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Abstract

Glucagon-like peptide-1 (GLP-1)-based therapy of type 2 diabetes is executed either by GLP-1 receptor agonists, which stimulate the GLP-1 receptors, or by dipeptidyl peptidase-4 (DPP-4) inhibitors, which prevent the inactivation of endogenous GLP-1 thereby increasing the concentration of endogenous active GLP-1. GLP-1 activates pancreatic receptors resulting in improved glycemia through glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. There is also a potential beta cell preservation effect, as judged from rodent studies. GLP-1 receptors are additionally expressed in extrapancreatic tissue, having potential for the treatment to reduce body weight and to potentially have beneficial cardio- and endothelioprotective effects. Clinical trials in subjects with type 2 diabetes have shown that in periods of 12 weeks or more, these treatments reduce HbA_{1c} by ≈0.8-1.1% from baseline levels of 7.7-8.5%, and they are efficient both as monotherapy and in combination therapy with metformin, sulfonylureas, thiazolidinediones or insulin. Furthermore, GLP-1 receptor agonists reduce body weight, whereas DPP-4 inhibitors are body weight neutral. The treatment is safe with very low risk for adverse events, including hypoglycaemia. GLP-1 based therapy is thus a novel and now well established therapy of type 2 diabetes, with a particular value in combination with metformin in patients who are inadequately controlled by metformin alone.

Key words: GLP-1, DPP-4 inhibition, type 2 diabetes, exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide, sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin

Introduction

Oral glucose administration elicits a larger insulin secretion than intravenous glucose when glucose levels are matched. This is called the incretin effect. It is attributed to an augmented glucose-stimulated insulin secretion induced by the gut incretin hormones released after oral glucose, the most important being glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [1]. GLP-1 is a 30 amino acid peptide which is a product of the proglucagon gene in the intestinal L-cells and released after meal ingestion [1]. GLP-1 is the endogenous ligand of the G ($G_{\alpha s}$) protein coupled GLP-1 receptors, which are expressed in a number of organs, including the pancreatic beta cells. Activation of the GLP-1 receptors elevates cAMP levels through the action of adenylate cyclase; cAMP in turn activates protein kinase A and Epac 1 and 2, resulting in a stimulation of insulin secretion in a glucose-dependent manner [2].

GLP-1 also increases beta cell mass through stimulated neogenesis and proliferation and inhibited apoptosis, as shown in rodents [3]. Furthermore, GLP-1 inhibits glucagon secretion, which, as the stimulation of insulin secretion, is exerted in a glucose-dependent manner [4]. Other effects of GLP-1 include inhibition of gastric emptying [5] and induction of satiety with reduction in food intake [6]. Since all these effects are of potential value in the treatment of type 2 diabetes, GLP-1 has been explored as a pharmacological therapy for the disease.

The original evidence that GLP-1 might be a potential target in the treatment of type 2 diabetes was reported in the early 1990s in a study showing that intravenous infusion of

GLP-1 to subjects with diabetes reduces the insulin requirement to meal ingestion [7]. The antidiabetic action of GLP-1 was later confirmed in a number of other clinical and experimental studies; a particular important contribution was a study showing improved glycemic control and reduction in body weight after six weeks continuous subcutaneous infusion of GLP-1 in subjects with type 2 diabetes [8]. A challenge in the development of GLP-1 based therapy was that the active form of GLP-1 has a short half-life of only 1-2 minutes, because it is rapidly inactivated through truncation of the peptide by removal of the N-terminal dipeptide end through the enzyme dipeptidyl peptidase-4 (DPP-4) [1]. Two strategies have been explored to overcome this challenge. One strategy is the use of GLP-1 receptor agonists, which are largely resistant to the action of DPP-4, whereas the other approach is to inhibit the enzyme DPP-4, which prevents the inactivation of GLP-1 and thereby enhances and prolongs the action of the endogenous incretin hormone [9]. Both these approaches are now, after many years of development, established in the clinical management of type 2 diabetes over the world [9].

GLP-1 receptor agonists and clinical effects

GLP-1 receptor agonists are injectable proteins activating GLP-1 receptors, and they are of two different kinds [1]; structures are displayed in Table 2. One type is based on the structure of exendin-4, which is the peptide isolated from the salivary gland in the Gila monster. The other type is derivatives of the native GLP-1 molecule. The proteins can in addition be bound to or coupled to albumin, which further prolongs the biological action of the peptides. They are administered subcutaneously twice daily (exenatide), once daily (liraglutide, lixisenatide) or once weekly (taspoglutide, albiglutide). They have all been

shown to improve glycemia and reduce body weight. In 2005, the first GLP-1 receptor agonist, exenatide, was approved for clinical use, and this was followed by the second one, liraglutide, in 2009. Several other GLP-1 receptor agonists are in late clinical development.

Exendin-derived GLP-1 receptor agonists

The first GLP-1 receptor agonist which was developed and approved for clinical use was exenatide (Byetta^{R}, Amylin and Eli Lilly) [1]. Exenatide is the synthetic form of exendin-4, showing 53% homology to GLP-1 (Table 2); it binds to GLP-1 receptor with the same or even higher affinity as native GLP-1. It is resistant to DPP-4 inactivation and its half-life is approximately 1.5 to 2 hours with effective drug concentrations present for 6-8 hours after injection. It has to be given twice daily. In early clinical trials, exenatide was explored as add-on therapy to patients with type 2 diabetes who were inadequately treated with metformin and/or sulfonylurea [10]. The results of these studies showed that exenatide improves the glycemic control with a reduction of HbA_{1c} by ~0.8-0.9% after a 30 week study period from baseline HbA_{1c} of 8.2-8.6%. Subsequent clinical studies and clinical experience have confirmed the findings of improved glycemia by exenatide [11-13]. Exenatide also reduces body weight, as is seen in the early 30 week trials [10]; in an open-label 82 week study, exenatide reduced body weight by 5.3kg [11].

Exenatide is safe and well tolerated and associated with a low risk of hypoglycemia. In fact, occurrence of hypoglycaemia when exenatide is combined with metformin is the same as when metformin is given alone [10]. The only consistent adverse events with

exenatide are nausea and vomiting, which are observed in up to 40% of patients; the nausea is usually reduced during on-going treatment. A concern has been that antibodies are formed during treatment with exenatide; in most studies 20-40% of the patients develop antibodies. Most of these patients develop low titer antibodies with no apparent clinical consequences since the reduction in HbA_{1c} is similar in patients with versus without antibodies. After the approval of exenatide, postmarketing reports of several incidents of acute pancreatitis in patients treated with exenatide have been disclosed [14]. These cases have in general been mild or moderate in severity, but rare cases of fatal or nonfatal hemorrhagic or necrotizing pancreatitis have also been reported. Considering that diabetes per se is a risk factor for acute pancreatitis, it is not yet established whether exenatide can induce this serious adverse event. Nevertheless, patients should be informed about this risk when starting treatment with exenatide, and the compound should not be used in patients with a history of or increased risk for pancreatitis.

A further development of exenatide is exenatide LAR (Bydureon^{R}, Lilly), in which exenatide is used in a delivery system consisting of microspheres of biodegradable polymers, which prolongs the half-life of the compound, enabling once weekly administration. This long acting form is now in late clinical development and has been shown to have a better glycemic effect than conventional exenatide given twice daily in a study over 52 weeks [15]. The reduction in HbA_{1c} by exenatide LAR was 2.0% from a baseline of 8.3% and this was associated with a reduction in body weight by 4.1kg from 103 kg. Nausea, which was mild, occurred in only 7% of the patients.

Another exendin-4-based compound in late clinical development is lixisenatide (AVE-0010, Sanofi Aventis). In lixisenatide, the penultimate proline of exendin-4 has been deleted and the molecule has been prolonged by addition of six lysine-residues at the C-terminus [16; Table 2]. This prolongation enables the compound to be administered once daily. The clinical experience with lixisenatide is still limited with only one reported clinical study so far. This 13 week study showed a reduction in HbA_{1c} by 0.7% for the clinical dose of 20μg once daily from a baseline of 7.5% in patients with type 2 diabetes [17].

GLP-1 receptor agonists

The first GLP-1 analogue which was approved is liraglutide (Victoza ^{R}, Novo Nordisk A/S; approved in the US in 2009). In liraglutide, a C-16 acyl chain (palmitoyl) is linked to amino acid 20 via a γ-glutamic acid spacer, and the lysine in position 28 of native GLP-1 is exchanged with arginine [18, Table 2]. The incorporation of the acyl chain allows a non-covalent binding to albumin, which delays both inactivation by DPP-4 and renal clearance, resulting in a half-life of approximately 11-15 hours; it is therefore administered once daily. Clinical trials have demonstrated that liraglutide reduces HbA_{1C} and body weight both in monotherapy and in combination with metformin alone or sulfonylurea or thiazolidinedione in combination with metformin [18]. In these six months studies, the reduction in HbA_{1c} by liraglutide varied from 1.1 to 1.5% from baseline values of 8.2-8.5%, and the reduction in body weight was in the range of 2-3 kg. Liraglutide is also associated with a low risk of hypoglycemia. Similar to exenatide, the

most common adverse events for liraglutide are nausea and vomiting, which are seen in the beginning of treatment, although nausea is less common than with exenatide. Antibody formation against liraglutide is less than what is observed with exenatide and reported to be in the range of 10%. Furthermore, as for exenatide, also pancreatitis has been observed in patients treated with liraglutide (www.victoza.com). Hence, as for exenatide, liraglutide should not be given to patients with a history of or increased risk for pancreatitis. Finally, in rodents, liraglutide has been associated with increased risk of benign and malignant thyroid C-cell tumors (www.victoza.com). No such case has been observed in humans but nevertheless, liraglutide should not be given to patients with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

Two other long-acting GLP-1 analogues are in late clinical development (Table 2). Albiglutide (GSK) is a GLP-1 analog in which a dimer of GLP-1 (with amino acid number two exchanged for glycine) is genetically fused with human serum albumin. This substantially prolongs the action, because the molecule is both DPP-4 resistant and bound to albumin and it is therefore possible to administer the compound once weekly, once bi-weekly and once monthly [19]. Clinical experience with albiglutide is still limited, but one study has demonstrated that a 16 week treatment in patients with type 2 diabetes who are inadequately controlled with diet and exercise or metformin, albiglutide reduced HbA_{1c} by ~0.8% from a baseline of 8.0% in association with reduction in body weight (by 1.1-1.7 kg depending on the dose) with very low risk for hypoglycemia and a low frequency of nausea [19]. Further studies are on-going.

Another GLP-1 analogue in clinical development is taspoglutide (Roche). In this compound, amino acids number 2 (alanine) and 29 (arginine) of native GLP-1 are replaced by 2-aminoisobutyric acid (Table 2). After this change, the half-life is still short (≈4-5 min), but when taspoglutide is prepared in a zinc chloride formulation, it precipitates after subcutaneous injection, resulting in a slow dissociation from the site of administration. This prolongs the action, making it suitable for administration once a week. Recent reports have shown efficient reduction in HbA_{1c} by approximately 0.8-1.1% from a baseline of 7.9-8.3% when used in combination with metformin; the effect was superior to that of exenatide [24]. In September 2010, the company making taspoglutide (Roche) announced that it halted Phase III clinical trials, because of incidences of hypersensitivity reactions and gastrointestinal side effects. It is thus not clear whether development of taspoglutide will be finalized for approval in clinical use.

In conclusion, GLP-1 receptor agonists administered subcutaneously once or twice daily or once weekly reduce HbA_{1c} by approximately 1% in association with body weight reduction by 2-5 kg with the only consistent adverse event being transient nausea.

DPP-4 inhibition and clinical effects

DPP-4 inhibition prevents the inactivation of GLP-1 and therefore enhances and prolongs the action of the endogenously released incretin hormone [9]. A proof-of-concept study of this strategy was published in 2002 and showed improved metabolic control with reduced fasting and prandial glucose levels and reduction of HbA_{1c} after four weeks of treatment with the DPP-4 inhibitor, NVP-DPP728 [21]. Several DPP-4 inhibitors have

been identified and are in different stages in clinical development. Sitagliptin (Januvia^{R}, Merck) was the first DPP-4 inhibitor being approved, and now also vildagliptin (Galvus^{R}, Novartis) and saxagliptin (Onglyza^{R}, Bristol-Myers-Scribbs/Astra-Zeneca) are approved in several countries. Furthermore, alogliptin (Takeda) is approved in Japan, and linagliptin (Boehringer-Ingelheim) is in late clinical development. They are all orally active compounds which efficiently inhibit plasma DPP-4 activity [22-26]. Although they differ in chemistry, they are all small molecules (Fig. 1) and they rapidly inhibit DPP-4 activity after oral administration. Their mechanism of inhibiting the catalytic site of DPP-4 is different. Thus, vildagliptin and saxagliptin bind covalently to the catalytic site of the enzyme whereas sitagliptin, alogliptin and linagliptin are competitive inhibitors. The DPP-4 inhibitors also differ in their pharmacokinetic profiles, metabolism and elimination [27]. However, in spite of these differences, they all increase the circulating levels of GLP-1 and the anti-diabetic activity seems to be similar when comparing the different DPP-4 inhibitors. Thus, all DPP-4 inhibitors in clinical use or in late clinical development have been shown to reduce HbA_{1c} by approximately 0.5-0.8% when used in monotherapy and by 0.8-1.1% when used in combination with metformin, sulfonylureas or thiazolidinediones, although these values depend on the baseline values of the studied patients [22-26]. Furthermore, the DPP-4 inhibitors are body weight neutral and associated with very low risk for hypoglycaemia.

The DPP-4 inhibitors have been found to be particularly powerful when used in combination with metformin [28]. This is particularly evident when the effects of DPP-4 inhibitors (vildagliptin, sitagliptin or saxagliptin) have been compared with those of

sulfonylureas (glimepiride or glipizide) when added to on-going metformin therapy [29]. These studies have shown that over a two year period, HbA_{1c} is reduced by the same degree by DPP-4 inhibition and sulfonylureas, and that body weight does not increase by DPP-4 inhibition (it is increased by sulfonylureas) and the number of hypoglycaemic events are considerably lower in patients treated with DPP-4 inhibition than in those treated with sulfonylureas [29]. DPP-4 inhibitors can also be added to insulin, which reduces HbA_{1c}, minimizes the risk for hypoglycaemia [30].

Mechanisms of GLP-1 receptor agonists and DPP-4 inhibitors

Islet function. GLP-1 receptor agonists and DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion, as has been demonstrated in several studies with different methods for judging islet function [1,10,22-26,28]. Interestingly, as demonstrated for vildagliptin [31] and exenatide [32], during hypoglycaemia, the counterregulatory increase in glucagon levels is preserved, showing that even though GLP-1 based therapy inhibits glucagon secretion as a part of the antidiabetic action, the defence by increasing glucagon in hypoglycaemia is not compromised. This further illustrates the safety of this treatment in relation to hypoglycaemia.

In animal studies, GLP-1 increases beta cell mass by stimulating proliferation and inhibiting apoptosis [3]. This has also been demonstrated for DPP-4 inhibition [33]. Whether GLP-1 based therapy also increases islet cell mass in type 2 diabetics has not yet been established. Attempts to show this have used the approach of study insulin secretion after discontinuation of therapy; the hypothesis has been that if an increased beta cell

mass has evolved, increased insulin secretion would be maintained even after discontinuation of therapy. Long-term studies have thereby shown that after three years of treatment with exenatide [34] or two years treatment with vildagliptin [35], sustained increase in insulin secretion is seen after four weeks of discontinuation of therapy, which might support the notion that islet cell preservation has been induced in patients. However, more studies are required on long-term influences on islet function of GLP-1 based therapy.

Appetite, satiety and body weight. GLP-1 is known to induce satiety, which results in reduced food intake and reduced body weight. This effect is seen clinically after treatment with GLP-1 receptor agonists, where reduction in body weight by 3-5% occurs after 1-3 years of treatment [11,12]. In contrast, DPP-4 inhibitors are body weight neutral, meaning that body weight usually does not change during treatment. It should be emphasized, however, that body weight neutrality in the presence of improved glycemic control may suggest an effect on satiety and body weight, since as shown after treatment with sulfonylureas and insulin, body weight is usually increased by treatment [29].

Other effects. GLP-1 receptors are widely expressed in several extrapancreatic organs throughout the body, such as endothelial cells, cardiac cells and in the lungs, and it is therefore possible that GLP-1 based therapy also stimulate these receptors. Of particular interest has been whether GLP-1 based therapy improves cardiovascular function. Up to now, clinically important markers for cardiovascular events, such as blood lipids and blood pressure have been shown to be improved by GLP-1 based therapy [13,36]. What

is now important is to perform long-term studies on cardiovascular events to examine whether GLP-1 based therapy improves cardiovascular outcomes.

Comparisons between GLP-1 receptor agonists and DPP-4 inhibitors

Although both strategies are based on the effects of GLP-1, several differences between the two approached exist. Table 1 compares major characteristics of GLP-1 receptor agonists and DPP-4 inhibitors. An obvious difference is that GLP-1 receptor agonists are injectables, given subcutaneously, whereas DPP-4 inhibitors are oral agents. Also the duration of their pharmacodynamic activity differs. GLP-1 receptor agonists have a variable duration enabling administration twice daily, once daily or once weekly, whereas DPP-4 inhibitors are given once or twice daily. From a GLP-1 receptor activation point of view, interesting differences exist. Thus, GLP-1 receptor agonists stimulate GLP-1 receptors supraphysiologically, since high doses of the agonists occur after administration, whereas DPP-4 inhibitors stimulate the receptors at physiological concentrations of GLP-1. Furthermore, GLP-1 receptor agonists stimulate the receptors continuously over the time when their concentrations are elevated, whereas after administration of DPP-4 inhibitors, GLP-1 levels retain their diurnal pattern with increase after meal ingestion. For DPP-4 inhibitors, there is also a potential that other bioactive peptides, apart from GLP-1, may contribute to their effects, because also other peptides, like GIP and pituitary adenylate cyclise activating polypeptide (PACAP), may be inactivated by DPP-4 and therefore stabilized during treatment with DPP-4 inhibitors. However, to what extent these potential differences indeed contribute to the clinical effects of the two approaches remain to be studied further.

In terms of islet effects, both GLP-1 receptor agonists and DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion by glucose-dependent mechanisms. In contrast, in regard to gastric emptying and satiety, two other effects of GLP-1, these are affected only by GLP-1 receptor agonists and not by DPP-4 inhibitors. In terms of clinical effects, both approaches reduce fasting and prandial glycemia and HbA_{1c}; GLP-1 receptor agonists seem to have a higher efficacy for improving glycemia, and body weight is reduced only by GLP-1 receptor agonists, although in some studies, slightly lower body weight has been found after treatment with DPP-4 inhibitors. In regard to adverse events, GLP-1 receptor agonists are associated with nausea and vomiting, whereas no specific adverse events have been reported for DPP-4 inhibitors, and hypoglycaemia is rarely seen with both approaches.

A few head-to-head studies have been undertaken to compare GLP-1 receptor agonists versus DPP-4 inhibitors. One study compared liraglutide (1.2 or 1.8 mg daily) versus sitagliptin (100 mg daily) as ad-on to metformin for 26 weeks in subjects with type 2 diabetes with inadequate glycemic control when treated with metformin alone; baseline HbA_{1c} 8.5% [37]. HbA_{1c} was reduced by 1.5% by liraglutide at 1.8mg, by 1.2% by liraglutide at 1.2 mg and by 0.9% by sitagliptin. Body weight was reduced by 3.4 and 2.9 kg by liraglutide and by 1.0 kg by sitagliptin. Hypoglycemic events were low (~5%) and not different between the groups, whereas nausea was much more prevalent in patients treated with liraglutide (27% and 21% for the two doses) than with sitagliptin (5%).

Similar results were reported when treatment with exenatide LAR [38] or taspoglutide [39] was compared with sitagliptin.

Within the GLP-1 receptor agonist group, the longer acting agonists seem more potent, as verified by head-to-head studies showing a larger reduction in HbA_{1c} by liraglutide than by exenatide [40] and by once weakly exenatide versus twice daily exenatide [15]. In regard to DPP-4 inhibitors, they seem all to have similar efficacy, which is supported by a head-to-head studies comparing sitagliptin with saxagliptin as add-on to metformin. The study was an 18 week trial in which baseline HbA_{1c} was 7.7%. HbA_{1c} was reduced by sitagliptin by 0.6% and by saxagliptin by 0.5%, which was not significantly different [27].

Place in therapy

GLP-1 receptor agonists and DPP-4 inhibitors are, with some differences between different compounds, approved for use in therapy of type 2 diabetes combination with treatment with metformin, sulfonylurea and/or thiazolidinedione in patients who are not satisfactorily controlled on these agents alone. For some of the compounds, there is also indication as monotherapy in patients in whom metformin is unsuitable, and there is in addition indication for use together with insulin. The advantages of treatment with GLP-1 based therapy is that it improves glycemic control without the increase in body weight and at the same time reduces the risk of hypoglycaemia when compared with existing treatment. The discussion which is on-going among clinicians today is whether GLP-1

based therapy may be considered as the main treatment to add to metformin, when metformin alone is insufficient, or whether sulfonylurea or TZD is the main second-line therapy. Advantages of GLP-1 based therapy is that it is efficient and highly tolerable with very few adverse events, it is associated with body weight reduction or neutrality and that it is associated with very low risk for hypoglycaemia. The drawback of GLP-1 based therapy is that the clinical experience is only a little more than five years and that the price for the compounds is still high. It is, however, clear, that GLP-1 based therapy has gained considerable interest in clinical practice, and the use of it increases every month.

Conclusion

GLP-1 based therapy was rationally developed based on knowledge of the physiology and metabolism of GLP-1 in association with knowledge that islet dysfunction is the key defect in type 2 diabetes. The development of this biotherapeutic is therefore a success for bench-to-bedside research and the development is a lesson of research-driven innovation. The successful development of GLP-1 based therapy thus was made possible by researchers with deep knowledge on pathophysiology of diabetes and the key involvement of islet dysfunction together with knowledge on integrated metabolism and a close cooperation between academic units and the research-oriented pharmaceutical industry.

After the years of clinical experience, which have accumulated now, the overall experience shows that GLP-1-based therapy is efficient and safe with a minimal risk for

hypoglycemic events. GL-1-based therapy is therefore an important contribution to the pharmaceutical arsenal in the management of type 2 diabetes.

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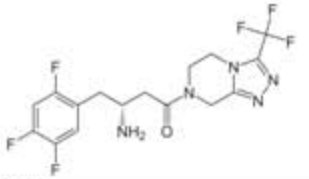
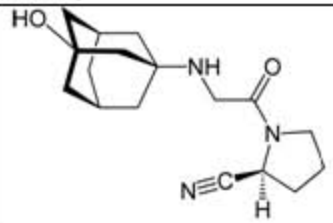
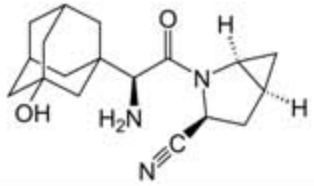
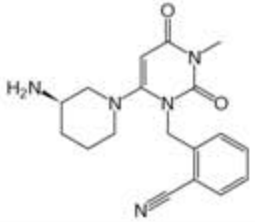
Table 1 Characteristics and effects of GLP-1 receptor agonists and DPP-4 inhibitors

	GLP-1 receptor agonists	DPP-4 inhibitors
Mode of administration	Subcutaneous	Oral
Duration	Daily - weekly	Daily
GLP-1 receptor activation	Supraphysiological Continuous	Close to physiological Retained diurnal pattern
Mediators of effect	GLP-1 receptor activation	GLP-1 receptor activation Other bioactive peptides?
Insulin secretion	Stimulation	Stimulation
Glucagon secretion	Inhibition	Inhibition
Gastric emptying	Inhibition	No effect
Appetite	Induction of satiety	No effect
Fasting glucose	Reduction by ~1 mmol/l	Reduction by ~1 mmol/l
Prandial glucose	Marked reduction	Slight reduction
HbA_{1c}	Reduction by ~1%	Reduction by ~0.8%
Body weight	Reduction	No change
Hypoglycemia	No	No
Adverse events	Nausea	No

Table 2. Structures of the GLP-1 receptor agonists that are on the market or in very late clinical development; for comparison the amino acid sequence of native GLP-1 is also shown.

Name	Structure
Native GLP-1	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg
Exenatide (Byetta^{R})	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser
Lixisenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys
Liraglutide (Victoza^{R})	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly | Glu – C16 fatty acid (palmitoyl)
Albiglutide	(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)$_2$– genetically fused to human albumin
Taspoglutide	His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (Aib = 2-aminoisobutyric acid)

Fig. 1. Structures of the DPP-4 inhibitors that are on the market or in very late clinical development.

Name	Structure
Sitagliptin (Januvia^{R})	
Vildagliptin (Galvus^{R})	
Saxagliptin (Onglyza^{R})	
Alogliptin	
Linagliptin