

Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes

Lotte Bjerre Knudsen[†]

Discovery Biology Management, Novo Nordisk, DK-2760 Maaloev, Denmark

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Introduction

Type 2 diabetes is increasingly becoming a worldwide epidemic. Currently there is much focus on the glucagon-like peptide-1 (GLP-1) peptide hormone as the basis for a potential new treatment paradigm for type 2 diabetes. The two major drawbacks of the drugs currently utilized in the treatment of type 2 diabetes are that (1) during their long-term administration body weight increases and (2) the disease progresses over time, also evidenced by an increasing loss of β -cell function.

GLP-1 was discovered in 1984 and found to be an important incretin.¹ It is a product of the preproglucagon gene and is released from the L-cells in the intestine upon food intake and potently releases insulin from the β -cells in the pancreas. Numerous effects other than stimulation of insulin release have been ascribed to GLP-1. In the pancreas, not only does GLP-1 release insulin but it does so in a glucose-dependent manner,^{2,3} and it has a number of other functionally important effects: stimulation of insulin biosynthesis, restoration of glucose sensitivity to the islets, and stimulation of increased expression of the glucose transporter GLUT-2 and glucokinase.^{4–6} GLP-1 also has a number of effects on regulation of β -cell mass: stimulation of replication and growth and inhibition of apoptosis of existing β -cells, and neogenesis of new β -cells from duct precursor cells.^{7,8} GLP-1 inhibits glucagon secretion,⁹ which then leads to reduced hepatic glucose output. In the gut, GLP-1 is a potent inhibitor of motility and gastric emptying and has also been shown to inhibit gastric acid secretion.¹⁰ The inhibition of gastric emptying leads to decreased food intake and reduced body weight.^{11,12} Thus, the current belief is that the GLP-1 compound class may be able to control the progression of the type 2 diabetes disease not only by controlling blood glucose but also via several other effects. GLP-1 has also been proposed to have direct effects on glucose uptake in liver, muscle, and adipose tissue, but the quantitative significance of these effects has been questioned.¹³ New publications even suggest that the beneficial effects of GLP-1 compounds go beyond the treatment of diabetes. There may be specific receptors in the heart that along with the benefits of reducing blood glucose may protect from cardiovascular complications,¹⁴ and GLP-1 stimulates memory and learning capabilities.¹⁵ A comprehensive review exists on the glucagon-like peptides.¹³

Clinically, GLP-1 has been shown to be very effective in lowering blood glucose in quite a broad range of

diabetes stages.¹⁶ Very importantly, little risk of hypoglycaemia has been observed.² This is because GLP-1, unlike sulfonylureas, only stimulates the natural glucose-induced insulin secretion. Up to 6 week studies have been performed with natural GLP-1 in a subcutaneous pump. In this study a lowering of body weight was also seen.¹² The only known pharmacological side effect of GLP-1 is nausea and vomiting when administered in high doses. These unwanted effects are mediated by inhibited gastric emptying. However, the vast majority of clinical data indicate that the nausea is transient and that efficient glucose control can be obtained without this side effect. Thus, from a clinical point of view, GLP-1, with its efficacious lowering of blood glucose with little risk of hypoglycemia and its potential for prevention of disease progression, seems ideal for the treatment of type 2 diabetes.

The GLP-1 receptor was cloned in 1992 and is a G-protein-coupled receptor from the B family also referred to as the secretin/glucagon family.¹⁷ The ligands in this family are mainly large peptide hormones. Small-molecule antagonists especially for the glucagon receptor have been described, but no small-molecule agonists have been described in the literature. Thus, the GLP-1 based compound class will most likely be peptides and the challenge is that the natural hormone is degraded rapidly by the enzyme dipeptidyl peptidase IV (DDP-IV) and cleared by the kidneys resulting in a half-life of less than 2 min after iv administration and a clearance higher than that of the normal cardiac output.^{18–20} GLP-1 exists in two equipotent naturally occurring forms, GLP-1(7–37) and GLP-1(7–36)amide, the former corresponding to proglucagon(78–108). The numbering of GLP-1 starts with 7 because it was originally believed that GLP-1(1–37) was the active hormone. It was later discovered that the real hormone was formed after cleaving off the first 6 N-terminal amino acids and then the 7 numbering system begun. The primary metabolite of GLP-1, GLP-1(9–36) amide or GLP-1(9–37), has a greatly decreased affinity for the GLP-1 receptor and may even be an antagonist or a partial agonist. The magnitude and duration of the blood glucose lowering ability of natural GLP-1 have been shown to be dependent on a continuous supply of pharmacological levels.²¹ Thus, the efficacy of a GLP-1-like drug will be dependent on the duration of action of the compound or the formulation even though some of the long-term benefits of GLP-1 compounds, like increasing β -cell mass, may not require constantly elevated GLP-1 levels. Another potential limitation is that the only known pharmacologically induced side effect is nausea, occurring via the inhibition of gastric

[†] Phone: +45 44434788. Fax: +45 44663939. E-mail: lbkn@novonordisk.com.

Table 1. Overview of GLP-1 Based Compounds in Development^a

compd	structure	half-life in humans	principle of protraction	clinical phase and dosing used	refs
exenatide, AC2993	exendin-4	4–5 h	inherent in exendin-4 amino acid sequence	phase 3, twice daily	31, 38, 46
liraglutide, NN2211	(γ -L-glutamyl(<i>N</i> - α -hexadecanoyl))-Lys ²⁶ Arg ³⁴ -GLP-1(7–37)	11–15 h	self-association and albumin binding	phase 2 completed, once daily	39, 40, 48
CJC-1131	D-Ala ⁸ Lys ³⁷ [2-[2-[2-maleimidopropionamido(ethoxy)ethoxy]acetamide-GLP-1(7–37)]	10–12 days	in vivo covalent conjugation to albumin	phase 1/2, once daily	41
ZP10	structure not published	-	inherent in exendin-4 sequence and added C-terminal stability	phase 1/2, acute dosing only	42
albugon	structure not published	-	genetic fusion protein with albumin	preclinical	-
BIM-51077	structure not published	-	enzymatically stabilized GLP-1 analogue	preclinical	43
-	(2-sulfo-9-fluorenyl methoxycarbonyl) ₃ exendin-4	-	prodrug of exendin-4	preclinical	44

^a Compound names, structure if published, principle of protraction, development phase if known, and dosing frequency used in clinical trials if known.

emptying. However, there seems to be tachyphylaxis to this side effect so that long-term efficacy can be obtained without major gastrointestinal side effects. Nevertheless, this issue of nausea as a side effect is probably the most important one to resolve in future clinical trials.

Type 2 Diabetes as a State of Hormonal Disorder and Incretin Deficiency.

At least three hormonal disturbances may be corrected upon treatment with a GLP-1 compound: decreased effect of Gastric Inhibitory Polypeptide (GIP), decreased secretion of GLP-1, and hypersecretion of glucagon.

Type 2 diabetes has been described to be an incretin deficiency state because patients have a decreased release of GLP-1 upon ingestion of food compared to healthy subjects and because the other major incretin, GIP, stimulates release of insulin to a much smaller extent in type 2 diabetes compared to healthy subjects.^{22,23} There is some evidence to support that the decreased GLP-1 secretion occurs as a slow deterioration with disease progression, since subjects with glucose intolerance have a tendency to also have a smaller amount released after a meal.²⁴

GIP was the first known incretin, and it was proposed as a treatment for type 2 diabetes in the 1980s. However, it was found that GIP only leads to insulin secretion in healthy volunteers and not in type 2 diabetes.²² Recently it has been found that GIP does lead to some insulin secretion in type 2 diabetes but that it is especially the first-phase secretion that GIP is responsible for and that this is lost to a large extent.²⁵ There is no impaired secretion of GIP in type 2 diabetes nor have any receptor mutations been found that could be responsible for the lack of effect. By comparison, GLP-1 has a full effect on both first- and second-phase insulin secretion in type 2 diabetes, and thus, GLP-1 may substitute the physiological role of GIP that is lacking in type 2 diabetes.²²

nists have been proposed as a potential drug class for type 2 diabetes.²⁶ Neutralization of glucagon with antibodies leads to lowering of blood glucose in several animal models.²⁷ Glucagon hypersecretion leads to increased hepatic glucose output by increased gluconeogenesis and glycogenolysis and thus contributes to elevated blood glucose.²⁸ GLP-1 decreases glucagon secretion and thus partly or fully corrects this hypersecretion.

Thus, treatment with GLP-1 may correct or replace three hormonal disturbances in type 2 diabetes. On top of that, GLP-1, as mentioned above, has several other beneficial effects.

Overview of Compounds in the GLP-1 Class (Table 1)

There are two subclasses of GLP-1 in clinical development. One is natural GLP-1. The other is exendin-4, a peptide agonist isolated from the venom of the lizard *Heloderma Suspectum*, also known as the Gila monster. There is high structural homology between GLP-1 and exendin-4: 53%. The structures of GLP-1 and exendin-4 are shown in Figure 1. Both exendin-4 and GLP-1 are found in the Gila monster. It is not fully understood why it has two separate peptides with a large overlap in function, but there is a belief that it may be that the animal needs two incretins in preparation for large infrequent meals. The amino acid sequence of GLP-1 is highly preserved across species. Exendin-4 is a very potent molecule with a reported potency ranging from 2–3 to 5–10 times greater than the potency reported for GLP-1.²⁹ However, when potency is compared in vivo, it is important to take into account the large difference in half-life. The apparent potency may seem much greater for exendin-4, but when taking into account that GLP-1 has a half-life of less than 2 min, a valid comparison may be difficult or impossible to obtain. As mentioned above, natural GLP-1 has a very short half-life because of cleavage by DPP-IV and rapid

GLP-1:

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly-Arg-Gly³⁷

Exendin-4:

His⁷-Gly-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Leu-Ser-Lys-Gln-Met²⁰-Glu-Glu-Glu-Ala-Val²⁵-Arg-Leu-Phe-Ile-Glu³⁰-Trp-Leu-Lys-Asn-Gly-Gly-Pro³⁷-Ser-Ser-Gly-Ala-Pro-Pro-Ser**Figure 1.** Amino acid sequence of GLP-1 and exendin-4. Dipeptidyl peptidase IV cleaves between Ala⁸ and Glu⁹.

Liraglutide:

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Arg-Gly-Arg-Gly³⁷

Exenatide (natural exendin-4):

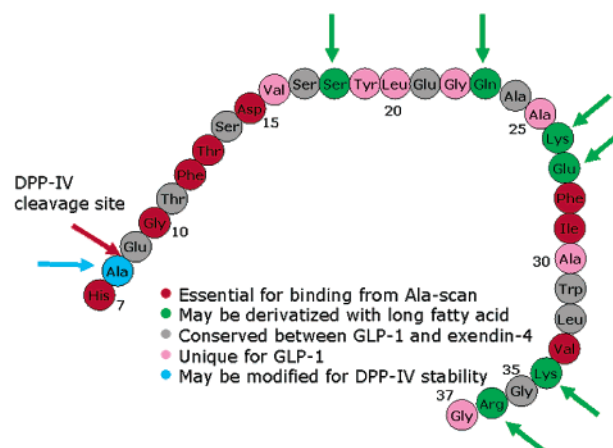
His⁷-Gly-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Leu-Ser-Lys-Gln-Met²⁰-Glu-Glu-Glu-Ala-Val²⁵-Arg-Leu-Phe-Ile-Glu³⁰-Trp-Leu-Lys-Asn-Gly-Gly-Pro³⁷-Ser-Ser-Gly-Ala-Pro-Pro-Ser**Figure 2.** Structures of liraglutide and exenatide, the two first-generation products in the GLP-1 class.

degradation of GLP-1.³⁰ By comparison, exendin-4 is much more resistant to proteolytic cleavage by both DPP-IV and NEP,³¹ and its half-life in humans is 26 min after iv administration. Exendin-4 has a 9 amino acid long proline-rich C-terminal tail, which is believed to stabilize the agonist conformation, and affinity is decreased when the tail is removed.³² Thus, on the basis of the exendin-4 sequence, more enzymatically stable molecules can be obtained, but it may then be at the expense of an immune reaction against the peptide.

Hitherto, it is clear that therapeutics for the GLP-1 receptor will be peptides, and thus, the drug discovery challenge is to make a stable compound with a long half-life. Amino acid sites 7, 10, 12, 13, 15, 28, and 29 have previously been shown, in an alanine scan of GLP-1, to be sensitive to changes, and it has been proposed that the N-terminal part of the peptide is responsible for the high-affinity binding to the core of the receptor, whereas the C-terminal is more responsible for the selectivity by interacting with the large N-terminal of the receptor.³³ A number of early studies aimed at making protease stabilized analogues of GLP-1 are available.^{34,35} However, none of these GLP-1 analogues have proceeded beyond drug candidates presumably because they are still rapidly cleared by the kidneys and thus require some other form of protraction.³⁴

Lilly and Amylin are in phase 3 clinical development with exenatide (exendin-4, AC2993) as a twice daily injection therapy. A large amount of preclinical data on exendin-4 have been published from several independent labs, especially a number of reports of exendin-4's ability to stimulate β -cell growth, replication, and neogenesis.³⁶ Several clinical studies have been published. Side effects have been (as expected for the whole class) transient nausea.³⁸ Antibody formation against exenatide has been reported.³⁸ Since exenatide is synthetic exendin-4, no systematic SAR exists from which the compound was originally chosen. The companies have reported that they are pursuing a slow release formulation of exendin-4.

Novo Nordisk has completed phase 2 clinical trials with liraglutide(γ -L-glutamoyl(*N*- α -hexadecanoyl))-Lys²⁶,Arg³⁴-GLP-1(7–37) (NN2211) (Figure 2) as a once daily injection therapy. Several preclinical and clinical studies have been published. Liraglutide is equipotent to GLP-1 and has a half-life that is more than 10-fold

**Figure 3.** SAR figure of GLP-1. All sites essential for binding from Ala-scan are also conserved between GLP-1 and exendin-4. Sites that are possible to modify with fatty acids are only color-coded as such. They are all unique for GLP-1 at the same time.

a series of acylated derivatives of GLP-1 that are aimed at being long-acting via two independent mechanisms, self-association and noncovalent binding to plasma albumin fatty acid binding sites, resulting in a pharmacokinetic profile with slow absorption and a long half-life.⁴⁰ Albumin thus serves as a buffer reservoir for liraglutide. GLP-1 can be acylated at multiple sites with a hexadecanoyl fatty acid and a γ -Glu amino acid as a spacer, and the acylated GLP-1 exhibits retained potency and a long half-life after subcutaneous administration. Also, with a slightly shorter fatty acid, dodecanoyl, it is possible to attach two fatty acids and still have a potent compound with a significantly protracted profile. Spacers other than γ -Glu can be used, e.g., GABA or β -Ala. A potency-destroying SAR has also been generated in which acylation in the N-terminus position 8 leads to a compound about 20 times less potent than GLP-1. Acylation with two fatty acids on both naturally present lysines in positions 26 and 34 destroys potency. Last, simultaneous acylation in position 34 combined with a modification of the natural histidine in position 7 (des-aminohistidine) aimed at making the N-terminus more resistant to DPP-IV also destroys potency. Thus, for acylated derivatives of GLP-1 the SAR is well understood.⁴⁰

Other companies are in the discovery phase or in small-scale phase 1/2 clinical development. However, very little is published in peer-reviewed journals. Several patent applications claim different analogues of mainly exendin-4, but also a few claim analogues of GLP-1. The biggest question for these approaches is if they can become a convenient product with administration once daily or less. To achieve this, the companies need to make a slow release formulation in such a way that an initial burst can be avoided or they have to build some other principle of protraction into the molecule. A slow release formulation for peptides without a significant initial burst effect has yet to be reported, and such a burst effect will no doubt give rise to nausea.

Conjuchem is developing a reactive analogue of GLP-1 (CJC-1131) that has also been modified at site 8 to protect against DPP-IV degradation and that is designed to form a covalent bond to albumin after sc injection by specific interaction between the Cys³⁴ moiety of albumin and the C-terminus of the GLP-1 analogue.⁴¹ Thus, in principle the conjugates will have the half-life of albumin, which is 19 days in man but shorter in rodents. They have reported a very long half-life in man, 10–12 days, but so far clinical trials have been performed with once daily injections in a relatively small number of patients. The challenge for this approach is perhaps slightly greater than for the others because of the *in vivo* covalent attachment to albumin. On the other hand, this approach does not have the challenge of having to invent a protracted formulation.

Human Genome Sciences is in the discovery phase with Albugon, a fusion protein between an analogue of GLP-1 and albumin. This approach is similar to that of Conjuchem, using covalent binding to albumin as a principle of protraction. There is one important difference, though: this is an injection of a stable fusion protein, whereas Conjuchem is injecting a reactive molecule. Human Genome Sciences have reported, but not yet published, a half-life of Albugon in monkeys of 3 days.

Zealand is developing an analogue of exendin-4 (ZP10) that Aventis recently in-licensed. Neither the structure nor the half-life of ZP10 has been published, just the fact that it is an amino acid analogue that may be dosed twice daily to mice.⁴² Clinical data have been announced but not published. Thus, it is to be expected that this compound will have to be dosed twice daily in humans unless a protracted formulation can be developed.

Ipsen is also working on a protease stabilized analogue of GLP-1, BIM-51077.⁴³ Neither the structure nor the receptor potency of the compound has been published, but the compound is referenced to be stabilized against both C-terminal and N-terminal enzymatic degradation. The development status of this compound is preclinical.

Theratechnologies and ALZA are working on a transdermal formulation of an analogue of GLP-1 using Theratechnologies long-acting peptide technology. The structure of the compound has not been published.

An Israeli group has published a prodrug approach on exendin-4 where they attach a 2-sulfo-9-fluorenyl-

resulting in a pharmacodynamic profile somewhat longer than exendin-4 itself in diabetic mice.⁴⁴

While a number of companies or institutions have programs aimed at identifying new compounds in the GLP-1 compound class, very little has been published about this except in the patent literature. Several other companies have had programs that have not proceeded into development, including Watson and Genzyme. Lilly has a patent application on fusion proteins. Two companies Alizyme and Neurogen have had programs aimed at finding small-molecule agonists, but both have reported these programs to be suspended. Novo Nordisk has a patent application on small-molecule agonists.

Outlook for the Clinical Promise and Challenges of the GLP-1 Class of Drugs

One of the biggest challenges to the GLP-1 compound class is that these compounds are peptides and thus have to be injected. This is probably the main reason the compound class has been so relatively long on its way.

Alternative delivery forms may be pursued but most attempts to make large peptide drugs available by the oral, transdermal, or nasal route have failed because of either low bioavailability or the toxicity of necessary enhancers. Pulmonary administration is currently being investigated for insulin by several companies, and if successful, it will most likely be investigated as a more generally utilized route for other peptides. However, because subcutaneous injection always gives some protraction that cannot be expected from pulmonary administration, a relatively higher dose of a peptide would have to be given, which in the case of GLP-1 might lead to nausea.

A more specific challenge for a successful GLP-1 drug is to have as few gastrointestinal side effects as possible. This is a pharmacological side effect and is thus correlated to the pharmacokinetic properties; i.e., nausea will occur with peak concentrations. Nausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations.

The true clinical potential of the compound class in terms of the extent of the glucose lowering, control of body weight, and disease progression still remains to be shown. Perhaps the best published study addressing this potential to date is with 6 weeks of infusion of natural GLP-1 via MiniMed insulin pumps, as shown in Figure 4.¹² This study demonstrated a potential for GLP-1 to rapidly lower fasting blood glucose with 4–5 mM, mainly with the first week of treatment. This is an impressive effect, not met by any other major oral drug category available today such as sulfonylureas and metformin or insulin sensitizers. This effect is of course met by insulin, but there GLP-1 offers a major advantage in terms of safety because it, unlike insulin, does not induce hypoglycemia. The study also showed a significant weight lowering effect of treatment with GLP-1 compared to vehicle treatment. Another study of natural GLP-1 in 55 patients showed that regardless of the blood glucose levels of the type 2 diabetic patient, GLP-1 administered over a 4 h infusion period markedly

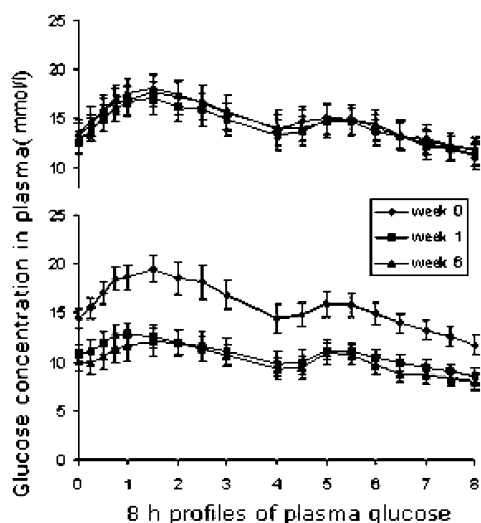


Figure 4. The 8 h profiles of plasma glucose levels. Data are presented as a mean \pm SEM. The top panel shows plasma glucose levels for patients receiving saline. The panel at the bottom shows plasma glucose levels for patients receiving GLP-1. For patients receiving saline, fasting plasma glucose levels remained unchanged over the 6 weeks, $P = 0.13$, and the 8 h value throughout the day (8 h mean) remained unaltered, $P = 0.95$. The postprandial glucose excursions (expressed as incremental AUC of 0–3 h) remained unaltered, $P = 0.87$, as did postprandial peak values, $P = 0.3$. In the GLP-1 group, fasting plasma glucose was reduced by 3.6 CI (2.9–4.3 mmol/L (week 1)) and 4.3 CI (2.4–6.2 mmol/L (week 6), $P < 0.001$; Δ values, $P < 0.0001$. The 8 h mean levels were reduced by 4.9 CI (4.0–5.7 mmol/L (week 1)) and 5.6 CI (3.7–7.5 mmol/L), $P < 0.0001$, Δ values $P < 0.0001$. Postprandial glucose excursions decreased, $P < 0.001$, Δ values $P < 0.0001$, as did postprandial peak values, $P = 0.003$, Δ values $P < 0.0001$. Reprinted with permission from *Lancet*.¹² Copyright 2002 Elsevier..

significantly better than any of the oral drugs currently on the market for type 2 diabetes.

Also, data of the two compounds in large-scale clinical trials, exenatide and liraglutide, are beginning to become available. Exenatide has a half-life after iv administration of 26 min³¹ and approximately 4–5 h after sc administration. Exenatide has shown a markedly improved postprandial profile after 28 days dosing of only 0.08 μ g/kg given twice or three times daily.⁴⁵ Independent studies of exendin-4 in man have shown a potential for glucose lowering of about of 3–6 mM, but the study was performed without a control group,³⁷ which makes comparison difficult. Liraglutide has been shown to have linear dose-dependent pharmacokinetic properties in man, with a half-life of 11–15 h and a t_{max} of 9–11 h after sc administration and an absolute bioavailability of 55%.^{39,46} Thus, the half-life should be in agreement with full efficacy following once daily administration.

Apart from the control of blood glucose, the potential long-term ability of GLP-1 to improve the β -cell function is a very important point. Indeed, because of the combined effects, GLP-1 may even be called a vitamin for the β -cell. For example, as shown in Figure 5, one injection of liraglutide has been shown to restore glucose sensitivity to β -cells in patients with type 2 diabetes.⁴⁷ These data are promising for the potential ability of the

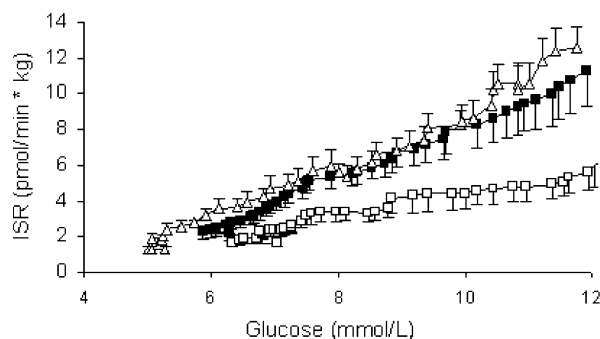


Figure 5. Relationship between insulin secretion rate (ISR) and plasma glucose levels during the graded glucose infusion protocol in subjects with type 2 diabetes who received liraglutide ("black squares") or placebo ("white squares"). ISR was derived by deconvolution of peripheral C-peptide concentrations. ISR was substantially increased with liraglutide compared to placebo over the glucose range 6–12 mmol/L and was similar to values in healthy control subjects ("white triangles") who did not receive the drug. Data are the mean \pm SE, $n = 10$, for each group. Reprinted with permission from *Diabetes*.⁴⁷ Copyright 2003 The American Diabetes Association.

Last, it has been shown in rodents that GLP-1 leads to undesirable effects such as increased heart rate and blood pressure.⁴⁸ However, studies with the two compounds in large-scale clinical trials have not reported such important side effects, so it seems that these effects are rodent-specific. In fact, it has been suggested that GLP-1 may even exert a cardiovascular protecting effect either indirectly via lowering of blood glucose and plasma lipids or directly via specific GLP-1 receptors on the heart.¹⁴

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Biography

Lotte Bjerre Knudsen obtained her degree in Chemical Engineering from the Technical University of Denmark in 1989. She has been working for Novo Nordisk since 1989 as a Scientist in Molecular Pharmacology and as Project Leader of the GLP-1 project and is currently Director of the preclinical GLP-1 area.

References

- (1) Nauck, M. A.; Kleine, N.; Orskov, C.; Holst, J. J.; Willms, B.; Creutzfeldt, W. Normalization of Fasting Hyperglycemia by Exogenous Glucagon-Like Peptide-1 (7–36 Amide) in Type-2 (Non-Insulin-Dependent) Diabetic-Patients. *Diabetologia* **1993**, *36*, 741–744.
- (2) Vilsboll, T.; Krarup, T.; Madsbad, S.; Holst, J. J. No Reactive Hypoglycaemia in Type 2 Diabetic Patients after Subcutaneous Administration of GLP-1 and Intravenous Glucose. *Diabetic Med.* **2001**, *18*, 144–149.
- (3) Gromada, J.; Holst, J. J.; Rorsman, P. Cellular Regulation of Islet Hormone Secretion by the Incretin Hormone Glucagon-Like Peptide 1. *Pfluegers Arch.* **1998**, *435*, 583–594.
- (4) Holz, G. G.; Kühtreiber, W. M.; Habener, J. F. Pancreatic Beta-Cells Are Rendered Glucose-Competent by the Insulinotropic Hormone Glucagon-Like Peptide-1(7–37). *Nature* **1993**, *361*, 362–365.
- (5) Drucker, D. J.; Philippe, J.; Mojsov, S.; Chick, W. L.; Habener, J. F. Glucagon-Like Peptide I Stimulates Insulin Gene Expression and Increases Cyclic AMP Levels in a Rat Islet Cell Line. *Proc Natl Acad Sci USA* **1987**, *84*, 2401–2405.

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