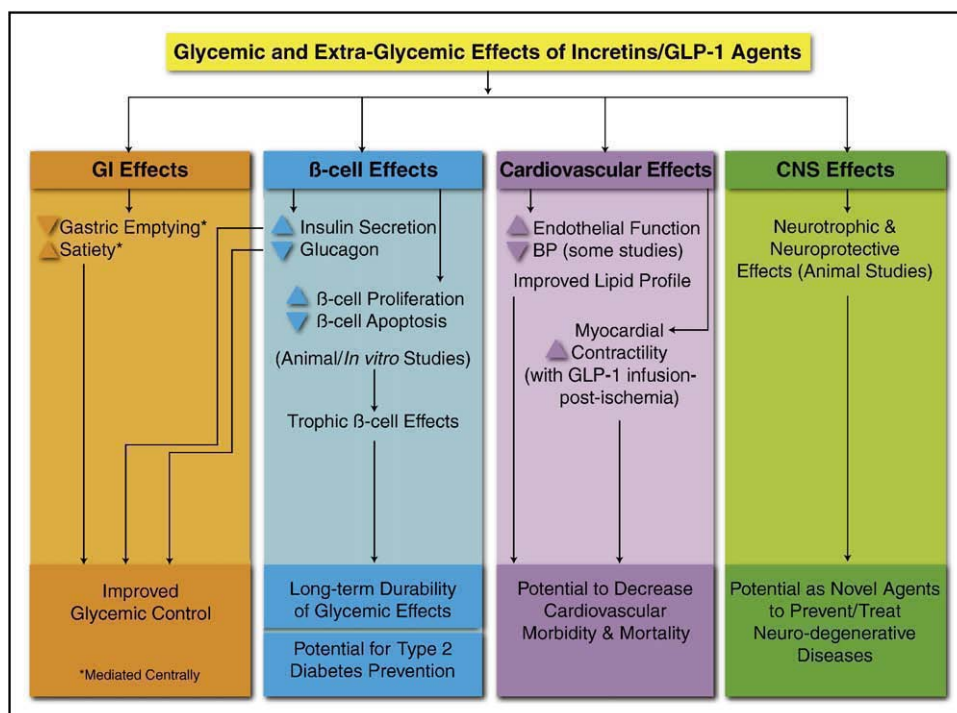


Figure 1. Glycemic and extraglycemic effects of incretins/glucagonlike peptide-1 (GLP-1) agents. BP = blood pressure; CNS = central nervous system; GI = gastrointestinal. *Mediated centrally.

groups decreased by 1% to 1.5% as compared with placebo. In addition, the 2 highest doses of liraglutide (1.25 and 1.9 mg/day) significantly increased first-phase insulin secretion, by 118% and 103%, respectively. Second-phase insulin secretion was significantly increased only in the 1.25-mg/day group compared with placebo. Arginine-stimulated insulin secretion also increased significantly at the 2 highest dose levels compared with placebo, by 114% and 94%, respectively. Thus, in this study, 14 weeks of treatment with liraglutide resulted in improvements in first- and second-phase insulin secretion, together with improvements in arginine-stimulated insulin secretion during hyperglycemia. Of note, in this study, there was no significant treatment effect on insulin sensitivity.

The effects of DPP-4 inhibition on β -cell function were studied by Xu and associates [8], who assessed the effect of sitagliptin on pancreatic β -cell function by using a model-based analysis. They analyzed data from 3 large placebo-controlled clinical studies ($N = 278$) that examined sitagliptin 100 mg once daily as monotherapy or as add-on to metformin therapy over 18 or 24 weeks. In these studies, subsets of patients underwent additional blood sampling as part of a 9-point meal tolerance test performed at baseline and at the end of the study. Using the C-peptide minimal model, the authors estimated the following components of the ISR: basal ISR (at basal glucose concentrations), static ISR (ISR at above basal glucose concentrations following a meal), and dynamic ISR (ISR in response to the rate of increase above basal glucose concentrations following a meal). They also calculated the total responsivity index (average ISR over the average glucose concentration as a function of the above 3 components). The results indicated that when administered in combination with ongoing metformin therapy or as monotherapy, sitagliptin was not only associated with substantial reductions in postprandial glycemic excursions but also produced significant improvements in the static ISR and the average ISR over the average glucose concentrations. For dynamic ISR, there was a numerical, but not statistically significant, improvement with sitagliptin relative to placebo. Further, treatment with sitagliptin increased basal ISR, but the difference relative to placebo was only significant with monotherapy. The authors concluded that in this model-based analysis, sitagliptin improved β -cell function relative to placebo in both fasting and postprandial states in patients with type 2 diabetes.

Vildagliptin's effects on β -cell function have also been demonstrated by using a similar model-based assessment. Mari and associates [9] examined the effects of 28 days of treatment with vildagliptin 100 mg bid ($n = 9$) versus placebo ($n = 11$) on β -cell function in patients with diabetes by using a 24-hour meal tolerance test and a mathematical model that describes the ISR as a function of glucose levels (β -cell dose response); the change in glucose with time (derivative component); and a potentiation factor, which is a function of time and may reflect the actions of nonglucose secretagogues and other factors. At the end of treatment, vildagliptin significantly increased the ISR. However, the slope of the β -cell dose response, the derivative component, and the potentiation factor were not affected. The authors concluded that vildagliptin improves β -cell function in patients with diabetes by increasing the insulin secretory tone.

Of note, all of the above studies have evaluated the effects of the incretins on meal-stimulated β -cell function. This would seem logical because the incretins increase/potentiate postmeal GLP-1 levels. However, it has been noted that the DPP-4 inhibitors, in addition to lowering postprandial glycemia, also lower fasting glucose levels, and to an extent greater than what would be expected of drugs working mainly in the postprandial state. To better understand the actions of DPP-4 inhibitors in regulating basal β -cell function, D'Alessio and coworkers [10] studied 39 subjects with type 2 diabetes that was well controlled by metformin or diet ($HbA_{1c} \sim 6.7\%$). Subjects were randomized to treatment with vildagliptin or placebo, and IV glucose stimulus tests (rather than meal tolerance tests or oral glucose tolerance tests) were used to determine

fasting β -cell function. The use of an IV glucose stimulus eliminates the incretin response and determines the effect of the drug itself on fasting β -cell function [10]. After 3 months, the declines in HbA_{1c} (6.7% to 6.3% and 6.5% to 6.3%) and fasting glucose (119 to 108 mg/dL and 126 to 119 mg/dL [$1 \text{ mg/dL} = 0.5551 \text{ mmol/L}$]) were similar in the vildagliptin and placebo groups. Fasting levels of insulin and C-peptide (relatively insensitive markers of β -cell function) also were not changed from baseline in either group. However, vildagliptin treatment caused a significant improvement in the acute insulin response to glucose, the sensitivity of insulin release to glucose, and maximal arginine stimulated β -cell secretion, measures of insulin secretion that are known to be affected in type 2 diabetes.

It is important to note that the above studies do not address the durability of effect that the incretins have on β -cell function. It is possible that their effects on insulin secretion are primarily due to a potentiation/prolongation of the endogenous incretin effect after a meal or glucose challenge in the presence of the drug. It is not possible to determine whether the improvements in insulin secretion are due to direct trophic effects on the β -cell per se, independent of the ongoing incretin effect on insulin secretion. A recent study with vildagliptin was designed to address this question and evaluate the effects of the incretins on β -cell function after a washout period to determine whether the effects are sustained even after discontinuation of the drug for a period of time [11]. This study was performed not in subjects with diabetes, but rather in subjects with impaired fasting glucose (IFG), or prediabetes. A total of 22 subjects with IFG received placebo for 2 weeks (run-in period) followed by vildagliptin 100 mg daily for 6 weeks (treatment period) and then placebo for 2 weeks (washout period). An FSIVGTT was performed at 2, 8, and 10 weeks to determine the acute insulin response to glucose (AIRg), insulin sensitivity index (Si), and the disposition index ($\text{AIRg} \times \text{Si}$) as measures of β -cell function. A 2-hour meal tolerance test (MTT) was also performed to determine postprandial glycemia. After 6 weeks of vildagliptin treatment, although fasting plasma glucose did not change, the incremental area-under-the-glucose curve (AUC) during the MTT was significantly decreased, by 20%. More importantly, the AIRg increased by 28%, the Si improved by 25%, and the disposition index improved by an impressive 69%. However, none of these effects was sustained after washout, suggesting that the incretin effect on β -cell function was present only during active treatment with the drug. It is possible, however, that a treatment period of 6 weeks is too short to produce a durable and sustained increase in β -cell mass. Even so, the results from this study are encouraging because 6 weeks of treatment with the DPP-4 inhibitor vildagliptin significantly improved insulin sensitivity and β -cell function and led to improved postprandial glycemia in subjects with prediabetes, who are well known to have β -cell dysfunction. If these effects persist with longer-term treatment, it is possible that vildagliptin treatment may prevent progression to diabetes in subjects with prediabetes. Only a long-term clinical trial will be able to definitively answer this important question.

Currently, studies are in progress to determine the longer-term effects of the incretin hormones on functional β -cell mass and also to determine whether there are differences between the GLP-1 agonists and the DPP-4 inhibitors in terms of these effects [12,13].

1.2. Effects on Insulin Sensitivity

Along with impaired insulin secretion, decreased insulin sensitivity is a major pathophysiologic abnormality in patients with type 2 diabetes. Although it is well established that the incretin hormones increase insulin secretion, their effects on insulin action and glucose effectiveness (glucose-mediated uptake) are less clear. In animal studies, exenatide treatment has been shown to improve insulin sensitivity [14]. In humans, the results are mixed: some studies show benefits and others show none. An early hyperinsulinemic

euglycemic-clamp study (1992) showed that GLP-1 infusion significantly increased insulin-mediated glucose utilization in patients with type 1 diabetes (saline vs. GLP-1, 7.2 ± 0.5 vs. 8.6 ± 0.4 mg/kg per min) [15]. However, in a subsequent study, Meneilly and colleagues [16] found that GLP-1 does not augment insulin-mediated glucose uptake in lean patients with type 1 diabetes. In healthy, nondiabetic individuals, D'Alessio and colleagues [17] demonstrated that an IV infusion of GLP-1 improved insulin-independent glucose disposition during an FSIVGTT (an increase in glucose effectiveness from 1.77 ± 0.11 to $2.65 \pm 0.33 \times 10^{-2}/\text{min}$). However, a subsequent study found that neither exendin-4 nor GLP-1 alters insulin action in nondiabetic human subjects [18].

In patients with type 2 diabetes, the effects of the incretins in improving insulin action and glucose effectiveness are also mixed. In 1 study in 12 subjects with type 2 diabetes, Vella and coworkers [19] found that when insulin and glucagon concentrations are matched, GLP-1 has negligible effects on either insulin action or glucose effectiveness in people with type 2 diabetes. Similar results were obtained by Vilsbøll and associates, [20] who demonstrated that although 14 weeks of treatment with liraglutide resulted in improvements in first- and second-phase insulin secretion, there was no significant treatment effect on glucose effectiveness or insulin sensitivity. However, in a study in older subjects with diabetes, Meneilly and colleagues [21] found that GLP-1 significantly enhanced non-insulin-mediated glucose disposal (glucose effectiveness) during hyperglycemia (~ 200 mg/dL) by 15%. The discrepancy between results obtained in the above studies may be a result of the differences in the study population, differences in the experimental design, and also differential effects of GLP-1 on glucose disposal at different levels of glucose and insulin.

1.3. Effects on Gastric Emptying, Appetite, and Food Intake

It is well established that the GLP-1 receptor agonists and the DPP-4 inhibitors significantly improve glycemia by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. However, some of their glycemic effects may also be mediated through their effects on gastric emptying, satiety, and food intake. Several studies have demonstrated that peripheral infusions of GLP-1 significantly enhance satiety and decrease food intake in lean healthy volunteers and obese nondiabetic and diabetic subjects [22–24]. In one of the early studies, Flint and coworkers [22] demonstrated that GLP-1 infusion (as compared with a saline infusion) significantly enhanced satiety and fullness and reduced spontaneous energy intake during an ad libitum meal by about 12%. Similar results were seen in a randomized, blinded, crossover study in obese, nondiabetic subjects in whom an 8-hour infusion of GLP-1 decreased feelings of hunger and reduced ad libitum energy intake at lunch and dinner by 21% [23]. In this study, gastric emptying (using a paracetamol absorption technique) was also significantly decreased. In a similarly designed study in 12 subjects with type 2 diabetes, Gutzwiller and coworkers [24] demonstrated that GLP-1 infusion enhanced satiety and fullness and reduced energy intake by 27% compared with saline. The exact mechanisms through which peripherally administered GLP-1 affects satiety and food intake are not yet known. GLP-1's ability to inhibit gastric emptying, leading to gastric distension, could cause a decrease of food intake through activation of vagal afferents, resulting in signals from the stomach to the brain and in the perception of fullness and satiety [25]. Vagal afferents could also be activated by receptors in the portal bed [26]. Another possible mechanism is the direct activation of brain/hypothalamic GLP-1 receptors by intracerebroventricular GLP-1 administration, which has been shown to inhibit food intake in animal studies [27]. Recent studies now show that GLP-1 is able to cross the blood–brain barrier [28]. Thus, it is reasonable to postulate that peripherally administered GLP-1 exerts at least a part of its effects through the brain GLP-1 receptors.

Irrespective of the mechanisms through which GLP-1 activates the hypothalamic centers controlling energy intake, GLP-1 agonism leads to an increase in satiety and a decrease in food intake. However, it is important to note that these food-regulatory effects are only seen with the GLP-1 agonists (exenatide and liraglutide) and not with the DPP-4 inhibitors. From the evidence to date, only the GLP-1 agonists (exenatide and liraglutide) have any significant effects on gastric emptying, appetite, and food intake. Furthermore, these effects translate into significant reductions in body weight with the clinical use of the GLP-1 agonists as compared with neutral effects on body weight with the DPP-4 inhibitors. This differential food-regulatory effect of the incretins has been elegantly demonstrated in a recent study by DeFronzo and colleagues [29] in patients with type 2 diabetes. They directly compared exenatide (a GLP-1 agonist) and sitagliptin (a DPP-4 inhibitor) in a 4-week, randomized, double-blind, crossover study in 61 metformin-treated patients with type 2 diabetes. Caloric intake was assessed by food consumption during an ad libitum dinner, and gastric emptying was assessed by acetaminophen absorption. In this study, exenatide ($5 \mu\text{g}$ bid for 1 week and $10 \mu\text{g}$ bid for another week) significantly slowed gastric emptying (acetaminophen AUC ratio exenatide to sitagliptin: 0.56 ± 0.05) and reduced total caloric intake compared with sitagliptin 100 mg daily (-134 ± 97 kcal vs. $+130 \pm 97$ kcal [$1 \text{ kcal} = 4.2 \text{ kJ}$]; $N = 25$). In addition, in this 4-week crossover study, although reduction in fasting glucose was similar with exenatide and sitagliptin (-15 ± 4 mg/dL vs. -19 ± 4 mg/dL), postprandial glucose parameters were significantly lower with exenatide than sitagliptin. Exenatide also had a more potent effect than sitagliptin in increasing insulin secretion and reducing postprandial glucagon secretion in these metformin-treated patients with type 2 diabetes [29]. Of note, in this study, the mean postprandial plasma exenatide concentration was approximately 4-fold greater than the mean postprandial GLP-1 concentration with sitagliptin 100 mg daily. It is conceivable that this pharmacologic increase after exenatide $10 \mu\text{g}$ bid results in greater GLP-1 receptor activation and downstream effects than is seen after the physiologic increases in plasma GLP-1 levels seen after the administration of sitagliptin 100 mg daily. The adverse gastrointestinal effects of nausea and vomiting were also significantly worse in the exenatide group (possibly related to the more aggressive titration of the exenatide dose from $5 \mu\text{g}$ to $10 \mu\text{g}$ bid after 1 week). It is important to note that this was only a short-term study and that there was no washout period between the 2 treatment periods.

As compared with exenatide, the other GLP-1 receptor agonist in clinical trials, liraglutide, has not demonstrated consistent effects on gastric emptying, appetite, or body weight. In an 8-week randomized, double-blind, placebo-controlled study in 33 patients with type 2 diabetes, despite significantly improved glycemic control with liraglutide, (-0.33% vs. placebo $+0.47\%$), there was no significant change in body weight (liraglutide -0.7 kg vs. placebo -0.9 kg) and also no effects on appetite and food intake [30]. In another double-blind, placebo-controlled crossover design study, liraglutide ($6 \mu\text{g}/\text{kg}$) was administered subcutaneously once daily to 13 patients with type 2 diabetes. In this study, 1 week's treatment with liraglutide markedly improved 24-hour glycemia and α - and β -cell function and reduced endogenous glucose release. However, gastric emptying was not influenced at the dose of liraglutide used [31]. The differences in results with liraglutide as compared with exenatide for effects on gastric emptying and appetite may be due to different populations being studied and the relatively lower doses of liraglutide used. To date, there have been no head-to-head studies published comparing the food-regulatory effects of liraglutide and exenatide.

As compared with the short-term studies above, in longer term studies liraglutide monotherapy and in combination with metformin has been associated with body weight reductions of ~ 2 – 2.5 kg as compared with a gain in weight of ~ 1 kg with glimepiride (the active comparator drug) [32,33]. Of note, in one of these studies (Garber and

colleagues [33]), reductions in body weight were not different in those who did or did not have nausea for >7 days (a known side effect of liraglutide and GLP-1 agonists).

1.4. Cardiovascular Effects

Type 2 diabetes is well known to accelerate the clinical course of atherosclerosis and is associated with significant cardiovascular morbidity and mortality. Indeed, coronary heart disease mortality is increased 2- to 4-fold in the diabetic population, and diabetes has been termed a coronary artery disease “risk equivalent” [34]. The higher prevalence of atherosclerosis in diabetes has been associated with several metabolic abnormalities including hyperglycemia, insulin resistance, dyslipidemia, and myocardial and endothelial dysfunction [35]. Because high-affinity receptors for GLP-1 are present in the heart and vascular tissue, it is conceivable that the incretins, at least in part through their pleiotropic GLP-1-mediated effects, may improve cardiovascular function [36]. The data emerging from recent studies appear to support a potential role for GLP-1 in improving cardiovascular risk.

1.4.1. Effects on Myocardial Function

The adult human heart is able to use several substrates to generate high-energy phosphates for its energy requirements. Although free fatty acids are the preferred substrate in normal times (because of the higher yield of adenosine triphosphate when fully oxidized), under conditions of metabolic stress and limited oxygen availability, glucose becomes a more energy-efficient fuel (because this process requires less oxygen). Because GLP-1 plays an important role in glucose metabolism and its receptors are present in the myocardium, it is certainly feasible that GLP-1 agonists may have beneficial myocardial effects. Several small studies have demonstrated beneficial effects of GLP-1 infusion in patients undergoing angioplasty and coronary artery bypass grafting (CABG) and in those with chronic heart failure. In a single-center, pilot study, 10 high-risk patients (5 with diabetes) with acute myocardial infarction and left ventricular (LV) systolic dysfunction (after successful reperfusion with primary angioplasty) were treated with a 72-hour GLP-1 infusion. When compared to a control group of 11 subjects (4 with diabetes) with similar risk factors (who chose not to receive the infusion), the use of GLP-1 significantly improved regional wall motion at the infarct site; increased global LV function from $29\% \pm 2\%$ to $39\% \pm 2\%$ ($P < 0.01$), and was associated with lower in-hospital mortality (27% vs. 10%). Minor side effects included nausea, vomiting, and asymptomatic hypoglycemia [37]. In a double-blind, placebo-controlled study, 20 patients with coronary artery disease and preserved LV function who were scheduled to undergo CABG were randomized to either GLP-1 infusion or saline, which was started 12 hours before surgery and continued for 48 hours. The perioperative use of GLP-1 infusion in this study resulted in better glycemic control and comparable hemodynamic recovery with lesser requirements for insulin and inotropic/vasoactive infusions. There also were fewer arrhythmias requiring antiarrhythmic treatment in the GLP-1 group. No nausea or vomiting was reported in this study, and there was 1 episode of asymptomatic hypoglycemia in the GLP-1 group versus 2 episodes in the control group [38].

As compared with short-term infusions of GLP-1, which showed benefits in the studies above, in a recent case-control study, a chronic (5-week) infusion of GLP-1 was given to 12 patients with severe New York Heart Association (NYHA) class III–IV heart failure. In these patients, chronic GLP-1 infusion was shown to significantly improve LV function, functional status, and quality of life as compared with a similar group of 9 patients who received standard heart failure therapy without GLP-1 infusion [39].

Despite the fact that only 1 of the above studies was a randomized, placebo-controlled study, the results from these studies nevertheless

highlight the potential of GLP-1 infusions to improve myocardial function. So far, however, no human data are available concerning the possible beneficial effects of the GLP-1 agonists (exenatide and liraglutide) or the DPP-4 inhibitors (sitagliptin and vildagliptin) on myocardial function. In animal studies, both exenatide and liraglutide have demonstrated protective effects against ischemic myocardial injury, and in rodent and murine models, have been shown to reduce infarct size and improve mechanical performance [40]. A randomized study has been planned to evaluate the effect of exenatide compared with insulin glargine on cardiac function and metabolism in patients with type 2 diabetes with congestive heart failure [41]. If the results of the studies with the incretin hormones are similar to those obtained with GLP-1 infusion, this may portend a new role for the incretin hormones as adjunctive postischemic conditioning agents in clinical settings such as acute myocardial infarction treatment (thrombolysis or angioplasty) or CABG.

1.4.2. Effects on Endothelial Function

Endothelial dysfunction is strongly associated with insulin resistance and type 2 diabetes mellitus and may contribute to the adverse cardiovascular morbidity seen in patients with diabetes. As already mentioned, GLP-1 receptors are present on endothelial cells, and some studies suggest that GLP-1 can improve endothelial dysfunction in patients with type 2 diabetes and coronary heart disease. In a recent study, Nyström et al evaluated the effects of recombinant GLP-1 versus saline in a randomized crossover study in 12 patients with type 2 diabetes and stable coronary artery disease compared with 10 healthy subjects. Endothelial function was ultrasonographically measured at the brachial artery using postischemic flow-mediated vasodilation (FMD). Insulin sensitivity was also measured by the hyperinsulinemic isoglycemic clamp technique. GLP-1 infusion significantly increased relative changes in brachial artery diameter from baseline FMD ($3.1\% \pm 0.6\%$ to $6.6\% \pm 1.0\%$). However, there were no significant effects on insulin sensitivity. Of note, in the healthy subjects, GLP-1 infusion had no effects on either FMD or insulin sensitivity. The authors concluded that GLP-1 improves endothelial dysfunction but not insulin resistance in patients with type 2 diabetes with coronary heart disease [42]. At present, it is not known if any of the current incretin agents affect endothelial function. A clinical study currently recruiting subjects has been designed to assess the effects of liraglutide on endothelial function as determined by changes in forearm blood flow (measured by ultrasound brachial FMD) in subjects with type 2 diabetes managed with dietary and lifestyle changes or treated with metformin alone [43].

Further studies are needed to determine if the beneficial effects on endothelial function seen with GLP-1 infusion are confirmed and replicated with the GLP-1 agonists and DPP-4 inhibitors, and more importantly, to learn whether these changes have any therapeutic implications.

1.4.3. Effects on Blood Pressure

The effects of the incretins on blood pressure are mixed: small beneficial effects have been seen in some studies and neutral effects in others. In some animal studies, there actually is an increase in both systolic and diastolic blood pressure during GLP-1 treatment, possibly mediated by a central increase in sympathetic outflow [44,45]. However, in a study in Dahl salt-sensitive rats, which exhibit many phenotypic traits associated with salt-sensitive hypertension in humans, Yu and colleagues [46] showed that chronic GLP-1 treatment has antihypertensive and cardiac/renoprotective effects, mainly due to its diuretic and natriuretic effects, rather than improving insulin resistance. In another study in mice, GLP-1 was shown to have significant vasodilatory effects [36]. These differences in animal studies are possibly due to differences in species, dose, treatment duration, and other factors. In an early study in humans, 48-hour continuous subcutaneous infusion of GLP-1 in patients with type 2

diabetes slightly decreased both diastolic and systolic blood pressure levels (in addition to reducing appetite and lowering fasting and postmeal plasma glucose) [47]. In the clinical studies with the GLP-1 agonists and DPP-4 inhibitors so far, there have been modest beneficial changes. With exenatide, in the short-term studies (3 to 6 months), there was either no change in blood pressure [48,49] or modest decreases of 3 to 4 mm Hg in systolic blood pressure and ~2 mm Hg in diastolic blood pressure [50]. In the long-term, open-label, follow-up studies, decreases of ~3 mm Hg systolic blood pressure and ~2 mm Hg diastolic blood pressure have been seen over 3 years [51]. With liraglutide, in one 14-week study [20] there was a 5- to 8-mm Hg reduction in systolic blood pressure (and no change in diastolic blood pressure), and in another 26-week study of liraglutide in combination with metformin and a thiazolidinedione, there was a 5-7 mm Hg reduction of systolic blood pressure, but no change in diastolic blood pressure [52]. The DPP-4 inhibitor sitagliptin is also associated with small beneficial effects on blood pressure. In a randomized, double-blind, placebo-controlled, 3-period crossover study, 19 nondiabetic patients with mild-to-moderate hypertension and on stable treatment with antihypertensive medication received sitagliptin 100 mg bid, 50 mg bid, or placebo for 5 days with a ≥ 7 -day washout interval between periods. Sitagliptin produced small but statistically significant reductions of 2 to 3 mm Hg in 24-hour ambulatory blood pressure measurements acutely (day 1) and at steady state (day 5) and was generally well tolerated [53]. An ongoing study is currently evaluating the effect of sitagliptin not only on hypertension but also on arterial stiffness, oxidative stress, and inflammation [54]. Thus most of the data suggest that the incretin-based therapies have either a neutral or occasionally a modest beneficial effect on blood pressure.

1.4.4. Effects on Lipids

The effect of the incretin hormones on serum lipids, like their effects on blood pressure, are either neutral or beneficial, with small, nonsignificant decreases in low-density lipoprotein (LDL) cholesterol, increases in high-density lipoprotein (HDL) cholesterol, and occasionally significant decreases in fasting triglyceride levels. It is intriguing that although the GLP-1 agonists are usually associated with a decrease in body weight, this does not always translate into significant improvements in the fasting lipid profile, as might be expected. Also of interest is the fact that although the incretin hormones do not have appreciable effects on fasting lipid levels, they do have significant effects on postprandial lipemia.

In an early study in 14 nondiabetic healthy human volunteers, Meier and coworkers [55] studied the effects of GLP-1 on gastric emptying and postprandial lipid levels. After an IV infusion of GLP-1 or placebo over 390 minutes in the fasting state, subjects were served a solid test meal and gastric emptying was determined using a [13] C-labeled sodium octanoate breath test. As expected, GLP-1 administration significantly lowered fasting and postprandial glycemia and delayed gastric emptying. Interestingly, during GLP-1 administration, insulin-secretory responses were higher in the fasting state but lower after meal ingestion. More importantly, the postprandial increase in triglyceride levels was completely abolished by GLP-1 and the plasma concentrations of free fatty acids were suppressed by 39% in the fasting state and by 31% after meal ingestion. The authors concluded that GLP-1 improves postprandial lipemia, probably due to delayed gastric emptying and insulin-mediated inhibition of lipolysis. Other possible mechanisms contributing to the lipid-lowering effects of GLP-1 that cannot be excluded are an increased clearance or even reduced endogenous synthesis of triglycerides. It is important to note that in this study the subjects received only a single IV infusion of GLP-1, and only postprandial lipids were measured. Similar blunting of postprandial triglyceride levels were obtained by Cervera and associates [56] in a study using IV exenatide in 12 subjects with type 2 diabetes. In these patients a single IV infusion of exenatide resulted in an approximate 10% reduction from baseline triglyceride levels, as opposed

to an approximately 15% increase in postprandial triglyceride levels with IV saline after a mixed meal.

In contrast to the acute effects of exenatide to lower postmeal lipemia, short-term (3 to 6 months) studies with exenatide have not shown any significant improvements in the fasting lipid profile. However, longer-term follow-up of the participants of these short-term studies have shown significant improvements in the fasting lipid profile along with sustained and continued decreases in body weight. In a 3-year follow-up study, Klonoff and coworkers [51] noted a mean 5.3-kg weight loss at 3 years along with a 12% decrease in triglycerides, a 24% increase in HDL cholesterol, and a 6% decrease in LDL cholesterol. In another long-term follow-up study, Blonde and colleagues [57] recorded a mean weight loss of 3.5 kg along with a 16% decline in triglycerides and a 12% increase in HDL. Interestingly, in this study, the authors noted a definite correlation between decrease in body weight and improvements in the lipid profile. Those who lost the most weight had the greatest decreases in triglyceride levels and increases in HDL cholesterol levels. Decreases in fasting triglycerides have also been demonstrated with liraglutide [20]. In a 14-week study, liraglutide 1.9 mg/day was associated with a 2.99-kg mean reduction in body weight and a 22% decrease in fasting triglyceride levels.

The lipid effects of the DPP-4 inhibitor vildagliptin were evaluated in a single-center, double-blind study [58] in 31 drug-naïve patients with type 2 diabetes who were randomized to vildagliptin (50 mg bid or placebo). Lipid, glucose, insulin, glucagon, and GLP-1 responses to a fat-rich mixed meal were determined for 8 hours postprandially before and after 4 weeks of treatment. Compared with placebo, treatment with vildagliptin significantly decreased the postmeal triglyceride and chylomicron increments by 22% to 91%, mainly due to a decrease in intestinally derived apolipoprotein B-48-containing particles. The authors speculated that the influence of vildagliptin on postprandial lipemia may reflect incretin-mediated changes in pancreatic hormone secretion, an improved metabolic state, reduced insulin resistance secondary to improved islet function, incretin-mediated effects slowing gastric emptying, or perhaps even direct effects of GLP-1 and/or GIP on lipoprotein metabolism. Of note, there was no change in fasting triglyceride levels although 4 weeks of vildagliptin lowered the HbA_{1c} by 0.4% from a baseline of 6.7%.

Currently, although no data are available on the effects of sitagliptin on postmeal lipemia, a study is under way that is designed to examine its effects on postprandial lipemia in patients with type 2 diabetes [59]. However, data are available from a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with type 2 diabetes in whom there was a significant reduction in fasting triglycerides with sitagliptin compared with placebo, mainly due to stable mean triglyceride levels in the sitagliptin group compared with a significant increase of 12% from baseline in the placebo group. No significant between-treatment differences were detected in the other lipid parameters [60].

Delayed gastric emptying is one of the proposed mechanisms by which the incretins could reduce postprandial lipemia. Because there is greater inhibition of gastric emptying after exenatide administration than after sitagliptin administration (discussed above in the gastric emptying section), it should follow that there would be greater reductions in postprandial lipemia with exenatide administration than after sitagliptin administration. This is exactly what was seen in a double-blind, randomized, crossover, multicenter study conducted in metformin-treated patients with type 2 diabetes. A total of 61 patients received exenatide (5 μ g bid for 1 week, then 10 μ g bid for 1 week) or sitagliptin (100 mg every morning) for 2 weeks. After 2 weeks, patients crossed over to the alternative therapy. Gastric emptying was assessed by acetaminophen absorption and postprandial triglycerides were assessed after a standard meal test. Exenatide administration significantly slowed gastric emptying (acetaminophen AUC ratio exenatide to sitagliptin, 0.56 ± 0.05) and reduced postprandial triglycerides (AUC ratio exenatide to sitagliptin, 0.90 ± 0.04) [29].

It is clear from the cardiovascular effects discussed above that the effects of the incretin-based therapies exenatide, liraglutide, sitagliptin, and vildagliptin on blood pressure and lipids are modest at best. However, given that, in addition, the incretin hormones favorably influence myocardial metabolism and endothelial function, there is reason to believe that these beneficial short-term effects on surrogate markers and myocardial/endothelial function may translate in the longer term to reduced cardiovascular events like myocardial infarction and stroke. To determine this, however, large, randomized, controlled clinical trials will need to be conducted.

1.5. Central Nervous System Effects

It is well known that GLP-1 is not solely a gastrointestinal hormone and that it also has actions in other tissues including the central nervous system. In rat studies, GLP-1 has been shown to be synthesized in neurons in the hindbrain, and receptors for GLP-1 are highly expressed in various regions of the hypothalamus including the arcuate nucleus and the paraventricular nucleus [61]. Of note, although the sites of production of GLP-1 in the central nervous system are limited, GLP-1-immunoreactive fibers and GLP-1 receptors are widespread throughout the brain. In humans, *in vitro* GLP-1 receptor autoradiography [62] has revealed that the brain GLP-1 receptor mRNA is widely distributed throughout the cerebral cortex, hypothalamus (mainly ventromedial and arcuate nuclei), hippocampus, thalamus, caudate-putamen, and globus pallidum. In another study in humans, the most striking receptor expression was observed in the neurohypophysis, where the highest GLP-1 receptor density of all tissues was measured [63]. Thus, in addition to being an incretin hormone, GLP-1 may also be a brain neuropeptide. There also are growing data (from animal and human studies) linking central nervous system GLP-1 receptors to diverse physiologic functions, including gastric emptying and the control of food intake [64], regulation of glucose homeostasis by modulating both insulin secretion and glucose production [65], mediation of adaptive hypothalamic stress responses [66], and autonomic regulation of blood pressure and heart rate [44]. Recently, there have even been reports of neurotrophic and neuroprotective GLP-1 effects and effects on learning behavior [67,68].

1.5.1. Central Nervous System Effects on Gastric Emptying, Food Intake, and Satiety

There is growing evidence that the ability of GLP-1 and the incretin hormones to affect gastric emptying, satiety, and food intake is mediated centrally. Inhibition of gastric emptying by GLP-1 is mediated by vagal afferents and leads to gastric distension [69]. This in turn leads to further activation of vagal afferents and signals from the stomach to the brain, which leads to a perception of fullness and satiety [25]. Peripheral vagal afferent signals may also be activated by GLP-1 receptors in the hepatoportal bed [26]. It is also possible that there is direct activation of brain/hypothalamic GLP-1 receptors since intracerebroventricular GLP-1 administration has been shown to inhibit food intake in animal studies [27]. The unanswered questions are whether peripherally administered (or intestinally produced endogenous GLP-1) is mediating its effects through vagal (and other) afferents or whether peripheral GLP-1 is able to access the blood–brain barrier-free brain site, the area postrema, which receives direct information from the gastrointestinal tract via vagal afferents and which has projections to and from the nucleus of the solitary tract and hypothalamic paraventricular nucleus [70]. Recent studies now show that GLP-1 is able to cross the blood–brain barrier [28]. Yet another possibility is that the central effects are mediated by locally produced GLP-1 in the brain. Further studies are needed to answer the above questions and also to determine whether the central and

peripheral GLP-1 signaling systems are separate, complementary, or synergistic.

In the context of central GLP-1 effects on the brain and hypothalamic neurons regulating food behavior, it is interesting to note the results of a recent study in which positron emission tomography (PET) with 2-[¹⁸F]-2-fluoro-2-deoxy-D-glucose (FDG) was used to evaluate the effect of GLP-1 (7-36) amide on cerebral glucose metabolism in 10 healthy human subjects. Intravenous administration of GLP-1 (7-36) amide increased circulating levels of this peptide and reduced plasma glucagon concentrations but had no effect on plasma glucose or insulin levels. The authors, however, noted that peripheral administration of the GLP-1 agonist significantly reduced carbohydrate metabolism in selective areas of the brain, including the hypothalamus and brainstem, areas that both are involved in feeding behavior and rich in GLP-1 receptors. These findings open new doors for studying the effects of GLP-1 in humans under control and pathophysiologic conditions [62].

The clinical effects of the incretins in regulating gastric emptying and satiety have already been discussed above under “Effects on Gastric Emptying, Appetite, and Food Intake.”

1.5.2. Central Nervous System Effects on Glucose Homeostasis

The traditional view is that peripheral GLP-1 modulates glucose homeostasis and central GLP-1 affects food intake and satiety. However, in a recent study in a rat model, Sandoval and coworkers [65] demonstrated that central administration of GLP-1 (into the third cerebral ventricle) actually augments glucose-stimulated insulin secretion. They also found that administration of GLP-1 directly into the arcuate nucleus (but not the paraventricular nucleus) of the hypothalamus reduced hepatic glucose production. Consistent with a role for GLP-1 receptors in the arcuate nucleus, GLP-1 receptor mRNA was found to be expressed in 68% of arcuate neurons. In this study, the authors noted a site-specific effect of GLP-1 on food intake. Injection of GLP-1 into the arcuate nucleus (unilateral or bilateral) had no effect on food intake. However, cumulative food intake was significantly reduced after GLP-1 injection (compared with an equal volume of saline) directly into the paraventricular nucleus. These findings reveal that GLP-1 receptors within the arcuate nucleus regulate blood glucose without affecting food intake while GLP-1 receptors within the paraventricular nucleus regulate food intake without affecting blood glucose [65].

1.6. Neuroprotective and Neurotrophic Effects

Since GLP-1 and the GLP-1 receptor are expressed in most parts of the brain, it would be expected that GLP-1 agonism might have beneficial effects on brain physiology and function. This has been borne out in animal studies where centrally administered GLP-1 has been shown to improve learning behavior and provide neuroprotection against toxin-induced apoptosis and seizures [67,68]. In a rat model of Parkinson's disease [71], exendin-4 (a GLP-1 agonist) promoted neurogenesis *in vitro* and *in vivo*, normalized dopamine imbalance, and increased the number of cells positive for markers of dopaminergic neurons in the substantia nigra. These effects raise the exciting possibility that GLP-1 and its analog could prove to be novel therapeutic agents for use in enhancing cognition and delaying/preventing degeneration in neurodegenerative diseases like Parkinson's disease.

There is evidence in humans that GLP-1 regulates cerebral glucose balance and that its role may be neuroprotective. During hyperglycemia, GLP-1 is secreted from the gut into the bloodstream and may also be produced in the brain. Peripherally acting GLP-1 promotes increased insulin secretion and decreased glucagon secretion and leads to a lowering of circulating blood glucose, thereby limiting glucose transport across the blood–brain barrier. In a recent study, using PET scanning and a pituitary-pancreatic normoglycemic (~ 4.5 mmol/L) clamp with FDG as tracer, it was found that GLP-1 infusion in

healthy humans reduces glucose uptake across the intact blood–brain barrier even at normal glycemia (an effect that could be independent of insulin action). These actions of GLP-1 to lower blood glucose and limit hyperglycemic glucose fluctuations in the brain may be of neuroprotective significance [72].

Based on the findings in the above study, a group of investigators in Denmark designed a study to evaluate the effect of the GLP-1 analog exenatide on glucose metabolism in the central nervous system and heart during hyperglycemia in patients with type 2 diabetes. In a randomized, double-blind, crossover design study, they plan to compare the effect of exenatide and placebo on the consumption of glucose in the central nervous system (and heart) as assessed by uptake of FDG monitored by PET scan in patients with type 2 diabetes during a hyperglycemic pituitary–pancreatic clamp. Results from this study will help us to further understand whether the incretin hormones, by reducing blood–brain-barrier glucose transport and brain glucose metabolism, have neuroprotective effects from hyperglycemia on the brain in patients with type 2 diabetes [73].

1.7. Effects on Bone Metabolism

There is some emerging evidence that GLP-1 may play a role in the control of bone metabolism. In a mouse model, Yamada and colleagues [74] demonstrated that although GLP-1 had no direct effect on osteoclasts and osteoblasts, GLP-1 receptor knockout mice exhibited higher levels of urinary deoxypyridinoline (a marker of bone resorption) and reduced levels of calcitonin mRNA transcripts in the thyroid. Moreover, calcitonin treatment effectively suppressed urinary levels of deoxypyridinoline in GLP-1 receptor mice and the GLP-1 receptor agonist exendin-4 increased calcitonin gene expression in the thyroid of wild-type mice [74]. These findings suggest a role for endogenous GLP-1 receptor signaling in the control of bone resorption, likely through a calcitonin-dependent pathway. It is, however, important to note that these are preliminary findings that need confirmation and replication in human studies.

2. Summary

The incretin agents (GLP-1 receptor agonists and the DPP-4 inhibitors) belong to a unique class of antidiabetic agents that have pleiotropic effects extending well beyond their known ability to lower glucose. These include effects to improve β -cell function and mediation of trophic effects on the β -cell (in animal and in vitro models); effects to reduce postprandial lipemia; effects to lower blood pressure; effects to improve myocardial contractility and endothelial function (seen so far only with GLP-1 infusions); and potential neuroprotective, neurotrophic, and bone resorptive effects (seen only in animal models). These beneficial effects of the incretins (if confirmed in long-term studies) have the potential to favorably influence the course of the disease process and its complications in patients with type 2 diabetes. The effects of the incretins to potentially preserve/regenerate β -cells might translate into preserved β -cell function and perhaps even reversal of the progressive decline of pancreatic β -cell function. In high-risk individuals with prediabetes (and declining β -cell function), the incretins may even be able to delay or prevent diabetes. The ability of GLP-1 receptor agonists to improve myocardial contractility and endothelial function and favorably affect blood pressure and lipids (particularly postprandial lipemia) in the context of weight loss or weight neutrality has the potential to ameliorate some of the premature cardiovascular burden in patients with diabetes. Finally, the neurotrophic and neuroprotective effects of GLP-1 agonists seen in animal models have the potential to translate into new treatments for neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. Well-designed, long-term studies are needed to confirm and substantiate the above beneficial effects and to

determine whether the multipotential promise of the incretin hormones is ultimately fulfilled.

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