

Glucagon-Like Peptide 1–Based Therapies for Type 2 Diabetes: A Focus on Exenatide

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Glucagon-like peptide 1 (GLP-1) is produced by the proglucagon gene in L-cells of the small intestine in response to nutrients.¹ It stimulates glucose-dependent insulin release from the pancreatic islets. In addition to its insulinotropic effects, it is thought to exert antihyperglycemic effects by slowing gastric emptying,² inhibiting inappropriate glucagon release,³ stimulating β -cell proliferation⁴ and differentiation,⁵ and improving satiety.⁶

GLP-1 secretion is decreased in type 2 diabetes, thus making it a logical target for novel treatments of type 2 diabetes.⁷ In clinical trials, GLP-1 effects are evident regardless of the duration or severity of diabetes.⁸ Thus, modulating GLP-1 levels and GLP-1 activity through administration of the native hormone, analogs, and mimetics or by inhibiting its degradation has become a major focus of investigation for treating type 2 diabetes over the past decade.

Exenatide is a GLP-1 mimetic, a synthetic form of the naturally occurring reptilian hormone exendin-4. It has been submitted for review by the Food and Drug Administration and could become available on the U.S. market by mid-2005.

As shown in Figure 1, GLP-1 enhances essentially all steps of insulin synthesis and secretion, including insulin gene transcription⁹ and upregulation of glucokinase and GLUT2, the rate-limiting steps in β -cell glucose sensing.¹⁰ Its G-protein coupling to adenylyl cyclase also leads to activation of pancreatic and duodenal homeobox gene-1 via a pathway that is thought to regulate expres-

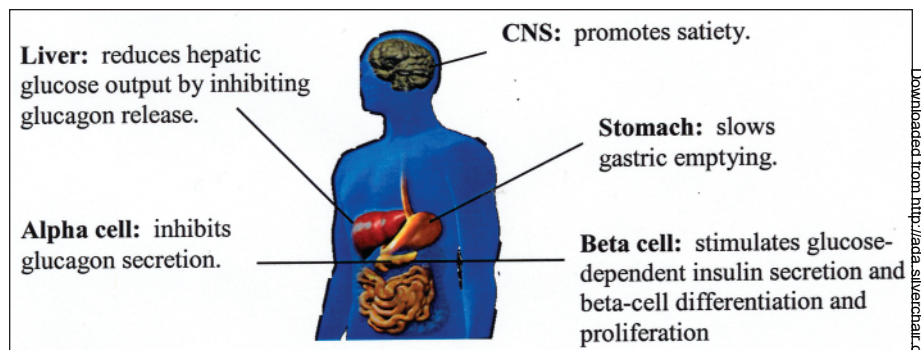


Figure 1. Multiple sites of action for GLP-1. CNS, central nervous system.

sion of genes for insulin and β -cell growth and differentiation.¹¹ GLP-1 binds to a seven-transmembrane G-protein–coupled receptor of the subfamily that includes receptors for secretin, vasoactive intestinal peptide, and gastric inhibitory peptide.¹² The receptor is found on pancreatic periductal cells and β -cells and in the kidney, heart, stomach, and brain.¹³ GLP-1 receptor (GLP-1R) knockout mice have fasting hyperglycemia and abnormal glucose tolerance but are not obese.¹⁴

GLP-1 exhibits a relatively short half-life (1–2 minutes) that necessitates continuous infusion to achieve steady

state in pharmacological studies.¹⁵ This is attributed to NH_2 -terminal degradation by dipeptidyl peptidase IV (DPP-IV).¹ Mice lacking DPP-IV exhibit reduced food intake, improved insulin sensitivity, and decreased loss of β -cell mass.¹⁶ Numerous analogs have been developed that have a longer half-life, mediated by resistance to DPP-IV degradation.

Exendin-4 is a naturally occurring component of the saliva of the Gila monster (*Heloderma suspectum*).¹⁷ It has 53% homology with mammalian GLP-1.¹⁷ It is resistant to DPP-IV because of a key difference in amino acid sequence: glycine at position 2.¹⁸ Exendin-4 has a very high affinity for the GLP-1R, an effect mediated by differences in its COOH terminus.¹¹ Interestingly, exendin-4 is transcribed via a gene that is distinct from the mammalian counterpart of GLP-1 and therefore likely serves some unique function for the Gila monster beyond that of the GLP-1 system.

There are some differences between exendin-4 and GLP-1 that suggest that not all of exendin-4's actions are mediated by the GLP-1R. Exendin-4 increases the insulin sensitivity of cultured L6 myotubes and 3T3-adipocytes, whereas

IN BRIEF

Therapies based on the incretin hormone glucagon-like peptide 1 are novel treatment options for type 2 diabetes that act through a variety of complementary mechanisms. Exenatide, which will likely become the first application to reach the market, has shown promise in phase III trials in reducing hemoglobin A_{1c} without causing significant hypoglycemia or weight gain.

GLP-1 increases the sensitivity of L6 myotubes only.¹⁹ Whether the GLP-1R is present in adipocytes is unclear, but if so, it must be structurally or functionally different.^{20,21} In addition, intraportal infusion of GLP-1, but not exendin-4, leads to hepatic vagal afferent stimulation, which in turn may regulate pancreatic hormone secretion.²²

In vitro, exendin-4 has been shown to bind to the GLP-1R of rat islets.¹⁵ Exendin-4 exhibits dose-dependent augmentation of insulin secretion; the 63% greater insulinotropic action of exendin-4 versus GLP-1 has been attributed to its slower clearance.²¹ Of interest, insulinotropic effects in vitro are seen at glucose concentrations as low as 55 mg/dl, but in humans this effect was suppressed as the plasma glucose approached 72 mg/dl.²³

Effects of Exendin-4 in Animals

Similar to in vitro studies, Harlan Sprague-Dawley rats administered exendin-4 exhibit a glucose-stimulated, dose-dependent increase in insulin levels, but there is a 100-fold greater potency in vivo than that observed in vitro.¹⁵ Thus, its effects are not entirely intrinsic to islets, but they are influenced by the surrounding biochemical and hormonal milieu. In *db/db* mice, fasting glucose is normalized after 12 weeks of therapy.²⁴ At 12 weeks, hemoglobin A_{1c} (A1C) was 4.1% lower in treated mice than in control mice. Exendin-4 also significantly and dose-dependently lowered fasting glucose in four diabetic rhesus monkeys by up to 37%.²⁵

Exendin-4 may enhance satiety and weight loss through slowed gastric emptying, as well as through centrally mediated mechanisms. It has been shown to cross the blood-brain barrier and enter the brain parenchyma in mice.²⁶ In addition, exendin-4 has been found to bind receptors in the hypothalamus and thalamus in a pattern identical to that for GLP-1.²⁷ Exendin-4 lowered food intake and body weight in *db/db* mice through 5 days of treatment, but this was not sustained.²⁸ Furthermore, GLP-1R knockout

mice do not exhibit obesity, suggesting that other mechanisms compensate for weight maintenance.¹⁴

Weight loss and decreased food intake were illustrated in two studies of Zucker rats, an animal model of type 2 diabetes in which a leptin receptor mutation causes overeating and subsequent obesity. In one study, exendin-4 produced a dose-dependent reduction in food intake and body weight (up to 5.6%) after 6 weeks.²⁵ Another study demonstrated significantly decreased visceral and subcutaneous fat deposition (70% gain in control rats vs. 42% gain in treated rats) after exendin-4 treatment for 8 weeks.²⁸ Twice-daily, but not once-daily, injections resulted in sustained decrease in food intake and significantly slower weight gain.

Exenatide Effects in Human Studies

Exenatide is synthetically produced exendin-4. Studies of exenatide's acute effects were performed by Egan et al.²³ Hyperglycemic clamps of seven healthy subjects and seven insulin-naïve patients with type 2 diabetes demonstrated four-fold potentiation of insulin response with a 1-hour exenatide infusion at 0.15 pmol/kg body wt/minute. This effect persisted several hours beyond the cessation of the infusion, demonstrating its substantial biological half-life. Furthermore, increased C-peptide levels suggest that the increase in insulin levels was related to increased secretion and not to a reduction in insulin clearance. Basal glucagon levels fell, and glucose clearance increased, in both groups with exenatide therapy. Exenatide also prevented the postprandial rise in insulin and glucose 3 hours after completion of the exenatide infusion. Finally, insulin levels dropped after stopping the glucose infusion as glucose levels fell, substantiating that the insulinotropic effect is glucose dependent.

A longer study²⁹ was completed using exenatide, 12 pmol/kg subcutaneously, up to twice daily in nine insulin-naïve patients with type 2 diabetes. A1C decreased significantly from

9.1 to 8.3% after only 1 month. Fasting glucose dropped significantly, but postprandial glucose decreased only immediately after breakfast, possibly reflecting inadequate dosage or duration. There was no waning of effect throughout the month, indicating that there was no significant down regulation of the GLP-1R. In this study, there was no change in BMI or in percentage of lean or fat mass as determined by dual energy X-ray absorptiometry after 1 month of therapy.

Hyperinsulinemic-euglycemic clamps in this study²⁹ were inconclusive in demonstrating effects on insulin sensitivity. Overall, the effect of exenatide on insulin sensitivity is unclear. Apparent increases in insulin sensitivity are confounded by the effects of ameliorating glucotoxicity, as well as by alterations in gastric emptying and insulin and glucagon secretion.³⁰

Kolterman et al.³¹ reported two blinded, placebo-controlled, crossover studies using exenatide. The first study examined the postprandial glucose response to 0.1 µg/kg of exenatide or placebo twice daily for 5 days. Exenatide resulted in significant reductions in postprandial glucose, insulin, and area under the curve for glucose and insulin, which did not wane through day 5. The drop in glucose appeared to be out of proportion to the stimulation of insulin secretion, suggesting that perhaps insulin sensitivity was enhanced.

Gastric emptying may paradoxically be accelerated in patients with diabetes.³² Gastric emptying was also reduced in the Kolterman, et al. study³¹ and likely contributed to exenatide's effects on satiety and hyperglycemia. This was also demonstrated in a study of patients with no residual β -cell function, and thus no insulin reserve, who nevertheless showed improvements in hyperglycemia on exenatide.³³

Kolterman also demonstrated a reduction in glucagon with exenatide therapy.³¹ Both fasting and postprandial glucagon were reduced, indicating that the reduction in gastric emptying was not likely to be the mechanism. Patients

with type 2 diabetes are known to exhibit inappropriate elevations of fasting and postprandial glucagons.³⁴ This therapeutic effect is unique to exenatide among antidiabetic agents.³⁵

A large, randomized, triple-blind, placebo-controlled trial was performed at 24 sites with 109 patients with type 2 diabetes (A1C 8–11%) treated concomitantly with sulfonylurea, metformin, or both over 28 days.³⁶ Patients received either three premeal injections per day of exenatide, one injection of placebo plus two injections of exenatide at variable mealtimes, or three injections of placebo. A1C had dropped significantly by 0.9% at 28 days. There were also significant reductions in postprandial but not fasting glucose. The homeostasis model assessment, an indicator of β -cell function, was significantly improved after therapy. This was ascertained when plasma concentration of exenatide was negligible, suggesting a fundamental change in β -cell function over 28 days. There was no significant effect of therapy on body weight, lipids, vital signs, or laboratory parameters. Antibodies to exenatide were detected in 19% of subjects, but there was no evidence for a diminished glycemic response in these patients. Nausea was reported in 31% of patients, most of which was mild to moderate and declined substantially after the first week. Hypoglycemia was seen in 15% of patients, but only in those who were simultaneously treated with sulfonylureas.

The possibility of the development of tolerance to exenatide-associated nausea was investigated in 123 type 2 diabetic patients at 31 sites.³⁷ This randomized, triple-blind, placebo-controlled trial found a reduction in severe nausea (47.5 vs. 31.1%) and vomiting (29.0 vs. 9.7%) in patients who had dose escalation as part of treatment initiation versus those who had not. Safety was further demonstrated in a study of 12 healthy volunteers, in which the counterregulatory response to insulin-induced hypoglycemia was preserved with exenatide therapy.³⁸

Long-term efficacy was demonstrated in a triple-blind, placebo-controlled trial at 101 sites with 377 type 2 diabetic patients.³⁹ Subjects were included if they had been on a maximally effective dose of sulfonylurea as monotherapy. Subjects underwent a 4-week, single-blind lead-in period with placebo injections followed by randomization to one of four treatment arms. Subjects received either 5 or 10 μ g of exenatide twice daily or one of two placebo arms using equivalent volumes of placebo. A 4-week dose escalation period was used in the 10- μ g arm. Results were analyzed in an intention-to-treat manner.

At 30 weeks, A1C had decreased by 0.86% in the 10- μ g arm and 0.46% in the 5- μ g arm (Figure 2). In the 10- μ g arm 34.2% and in the 5- μ g arm, 26.7% were able to reach an A1C of < 7%, with larger reductions occurring in those with higher baseline A1C levels. Furthermore, body weight decreased significantly at 30 weeks, by -1.6 kg in the 10- μ g group (Figure 3). Weight loss was not related to the incidence of nausea, and withdrawal because of nausea was low, at 4% in the 10- μ g arm and 2% in the 5- μ g arm. Anti-exenatide antibodies were reported in 41% of subjects, but there was no predictive effect on overall glycemic control.

Another study⁴⁰ using metformin plus exenatide for 30 weeks has also

been completed and has shown more impressive weight loss (Table 1) with similar efficacy. Finally, preliminary results from a trial adding exenatide to maximally effective doses of metformin plus sulfonylurea showed similar results at 30 weeks.⁴¹ An open-label extension to 52 weeks showed sustained improvement in A1C.

As noted above, exendin-4 has shown some benefit with respect to producing weight loss in patients with type 2 diabetes. In eight healthy humans, a randomized, double-blind, placebo-controlled crossover trial demonstrated a significant reduction (19%) in caloric consumption, despite no difference in reported satiety or nausea.⁴²

Other studies using native GLP-1 instead of exenatide have been performed in healthy subjects and in those with diabetes; most,^{43–46} but not all,⁴⁷ also show comparable reductions in caloric intake.

Effects of exenatide on cardiac function have not been examined to date. However, GLP-1 may have beneficial cardiac effects that are of obvious interest in diabetes management. Patients with coronary artery disease have shown improved endothelial dysfunction.⁴⁸ In a dog model of heart failure, GLP-1 has left ventricular hemodynamics, including a 57% increased cardiac output and increased myocardial glucose uptake.⁴⁹

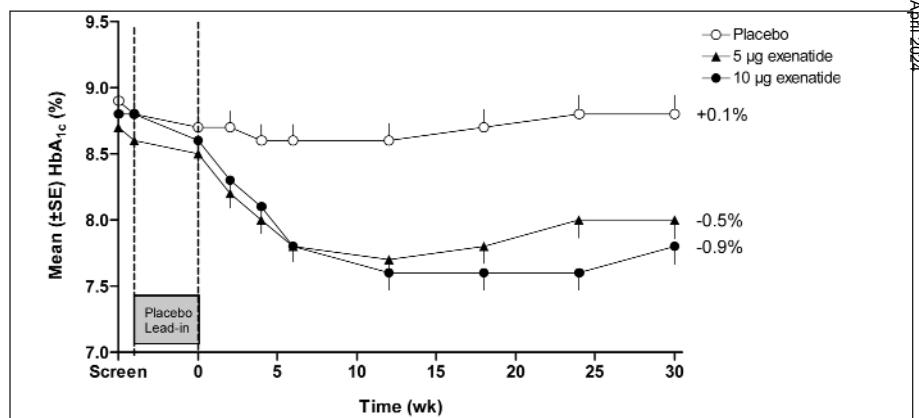


Figure 2. Effects of sulfonylurea plus exenatide or placebo on A1C in subjects with type 2 diabetes (intent-to-treat analysis). Placebo, $n = 123$; 5 μ g exenatide, $n = 125$; 10 μ g exenatide, $n = 129$. $P < 0.0001$ for reduction from baseline in both exenatide arms for weeks 6–30 versus placebo. Adapted from Buse et al.³⁹

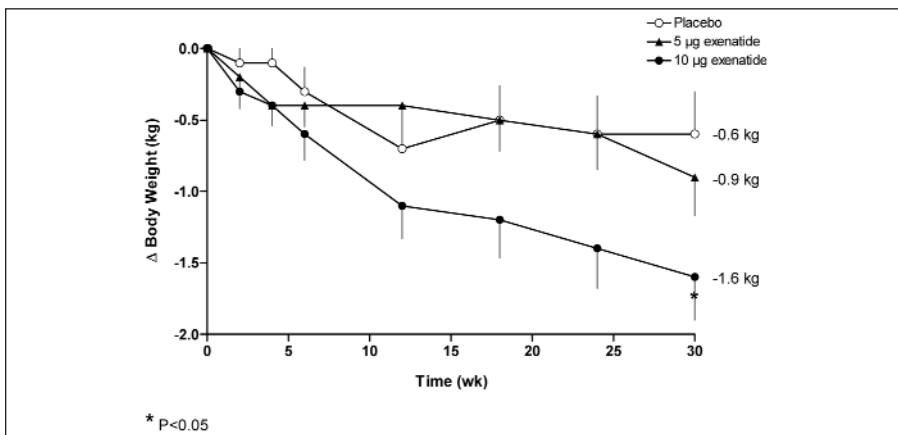


Figure 3. Change in body weight from baseline over time in subjects with type 2 diabetes treated with sulfonylurea and exenatide or placebo (intent-to-treat analysis). Baseline weights were 95.2 ± 1.6 kg in the 10 μ g exenatide arm ($n = 129$), 94.9 ± 1.7 kg in the placebo arm ($n = 123$). Data are means \pm SE. * $P < 0.05$ compared with placebo treatment. Adapted from Buse et al.³⁹

Additional Potential Effects in Humans: Diabetes Prevention and Augmentation of β -Cell Mass

The progressive loss of β -cell function and mass is an early feature of type 2 diabetes, eventually leading to insulin dependence in many patients.⁵⁰ Intervening early in the course of diabetes or perhaps in the prediabetic state to stimulate β -cell differentiation and/or reduce apoptosis could theoretically halt the progression of the disease. Both GLP-1 and exenatide have shown promise in this respect.

Exenatide may exert either a direct or an indirect effect on β -cell mass. Indirectly, exenatide may act by reducing hyperglycemia, which is known to cause β -cell dysfunction and interfere with neogenesis.^{51,52} However, even normoglycemic rats have shown β -cell neogenesis in response to exenatide.⁵³ Additionally, exenatide's effects on β -cell mass may simply result from the nonspecific growth factor effect of the augmented insulin supply itself.⁵⁴ On the other hand, a direct effect on β -cell mass may also be inferred from GLP-1R knockout mice, which display deficient β -cells.¹⁴ Furthermore, the GLP-1R was found in pancreatic ducts, a presumed site of origin for β -cell precursors,¹³ and in animal models treated with exenatide, neogenesis appeared to be derived from these

precursors.⁵⁵ In vitro, exenatide stimulated islet progenitor cells and pancreatic tumor cells to differentiate into insulin-producing cells.^{56,57}

In rats undergoing partial pancreatectomy, exenatide resulted in a 40% expansion of β -cell mass without a change in cell size, indicating that the increase resulted from hyperplasia or recruitment of precursors and not hypertrophy.⁵³ Unfortunately, the newly recruited β -cells did not attain a fully functional phenotype, and insulin secretion was not normalized.

The most dramatic results were seen in the intrauterine growth-retarded rat, a model of type 2 diabetes.⁵⁸ Exenatide was shown to prevent diabetes by com-

pletely rescuing the otherwise inevitable progressive 80% reduction in β -cell mass. By 18 months, untreated rats were all dead, whereas those treated with only 6 days of exenatide were indistinguishable from normal rats. There was also a significant reduction in obesity. These studies used very young animals that theoretically might be more ideal candidates for regeneration in general. However, aging glucose-intolerant rats treated with GLP-1 also showed beneficial results.⁵⁹

Future Directions

Other GLP-1 analogs that are resistant to DPP IV degradation have shown results similar to those of exendin-4.⁶⁰ In addition, a long-acting release form of exenatide, which may be given once a month, is being developed.⁶¹ DPP IV inhibitors have the distinct advantage of oral administration. In animal models, DPP IV resulted in sustained improvement in glucose tolerance, insulinemia, β -cell glucose responsiveness, peripheral insulin sensitivity, and β -cell mass.^{62–64} A 12-week randomized, double-blind, placebo-controlled study of 107 patients with type 2 diabetes on a stable dose of metformin monotherapy resulted in a significant 0.6% drop in A1C.⁶⁵ Fifty-eight of these patients participated in a 40-week extension resulting in stabilization of A1C and an overall 1.1% lower A1C than placebo. Of these GLP-1-based therapies, exendin-4

Table 1. U.S. Clinical Trials of Exenatide: Summary of Selected Outcomes

	Study with metformin	Study with maximum dose of a sulfonylurea	Study with metformin plus sulfonylurea
Change in A1C (placebo adjusted)	↓ 0.9%	↓ 1.0%	↓ 1.0%
Weight change	↓ 1.3–2.5 kg	↓ 0.3–1.0 kg	↓ 0.7 kg
Nausea (placebo vs. 10 μ g)	23 vs. 45%	7 vs. 51%	21 vs. 49%
Severe nausea (placebo vs. 10 μ g)	2 vs. 4%	2 vs. 5%	1 vs. 3%
Hypoglycemia (placebo vs. 10 μ g)	5 vs. 5%	3 vs. 36%	13 vs. 28%

in the form of exenatide, will likely be the first to reach the market.

Conclusions

GLP-1-based therapy would be a novel and complementary approach to diabetes management for several reasons. It is the first insulin secretagogue that does not cause hypoglycemia. It does not cause the weight gain that may be seen with insulin or sulfonylureas and may in fact facilitate weight loss. It may be used as a bridge to insulin therapy or to reduce insulin requirements of insulin-resistant patients in order to avoid weight gain. Although it has not been studied in patients with renal or hepatic insufficiency, its safety profile may make it the preferred agent in these patients. GLP-1 is also unique in that it has been shown to reduce the inappropriate rise in glucagon. It may also promote β -cell rescue and theoretically halt diabetes progression, although this has not been formally examined in humans. Currently, exenatide's injectable route of delivery and its potential side effects of nausea and vomiting may be the main barriers to widespread use. Further long-term studies are needed to determine its long-term efficacy, effects on weight, and potential for β -cell recovery and benefit to cardiac function.

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