



# Exenatide: a novel treatment of Type 2 diabetes

Bo Abbrén

Lund University, Department  
of Medicine, B11 BMC,  
SE-221 84 LUND, Sweden  
Tél: +46 462 220 758;  
E-mail: Bo.Abrén@med.lu.se

Glucagon-like peptide-1 is an incretin hormone with antidiabetic action due to stimulation of insulin secretion, and potentially also to an increase in  $\beta$ -cell mass, inhibition of glucagon secretion, delay in gastric emptying and induction of satiety. A problem in developing glucagon-like peptide-1 as a therapeutic compound is that the hormone is rapidly inactivated by dipeptidyl peptidase-4. To overcome this, long-acting dipeptidyl peptidase-4, resistant receptor agonists have been explored. One such promising agonist is exenatide, which was isolated as exendin-4 from the lizard Gila monster. Exenatide, administered twice daily subcutaneously, improves metabolic control in subjects with Type 2 diabetes, both when given alone and together with other treatments. The durability is good – a 30-week study showed that HbA<sub>1c</sub> was reduced by 1.0%. This observation is also seen in association with weight loss. Furthermore, clinical studies have shown that exenatide is safe and tolerable. Mild-to-moderate nausea and vomiting are the most consistent adverse events – it is seen in the early phases of treatment in approximately 30% of subjects given exenatide. The experience so far shows that exenatide offers a promising novel therapy for Type 2 diabetes, based on an interaction with glucagon-like peptide-1 receptors.

The prevalence of Type 2 diabetes is increasing throughout the world. It is currently reaching epidemic proportions with an estimated global prevalence in the year 2000 of 2.8%, corresponding to 171 million people with diabetes [1]. This development is serious for global health because Type 2 diabetes leads to the development of a number of secondary complications such as retinopathy, neuropathy, angiopathy, atherosclerosis, nephropathy, hyperlipidemia and hypertension, and is strongly associated with cardiovascular and cerebrovascular diseases, resulting in increased morbidity and mortality [2].

Two important risk factors for Type 2 diabetes are age above 65 years [1] and obesity, in particular, central body fat accumulation [3]. A primary event during the development of diabetes is a reduction in insulin sensitivity – insulin resistance. This is compensated by increased insulin secretion. However, subjects who do not adequately and sufficiently increase insulin secretion in relation to the insulin resistance become hyperglycemic and may develop impaired glucose tolerance (IGT) or Type 2 diabetes [4,5]. It has also been proposed that subjects with Type 2 diabetes have in addition a reduced  $\beta$ -cell mass due to increased  $\beta$ -cell apoptosis [6]. Another pathogenic factor for Type 2 diabetes is inappropriately high glucagon levels, which accentuate the increased insulin demand [for review see 7]. Reduced insulin

secretion leads to plasma insulin levels which are inappropriate for the ambient glucose concentrations, and this leads to subnormal elimination of glucose from the circulation. Furthermore, inappropriately high glucagon levels enhance the release of glucose from the liver. Both of these processes increase circulating glucose under fasting conditions and after meal ingestion. Therefore, a key defect and a mechanism for hyperglycemia in Type 2 diabetes is an islet dysfunction manifested in low insulin secretion and increased glucagon secretion and, perhaps, reduced  $\beta$ -cell mass.

Hyperglycemia in diabetes is a major factor contributing to diabetic complications [8,9]. Therefore, a major goal for the treatment of Type 2 diabetes is to re-establish normoglycemia, both under fasting conditions and postprandially [10]. The basis for treatment is adjusting lifestyle, with increased physical exercise and dietary modifications which increase insulin sensitivity, reduce metabolic challenge after meals and promote islet function [11]. If this is not sufficient, several efficient pharmacologic tools are available. These tools reduce circulating glucose by increasing insulin sensitivity, augmenting insulin secretion, reducing glucose entry into the bloodstream after meal ingestion or replacing insulin with exogenous administration [12]. These treatments, used alone or,

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preferably, in combination, are beneficial in improving the metabolic control. However, although efficient, these treatment modalities are in many subjects insufficient. This is evident from clinical experience and also from studies showing that even intense treatment with existing treatment modalities does not prevent the progression of diabetes [9]. The insufficiency of existing treatment modalities is also evident from the profile of pharmacologic tools. Thus, treatments do not target all pathophysiologic defects of the disease as high glucagon secretion and reduced  $\beta$ -cell mass are usually not targeted. Furthermore, they are associated with adverse events which limit their use. There is therefore a need for better modes of controlling hyperglycemia in Type 2 diabetes.

Novel treatment modalities for Type 2 diabetes should normalize the pathophysiologic defects underlying hyperglycemia in combination with high tolerability and a low degree of adverse events. Novel treatment methods should also take into consideration the importance of obesity as an underlying cause. A number of targets for improved treatment are currently being explored and have recently been reviewed [13]. A novel treatment for Type 2 diabetes is based on the beneficial and antidiabetic effects of the gut hormone glucagon-like peptide (GLP)-1. One of the most promising compounds within the class of GLP-1-based therapy is the GLP-1 mimetic, exenatide.

### Overview of the market

#### *Unmet needs of currently available therapies*

Sulfonylureas ([SUs], such as glyburide, glipizide and glimepiride) are compounds which potently stimulate insulin secretion through activation of a SU receptor (SUR). SUR activation causes a closure of ATP-regulated  $K^+$  channels of  $\beta$ -cells, which initiates depolarization, opening of voltage-sensitive  $Ca^{2+}$  channels, uptake of  $Ca^{2+}$  with a corresponding increase in the cytosolic concentration of  $Ca^{2+}$  and a marked stimulation of exocytosis [14]. SUs are efficient in reducing glucose, but they have important drawbacks, as they increase body weight, have a risk of hypoglycemia and, importantly, show a high degree of failure during long-term treatment [15]. Novel, more rapidly acting insulin secretagogues (repaglinide, nateglinide), which also close ATP-dependent  $K^+$ -channels, have been introduced. These have a shorter duration of action with a reduced risk of hypoglycemia; their long-term efficiency has, however, not been established in comparison with that of SUs. An

overall conceptual problem with the clinically used insulin secretagogues is that they target only one defect in diabetes, the impaired insulin secretion, and therefore, do not target the reduced  $\beta$ -cell mass, the reduced hyperglucagonemia or the insulin resistance [16].

The most frequently used compound that increases insulin sensitivity is metformin, which reduces hepatic glucose production and increases insulin sensitivity in peripheral tissues [17]. It is used alone or in association with insulin secretagogues. Drawbacks with metformin include gastrointestinal adverse events and a risk of lactic acidosis, particularly in subjects with kidney failure and tissue hypoxia. Nevertheless, metformin is efficient in improving metabolic control and is often used as a first-line treatment. Another class of compounds responsible for increasing insulin sensitivity is the thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone. TZDs enhance insulin sensitivity by activating the nuclear receptor peroxisome proliferator-activated receptor (PPAR)- $\gamma$  [18]. They are efficient, but their use is also associated with adverse events such as weight gain and edema [19]. Other currently used antidiabetic agents are the  $\alpha$ -glucosidase inhibitors such as acarbose and miglitol, which inhibit the breakdown of oligo- and disaccharides, thereby reducing glucose uptake and postprandial glycemia. They have however, limited long-term efficiency and are also associated with gastrointestinal adverse events. Finally, exogenous insulin administration, although very efficient, is associated with weight gain and hypoglycemia. Novel treatments must:

- Target the main defects of the disease such as impaired insulin secretion, reduced  $\beta$ -cell mass, increased glucagon secretion and insulin resistance
- Reduce both fasting and postprandial glycemia
- Show high durability with efficient long term effects preventing  $\beta$ -cell failure
- Demonstrate a favorable safety profile with a low degree of adverse events and limited risk of hypoglycemia
- Show no increase in body weight in spite of improved metabolic control

#### *Classes of compounds in late development*

Several classes of compounds are in development [13], some of which increase insulin secretion by targeting various  $\beta$ -cell signals. Meglitinide is a compound which, like the SUs repaglinide and nateglinide, targets the ATP-regulated  $K^+$  channels. However, in contrast to

the SUs, meglitinide is rapid acting and more  $\beta$ -cell selective [20]. Similarly, a guanidine derivative targeting ATP regulated  $K^+$  channels independent from  $S_{IR}$ s has shown promise by demonstrating antidiabetic effects without causing weight gain or adverse events [21]. Another class of compounds stimulating insulin secretion is the imidazoline derivatives [22]. Several other classes of compounds that stimulate insulin secretion in a manner independent of ATP-regulated  $K^+$  channels are at present under investigation in preclinical studies, such as JTT608, 4-hydroxyisoleucine and succinic acid esters [13]. However, their long-term efficiency and clinical effects are currently unknown.

To improve insulin sensitivity, several classes of compounds are currently under investigation. Most promising are dual PPAR- $\alpha$ / $\gamma$  agonists which have the advantage of preserving islet function during improved insulin resistance as well as reducing circulating lipids, as has been demonstrated for DRF-2519 and AZ42 [23,24]. Other targets for improving insulin sensitivity include glycogen synthase kinase (GSK3) and protein tyrosine phosphatase (PTP1B) [13]. In general, however, these new compounds and classes of compounds have not been examined in human studies and, most importantly, their long-term efficiency in subjects with Type 2 diabetes is not known.

**Glucagon-like peptide-1 as a basis for novel therapy**

GLP-1 is a gut incretin. Incretins are hormones, which are produced in the gastrointestinal tract, released into the bloodstream during meal ingestion and stimulate insulin secretion in a

glucose-dependent manner [for review see 25]. The main incretin hormones are GLP-1 and glucose-dependent insulinotropic peptide (GIP) [25]. These hormones contribute to more than 70% of the insulin response after meal ingestion [26]. The augmentation of glucose-stimulated insulin secretion following food ingestion is impaired in Type 2 diabetes [26]. This may be due to impaired release of GLP-1 [27] and impaired action of GIP [28].

GLP-1 is processed from proglucagon in the L-cells, which are distributed mainly to the lower part of the small intestine [for review see 29]. Large amounts of GLP-1 are also found in the large intestine and proglucagon processing also occurs in the brain [30]. Proglucagon is expressed both in the L- and  $\alpha$ -cells in the pancreatic islets. However, due to tissue-specific processing of the prohormone, GLP-1 is only produced in the L-cells. Tissue-specific expression is due to expression of proconvertases (PCs). PC1/3 (catalyzing proglucagon  $\rightarrow$  GLP-1) is expressed in L-cells, whereas PC2 (catalyzing proglucagon  $\rightarrow$  glucagon), is produced in the  $\alpha$ -cells. GLP-1 is a peptide consisting of 30 amino acids and occurs in two different forms with the C-terminal amino acid being amidated or nonamidated; the predominant form in humans is amidated (Figure 1). GLP-1 is released during ingestion of food and circulates in the bloodstream. It activates what is thought to be a single G-protein-coupled seven-transmembranous receptor type, which is expressed in a number of tissues, such as pancreatic islets, central and peripheral neurons, heart and kidney [for review see 25,31].

A prominent function of GLP-1 is to stimulate insulin secretion, which was first demonstrated in

**Figure 1. Amino acid sequence of exenatide in comparison with human GLP-1 and Gila monster GLP-1.**

	1	30	39																																	
Exenatide	H	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	E	A	V	R	L	F	I	E	W	L	K	N	G	P	S	S	G	A	P	P	S
Human GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R						
Gila monster GLP-1	H	A	D	G	R	Y	T	S	D	I	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	N	G	R						

Numbers indicate number for amino acid (from the N-terminal end); asterisks indicate identical amino acid in exenatide and human glucagon-like peptide (GLP)-1.

A: Alanine; D: Aspartic acid; E: Glutamic acid; F: Phenylalanine; G: Glycine; H: Histidine; I: Isoleucine; K: Lysine; L: Leucine; M: Methionine; N: Asparagine; P: Proline; Q: Glutamine; R: Arginine; S: Serine; T: Threonine; V: Valine; W: Tryptophan; Y: Tyrosine.

1987 [32,33]. This finding has been demonstrated repeatedly and it has also been shown that the action is glucose-dependent, that is, when glucose levels are reduced, the insulinotropic action disappears [34–36]. This insulinotropic action of GLP-1 is presumed to be a physiologic incretin action, as augmentation of insulin secretion is observed at physiologic dose levels of GLP-1 [37], the prandial increase in glucose is enhanced by a GLP-1 receptor antagonist [38], and due to the fact that the insulinotropic effect of oral glucose is reduced in GLP-1 receptor gene-deleted mice [39]. Recent studies have suggested that the insulinotropic action of GLP-1 is due both to a direct stimulation of the islet  $\beta$ -cells and to an indirect action through stimulation of the autonomic nervous system [40–41].

Important novel findings in rodent studies revealed that GLP-1 stimulates insulin gene expression and synthesis, and  $\beta$ -cell neogenesis and proliferation; and that GLP-1 inhibits  $\beta$ -cell apoptosis. Thus, a stimulation of insulin gene expression was demonstrated as enhanced insulin mRNA levels in the pancreas after 48 h infusion of GLP-1 in rats [42] and, similarly, GLP-1 increases proinsulin gene expression after incubation of insulin-producing cells with GLP-1 [43]. Furthermore, GLP-1 has been shown to increase the expression of proteins of importance for islet development, as for example PD $\chi$  1 [44,45]. Consequently, GLP-1 has been shown to stimulate differentiation of pancreatic ductal cell lines into insulin-producing cells [46] to act as a growth factor for insulin-producing cells [47] and to stimulate islet cell proliferation in ob/ob mice [48]. Furthermore, GLP-1 has been shown to inhibit apoptosis in islet cells as evident from a study in which Zucker diabetic fatty (ZDF) rats were treated with GLP-1 [49]. Recently, it has also been shown that GLP-1 is antiapoptotic in human islets [50]. Taken together, these actions of GLP-1 may result in enhanced and increased  $\beta$ -cell mass. This has convincingly been demonstrated after treatment of partially pancreatectomized rats with the GLP-1 receptor agonist, exendin-4. Both  $\beta$ -cell proliferation and differentiation of endocrine cells were augmented by exendin-4 [51]. Similarly, in db/db mice, exendin-4 stimulated  $\beta$ -cell differentiation and neogenesis [52]. Therefore, besides its stimulatory action of insulin secretion, GLP-1-based therapy could also increase  $\beta$ -cell mass. This may be of relevance considering the recently demonstrated reduction of  $\beta$ -cell volume in subjects with Type 2 diabetes [6].

GLP-1 also has a number of other potential antidiabetic actions. Thus, GLP-1 inhibits glucagon secretion, delays gastric emptying and induces satiety [53–55]. Taken together, these studies show that GLP-1, through a number of different actions, may be beneficial in the treatment of diabetes. In fact, GLP-1 targets several of the key defects in Type 2 diabetes.

Recent studies have indicated that GLP-1 also has important effects on cardiovascular function. Thus, rodent studies have demonstrated that GLP-1 dose-dependently increases arterial blood pressure and heart rate [56]. In addition, central administration of GLP-1 has been shown to increase blood pressure and heart rate in rats, in association with increased transcription of tyrosine hydroxylase in the brain, suggesting a neural effect [57]. To examine whether these effects of GLP-1 are physiologic, it has been shown that GLP-1R $^{-/-}$  mice had a lower heart rate in younger age, in association with elevated left ventricular end diastolic pressure and increased left ventricular thickness. The mice also had impaired cardiac response to challenges with insulin-induced hypoglycemia and administration of catecholamines [58]. This suggests that GLP-1 is of physiologic importance for cardiac function in rodents, and studies in humans are now highly warranted. Another interesting novel observation is that GLP-1 might protect from myocardial infarction, as evident in a study in rodents both *in vivo* and *in vitro* [59]. Furthermore, in humans suffering from myocardial infarction, GLP-1 has been shown to improve severe left ventricular heart failure [60], as also evident from studies in dogs [61]. Finally, recent studies have shown that GLP-1 improves endothelial function, both in animal studies [62] and in humans with Type 2 diabetes and stable coronary artery disease [63]. This is consistent with the expression of GLP-1 receptors in endothelial cells [63]. Hence, GLP-1 seems to be powerful in protecting cardiovascular malfunction, which adds to its beneficial effects in Type 2 diabetes.

The first study showing that GLP-1 is antidiabetic in humans was performed by Gutniak and collaborators in 1992 [64]. In that study, GLP-1 was administered intravenously to patients with Type 2 diabetes in conjunction with a meal intake. A variable rate of insulin infusion was given to maintain the baseline glucose level during the following hours after meal intake. The amount of insulin which was infused was taken as a measure of the insulin

requirement during the meal. It was found that during the control test, when no GLP-1 was given, 17 units of insulin were required for infusion in order to maintain baseline glucose. However, when GLP-1 was given, only 2 units of insulin were required. An antidiabetic action of the nonamidated GLP-1(7–37) was also demonstrated the same year [65]. These results were followed by a number of studies demonstrating the antidiabetic action of the hormone when given as continuous intravenous infusion, intermittent subcutaneous administration or as a buccal tablet [for review see 29]. In 2002, a 6-week study of a continuous infusion of GLP-1 in subjects with Type 2 diabetes demonstrated the potential of the hormone in long-term treatment, since it was found that circulating fasting glucose was reduced by 4 mmol/L, HbA1c was reduced from 9.2 to 7.9%, body weight was reduced by approximately 2 kg and the treatment showed high tolerability [66]. Hence, these studies established GLP-1 as a potential novel treatment for Type 2 diabetes.

A problem in the development of GLP-1 as a treatment for Type 2 diabetes is that the hormone is rapidly inactivated in the circulation. This is due to the activity of the enzyme dipeptidyl peptidase (DPP-4), which cleaves the hormone by removing the two N-terminal amino acids [67]. This results in deactivation of the hormone, since the cleavage product (GLP-1<sub>9–36</sub> amide) is devoid of glucose-reducing and insulinotropic action [68]. DPP-4 is a highly efficacious enzyme which is produced in a number of organs, including the gut, liver and kidney, and which is distributed to the endothelial cells and also circulates in plasma [for review see 67]. It has a high activity, which results in rapid inactivation of GLP-1. In fact, the circulating half-life of active, intact, GLP-1 is less than 2 min [69], and less than 20% of the total GLP-1 in the circulation consists of active GLP-1 [70]. Due to the high activity of DPP-4 in inactivating GLP-1, the hormone has to be given continuously for achieving sufficient antidiabetic action. However, this is unappealing as a treatment and to overcome this problem, two strategies have successfully evolved [71]. One strategy uses compounds which activate GLP-1 receptors but are resistant to DPP-4 (GLP-1 mimetics) [72]. The other uses compounds inhibiting DPP-4, which prolongs the circulating half-life of GLP-1 and therefore prolongs the action of endogenously released GLP-1 [73–75].

## Exenatide

A promising GLP-1 mimetic for the treatment of Type 2 diabetes is exenatide. The history of this GLP-1 mimetic goes back to 1982, when it was demonstrated that the venom of a lizard called the Gila monster *Heloderma horridum* stimulates pancreatic acinar cells and that this effect is due to a 39 amino acid peptide isolated from the venom and called exendin-3 [76]. Up to 10 years later, the same research group demonstrated that a homolog to exendin-3 obtained from the *Heloderma suspectum*, exendin-4, stimulates pancreatic acinar cells [77]. It was later demonstrated that the receptors activated by these two exendin-analogs were identical to the GLP-1 receptors; hence, exendin-4 is a GLP-1 receptor agonist [78]. The potency of exendin-4 in activating the GLP-1 receptors exceeds GLP-1 by two to ten times [79,80]. The function of exendin-4 in the Gila monster is unknown. Exendin-4 is however, not the Gila monster GLP-1, since GLP-1 is expressed in the Gila monster from a separate GLP-1 gene [81] and GLP-1 is produced in the gut of the lizard [82]. One possibility, which is however debated, is that exendin-4 is part of the poison of the venom in a yet not understood function. Another possibility is that exendin-4 is released from the salivary glands in the early stages during meal ingestion to prepare the gut. Since the lizard eats large meals infrequently it may require several incretins to cope with the homeostasis. It may also be hypothesized that exendin-4 is involved in sustaining satiety between the infrequent meals. In any case, the GLP-1 receptor agonistic properties of exendin-4 have been the basis for the development of this peptide into a novel therapeutic modality in Type 2 diabetes.

## Chemistry

The production of exendin-4 for pharmaceutical use is now performed by recombinant technique by Amylin Pharmaceuticals (CA, USA) and Eli Lilly (IN, USA). The produced peptide, which shows structural identity with exendin-4, is known as exenatide (previously AC2992). Exenatide is therefore, like exendin-4, a 39 amino acid peptide. It shows 53% amino acid homology with GLP-1 in its 30 N-terminal amino acid sequence (Figure 1). It has a 9 amino acid long C-terminal end, which is rich in prolines. This is thought to be of importance for affinity to GLP-1 receptors [83]. Exenatide is not a substrate for DPP-4, and, furthermore, exenatide is neither a substrate for neutral

endopeptidase, another enzyme, which is involved in the degradation of biologically active peptides [84]. Instead, exenatide is eliminated mainly by renal clearance. In humans, the circulating half-life of exenatide is 26 min after intravenous administration and 4 to 5 h after subcutaneous administration [85].

### Pharmacodynamics

#### *Stimulation of insulin secretion*

In a number of studies, it has been demonstrated that exenatide (or exendin-4) exerts the same effects as GLP-1 [86]. A most important effect of the peptide is to augment glucose-stimulated insulin secretion. This was first demonstrated in isolated rat islets in which exendin-4 potentiated insulin secretion in the presence of 10 mmol/l glucose at dose levels exceeding 0.1 nmol/l [87]. That study also demonstrated that exendin-4 interacts with GLP-1 receptors and increases cAMP formation and proinsulin gene expression in clonal insulin-producing tumor cells. A later study in perfused rat islets showed that the insulinotropic action of exendin-4 is glucose dependent, since the peptide did not display any effect in the presence of 3 mmol/l glucose but it did however, augment insulin secretion in the presence of 7.5 mmol/l glucose [88]. Exendin-4 has also been shown to augment glucose-stimulated insulin secretion *in vivo* in animals when administered together with glucose at 30 pmol/kg/min in anesthetized rats [88], or at 3 nmol/animal in anesthetized mice [89]. Furthermore, in both healthy humans and subjects with Type 2 diabetes, exendin-4 augments glucose-stimulated insulin secretion, as demonstrated by infusing exendin-4 at 0.5 pmol/kg/min during a hyperglycemic clamp [90]. It was also recently shown that the insulinotropic action of exenatide is glucose dependent in humans, since the effect was almost abolished after reducing the glucose level to approximately 4 mmol/l [91]. Hence, studies in a number of experimental conditions have shown that exendin-4 augments insulin secretion in a glucose-dependent manner.

#### *Inhibition of glucagon secretion & delay in gastric emptying*

Exendin-4 has been shown to inhibit glucagon secretion, as demonstrated when introduced at 1 nmol/l to the perfused rat pancreas in the presence of low glucose or arginine [92]. Since exendin-4 inhibited glucagon secretion in the presence of only 3.2 mmol/l glucose, when no

effect on insulin secretion was observed, the glucagonostatic effect of the peptide is achieved by a direct effect on the glucagon producing  $\alpha$ -cells rather than through a stimulation of insulin secretion. Also in humans, exenatide (0.1  $\mu$ g/kg subcutaneously) reduces glucagon levels after meal ingestion as evident for inhibition of glucagon secretion [93]. That study also demonstrated that exenatide delays gastric emptying, since the postprandial acetaminophen levels were reduced in the acetaminophen test. Hence, exenatide exerts all the effects seen after GLP-1 (stimulation of insulin secretion, inhibition of glucagon secretion and delay in gastric emptying), which underlie the reduction in circulating glucose.

#### *Reduction in circulating glucose*

An acute glucose reducing effect of exendin-4 was initially observed in db/db mice after a single subcutaneous injection [94]. By examining the glucose-reducing effect of different doses, the dose resulting in a half maximal effect ( $ED_{50}$ ) was 0.06  $\mu$ g/kg, and at doses exceeding 1  $\mu$ g, the effect remained for 4 h. Glucose reducing effects of exendin-4 were also observed in ob/ob mice ( $ED_{50}$  0.14  $\mu$ g/kg), in diabetic rhesus monkeys ( $ED_{50}$  0.5  $\mu$ g/kg) and in ZDF rats [94]. Also on a longer term basis, exenatide reduces glucose. This has been observed after once daily intraperitoneal injection of the peptide, approximately 100  $\mu$ g/kg for 13 weeks in db/db and normal mice [95]. In that study, it was also demonstrated in db/db mice, that  $HbA_{1c}$  was 4.7% after 13 weeks of treatment with exendin-4, compared with 8.8% in nontreated animals. In ZDF rats, exenatide was administered daily for 6 weeks and a clear reduction in both glucose and  $HbA_{1c}$  levels were observed with a half-maximal effect at 1  $\mu$ g [94]. In humans, a clear glucose reducing effect of exenatide has been demonstrated (*vide infra*).

#### *Effects on insulin action?*

An issue which has been discussed is whether exendin-4 or exenatide increases insulin sensitivity, that is improves insulin action. This was demonstrated *in vitro* in fully differentiated L6 myotubes and 3T3 adipocytes, where exendin-4 augmented insulin-stimulated glucose uptake, which was executed through augmented PI-3 kinase activity [96]. Similarly, in ZDF rats after 35 days of daily treatment with exendin-4, a hyperinsulinemic euglycemic clamp revealed an increased glucose infusion rate to maintain the desired glucose in the exendin-4-treated group [94]. However, in humans, infusion of exendin-4

(0.12 pmol/kg/min) did not significantly affect glucose disappearance in response to insulin, suggesting that there is no direct action of the peptide on insulin sensitivity [97]. This implies that improvement of insulin action by long-term exenatide is more likely dependent on indirect effects due to improved metabolism rather than on a direct action, although more studies are required for examining this possibility.

#### *Increase in $\beta$ cell mass*

A most interesting effect of exenatide is an increase in  $\beta$ -cell mass [98,99]. For example, exenatide increases  $\beta$ -cell mass by 40% when administered at 1 nmol/kg intraperitoneally 10 days after a partial pancreatectomy in rats, and this is observed in association with attenuation of the diabetes [100]. The basis for the increase in  $\beta$ -cell mass is both differentiation into endocrine cells of precursor cells, stimulation of growth of  $\beta$ -cells and inhibition of apoptosis. An important mechanism may be upregulation of the homeodomain transcription factor, *pdx-1*, which is essential for growth and development of the pancreatic  $\beta$ -cells [101]. However, it should be kept in mind that these actions have so far been demonstrated only in animal experiments and, therefore, whether an action on  $\beta$ -cell mass evolves also in humans is not known.

#### *Prevention of diabetes*

An important preclinical study has demonstrated that exenatide may delay the onset of diabetes in db/db mice [102]. Exenatide was given daily for 14 days at 1 nmol/kg to 6-week old db/db mice. It was found that this prevented the development of hyperglycemia and glucose intolerance during the 2 week study period, and this was seen in association with increased insulin secretion, increased  $\beta$ -cell mass and proliferation and reduced  $\beta$ -cell apoptosis. The activation of  $\beta$ -cell proliferation was seen in association with increased activation of protein kinase B.

#### *Induction of satiety & reduction in body weight*

As GLP-1, also exenatide has been reported to induce satiety, reduce food intake and suppress body weight [86]. For example, in ZDF rats, twice daily administration of exenatide for 6 weeks dose-dependently reduced food intake by as much as 30% ( $ED_{50}$  0.14  $\mu$ g/kg) and body weight by 5.6% (100  $\mu$ g) [94]. Similarly, in ZDF rats, once-daily exenatide (10  $\mu$ g/kg) reduced body weight over a study period of 42 days [103].

#### *GLP-1 versus exenatide*

Most effects of GLP-1 and exenatide are identical, although exenatide is more potent. It has, however, been reported that some GLP-1 effects are not shared by exenatide. For example, Nijima and collaborators reported that GLP-1, but not exenatide, activates the liver sensory nerves [104]. The reason for this discrepancy is not clear; one possibility might be that the GLP-1 receptor responsible for this action is different from the common GLP-1 receptor. Similar results have also been demonstrated *in vitro* in 3T3-adipocytes. In these cells, exenatide, but not GLP-1, improves insulin-stimulated glucose uptake [96]. This shows that exenatide might have additional effects than GLP-1, which in turn indicates different receptor mechanisms. However, more studies are required to solve this.

#### *Downregulation of receptors?*

A potential limitation of long-term treatment with a receptor agonist is downregulation of receptor activity. A recent study addressing this issue regarding exenatide in rodents have shown that although exenatide induces GLP-1 receptor downregulation *in vitro*, no such effect was observed after long-term treatment *in vivo* [105]. This indicates that at least in rodents, it is less likely that long-term treatment with exenatide will result in downregulation of GLP-1 receptors.

### **Clinical efficacy**

#### *One & five day studies*

A short-term placebo-controlled, double-blind, crossover study examined subcutaneously administered exenatide at 0.05, 0.1 or 0.2  $\mu$ g/kg in 13 subjects with Type 2 diabetes treated either with diet alone, metformin or TZD alone, or a combination of metformin and a TZD. It was found that exenatide reduced fasting glucose after 3 h of administration to  $7.6 \pm 0.6$ ,  $6.6 \pm 0.6$  and  $6.5 \pm 0.3$  mmol/l in the three groups versus  $10.8 \pm 0.7$  mmol/l in the placebo group [93]. A subsequent 5-day study examined continuous treatment with exenatide at 0.1  $\mu$ g/kg twice daily subcutaneously in 24 subjects with Type 2 diabetes. It was found that fasting glucose was  $9.5 \pm 0.5$  mmol/l after placebo treatment versus  $8.9 \pm 0.6$  mmol/l after exenatide and that the 2 h postprandial glucose was reduced from  $16.0 \pm 0.9$  to  $8.0 \pm 0.6$  mmol/l by exenatide. This was associated with a reduction in insulin and glucagon levels and also a delay in gastric

emptying. Exenatide was well tolerated and the most frequent adverse events were headache (27 events), vomiting (18 events) and nausea (17 events) [93].

#### One month studies

A subsequent study examined the efficiency of a 1 month treatment of subjects with Type 2 diabetes with exenatide given subcutaneously twice daily. A total of ten patients were included in the study. They had been treated with sulfonylurea alone or with metformin or a TZD, or, one patient, with TZD alone. The dose of exenatide started at 0.8 µg/kg and was adjusted upwards to a total daily dose of 0.4 µg/kg. It was found that glucose levels were reduced; maximally observed as reduction in self-monitored glucose before bedtime and this was associated with a reduction in HbA<sub>1c</sub> from 9.1 ± 0.4 to 8.3 ± 0.5%. Furthermore, a hyperglycemic clamp study performed after 1 month of treatment revealed increased β-cell sensitivity to glucose as a sign of improved β-cell function. Again, exenatide was safe and the nausea, which was observed in two patients during the first week of treatment, was mild and transient [10].

Another 1 month study examined the efficiency of the addition of exenatide to treatment with sulphonylurea or metformin in 109 patients with Type 2 diabetes [107]. Exenatide was given subcutaneously at the dose of 0.8 µg/kg, either twice daily (before breakfast and dinner, or before breakfast and bedtime) or thrice daily (before breakfast, dinner and bedtime). The mean baseline HbA<sub>1c</sub> levels in these patients was 9.3% and this was reduced by 0.7 – 1.1% by exenatide versus by 0% by placebo. Also prandial glucose was reduced by exenatide, as is illustrated in Figure 2. In contrast, the reduction in fasting glucose did not differ from placebo. Exenatide was safe and well tolerated. The most common adverse event was a transient mild-to-moderate nausea, which was observed in 31% of subjects receiving the compound. This nausea was, however, most pronounced during the initial days of treatment and declined to an incidence of only 13% by the end of the 28 day study period. Only 3.7% of the subjects withdrew from treatment due to nausea. Furthermore, there were a 15% overall incidence of hypoglycemia, which, all, however, were of mild or moderate intensity and did not require assistance of another individual. Body weight was not altered by exenatide in this study [107].

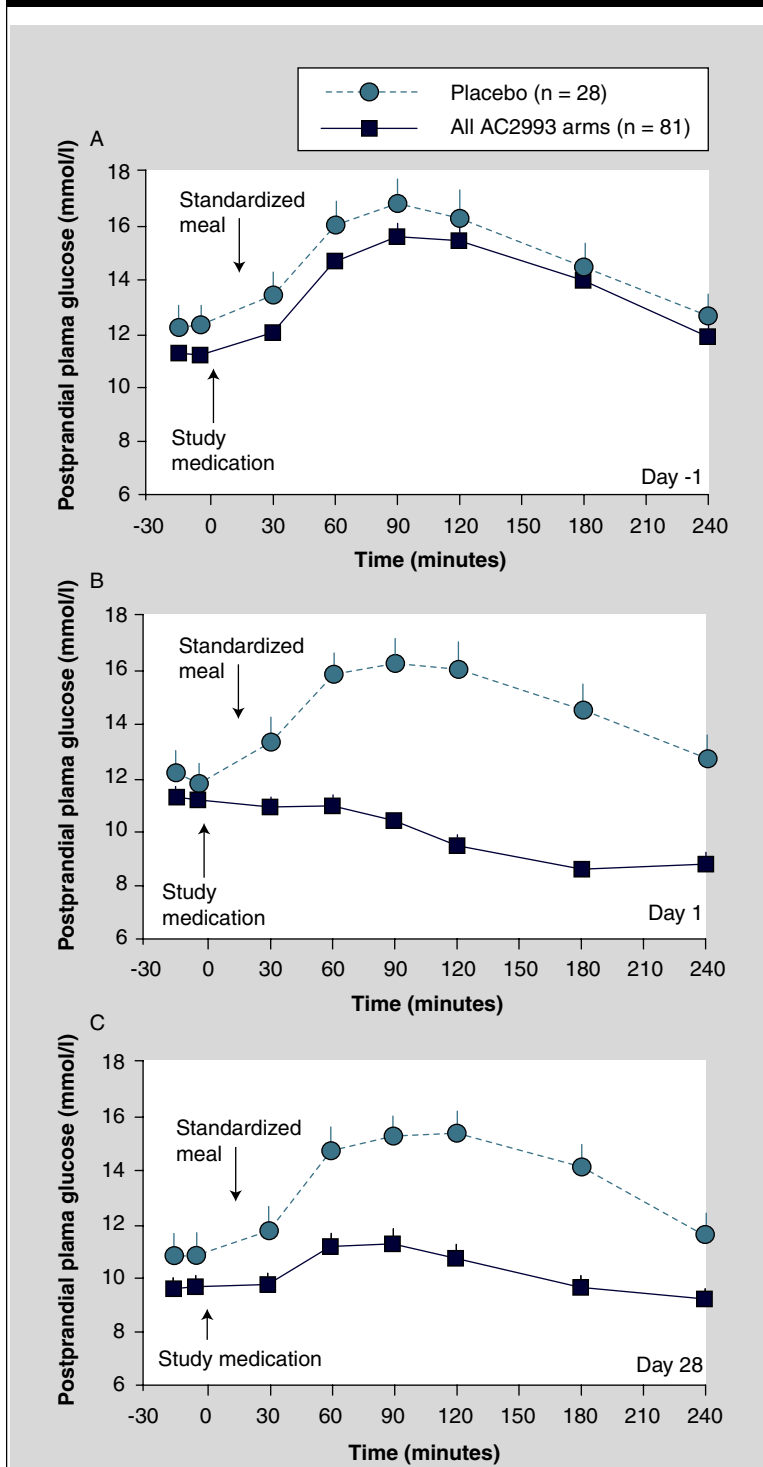
#### Phase III studies.

The encouraging results of the earlier clinical studies have taken exenatide into Phase III clinical trials. One 30 week study in subjects with Type 2 diabetes inadequately treated with metformin examined the efficiency and durability of exenatide given subcutaneously twice daily at 5 or 10 µg in each injection. A total of 336 subjects with a mean baseline HbA<sub>1c</sub> of 8.2 ± 1.1% took part in the study. The 30 week reduction in HbA<sub>1c</sub> was 0.86 ± 0.11% (10 µg) and 0.6 ± 0.11% (5 µg) versus 0.00 ± 0.11% in the placebo group, and this was associated with significant reductions in fasting and prandial glucose. Furthermore, body weight decreased significantly in the exenatide groups, by 2.8 ± 0.5 kg in the 10 µg group and by 1.6 ± 0.4 kg in the 5 µg group, compared to 0.3 ± 0.3 kg in the placebo group. The only significant adverse event was nausea, which was however, mild to moderate and seen during the beginning of the treatment. No severe hypoglycemia was observed and the incidence of mild hypoglycemia (7.5%) was the same in the exenatide as in the placebo group [10].

Another study examined the efficiency of 30 week treatment with exenatide in patients treated with a maximal dose of metformin and a sulphonylurea [109]. A total of 733 subjects entered the study; the mean baseline HbA<sub>1c</sub> was 8.5 ± 1.0%. Exenatide was again given subcutaneously at 5 or 10 µg twice daily and the placebo-adjusted HbA<sub>1c</sub> reduction after 30 weeks of treatment was 0.5 ± 0.07% and 0.77 ± 0.08% respectively, versus 0.3 ± 0.0% in the placebo group. Body weight reduced by 1.6 ± 0.2 kg in the exenatide-treated arms versus 0.9 ± 0.2 kg in the placebo arm, mild or moderate nausea was experienced in 40 and 39% of patients in the two exenatide arms versus 21% in the placebo arm, and the incidence of mild hypoglycemia was 28 and 19% in the exenatide arms versus 13% in the placebo arm [109]. It was also reported that a fifth of the subjects treated with exenatide developed antibodies to the compound. However, the improvement in glycemic control was not different from antibody-positive versus antibody-negative patients. Similarly, a 30 week study examined the action of exenatide when added to a sulfonylurea in a total 377 randomized patients from 10 centers [110]. In one arm of the study, exenatide was given at 5 µg subcutaneously twice daily throughout the study whereas in another arm, exenatide was given at 5 µg twice a day for 4 weeks and then the dose



**Figure 2. Mean ( $\pm$ SEM) postprandial plasma glucose concentration profile.**



Mean ( $\pm$ SEM) postprandial plasma glucose concentration profile at baseline and after 1 and 28 days of treatment with exenatide (= AC2993) at 0.08  $\mu$ g/kg times two or three (all arms combined) versus placebo in patients with Type 2 diabetes treated with metformin and/or sulfonylurea. Data from [107]. Published with kind permission from the *American Diabetes Association*.

was increased to 10  $\mu$ g twice a day in one arm of the study. It was found that HbA<sub>1c</sub> was significantly reduced by exenatide (by 0.86  $\pm$  0.11% in the 10  $\mu$ g arm and by 0.46  $\pm$  0.12% in the 5  $\mu$ g arm versus an increase by 0.12  $\pm$  0.09% in the placebo arm; baseline HbA<sub>1c</sub> was 8.6  $\pm$  1.2%; please observe that all patients continued with sulfonylurea). Figure 3 illustrates the HbA<sub>1c</sub> during the course of treatment. In the 10  $\mu$ g exenatide group, body weight was reduced by 1.6  $\pm$  0.3 kg. In the 10  $\mu$ g arm, 51% of the subjects experienced nausea and 13% vomiting. This was mainly noticed during the initial phase of the study. Nevertheless, 5% of subjects in the 10  $\mu$ g arm and 6% in the 5  $\mu$ g arm (versus 2% in the placebo arm) experienced severe nausea and 4% in the 10  $\mu$ g arm and 2% in the 5  $\mu$ g arm (versus 0% in the placebo arm) withdrew from the trial due to nausea. Furthermore, a considerable number of subjects experienced hypoglycemia, as defined as less than 3.3 mmol/l glucose. This was observed in 36% of subjects in the 10  $\mu$ g arm, versus 14% in the 5  $\mu$ g arm and 3% in the placebo arm. Hypoglycemic events were mild or moderate and no subject required assistance of another person. Finally, 41% of subjects given exenatide had developed antibodies against exenatide during the 30 week study period; most of them being low titer antibodies. The presence of antibodies did not predict effect on glycemic control [110].

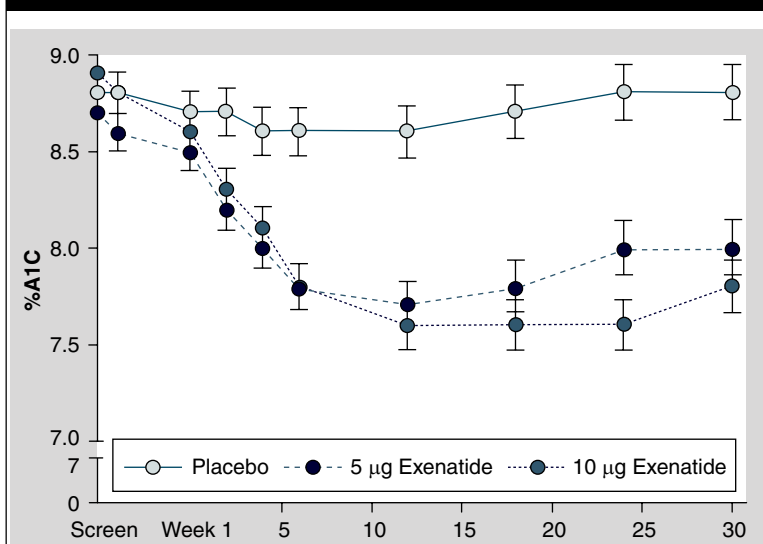
Recently, the result of a 6 month trial comparing treatment with exenatide with that of insulin glargine was disclosed. More than 500 patients were included in the study and it was found that exenatide and insulin glargine achieved similar reductions on HbA<sub>1c</sub>. Body weight was reduced by approximately 2.5 kg in the exenatide group versus increased by approximately 1.5 kg in the insulin group. The incidence of mild-to-moderate hypoglycemia was similar in the two groups and the most common adverse event in the exenatide group was nausea, which occurred most frequently early in the study [111].

In conclusion, exenatide has been examined in a number of Phase III studies in subjects with Type 2 diabetes. Based on the results, a New Drug Application for exenatide was submitted to the US Food and Drug Administration for regulatory approval on July 2, 2004.

### Safety & tolerability

No major serious adverse effects have been consistently reported during treatment with exenatide. The most common side effect has

**Figure 3. HbA<sub>1c</sub> levels in subjects with Type 2 diabetes treated with a sulfonylurea and exenatide.**



A1c levels in subjects with Type 2 diabetes treated with a sulfonylurea and exenatide at 5 or 10 µg twice daily or placebo over 30 weeks. Means ± SEM are shown.

Data from [110]. Published with kind permission from the *American Diabetes Association*.

been mild-to-moderate nausea, which, on the other hand, is very frequently observed. In some studies, more than 20% of patients face nausea. However, the nausea is generally transient, although also severe nausea has been reported (5–6% in a 30 week trial) [110]. The mechanism of the nausea is not established. It may depend on the inhibition of gastric emptying resulting in gastric distention. It may also depend on activation of afferent nerves by the peptide. Another possibility is that the nausea depends on central effects of GLP-1 receptor activation. It has, for example, demonstrated that GLP-1 receptors in the area postrema in which there are leaky fenestrated capillaries may signal the nausea [112]. The nausea is most likely a dose-dependent phenomenon, as evident from studies during infusion of GLP-1, where as dose level exceeding 60 pmol/l invariably results in nausea [113]. It has been discussed whether the nausea contributes to the weight loss observed with exenatide. This is, however, less likely, as judged from a 30 week trial in which the improvement in glycemic control did not differ in subjects experience nausea when compared to subjects having had no nausea [110]. A recent study has shown that the occurrence of the nausea is diminished by progressive dose-escalation of exenatide [111]. The regimen included a start

of exenatid at the dose of 0.02 µg/kg times three which was increased in 0.2 µg/kg per dose increment every 3 days for 35 days until the highest dose of 0.4 µg/kg was reached. A control group received 0.4 µg/kg per dose directly. It was observed that nausea and vomiting were 27% in the group receiving dose-escalation versus 56% in the group receiving the high dose from the beginning.

An important safety aspect is the risk of developing hypoglycemia from exenatide. A low degree of hypoglycemia is expected during treatment of exenatide from the glucose-dependency of the action of the peptide. Nevertheless, hypoglycemic values, as defined as plasma glucose less than 3.3 mmol/l, were reported 15% of subjects in the 28 day study with exenatide [10]. A higher occurrence of hypoglycemia was seen when exenatide was added to sulfonylurea (25% of subjects) [11]. This would suggest that there is an increased risk of hypoglycemia when exenatide is combined with sulfonylurea. It should be emphasized, however, that although not uncommon, these incidences of hypoglycemia were mild or moderate in intensity and there was no report of hypoglycemia requiring assistance of another individual. The experience of more long-term studies using exenatide is now important.

Another issue which has raised concern is the development of antibodies against exenatide, since the peptide shows only 53% homology with GLP-1 in its N-terminal end. Such antibodies indeed develop, and in one 30 week study, it was reported that 41% of subjects developed antibodies [11]. However, it was also reported that these antibodies were in general of low-titer characteristics and, furthermore, that the occurrence of antibodies did not predict the outcome in term of glycemic control. Hence, although common, these antibodies do not seem to be of biologic significance. Finally, a concern has been that the potential effect of exenatide to increase β-cell mass, due to augmented differentiation of precursor cells of pancreatic ductal origin in combination with inhibited apoptosis, might result in tumor formation. A recent rodent study examined this by treating a large number of mice and rats with exenatide over a 2 year study period. It was found that compared to placebo there was no difference in regard to pancreatic or islet lesions after this long-term treatment and no proliferative lesions were observed [114]. This suggest that the risk of tumor formation is marginal during treatment with exenatide.

### Conclusion

Exenatide is a DPP-4 resistant GLP-1 receptor agonist, which exhibits a number of actions which all are of potential value for the treatment of Type 2 diabetes. These actions include stimulation of insulin secretion, inhibition of glucagon secretion, delay in gastric emptying, increase in  $\beta$ -cell mass and induction of satiety with reduction in body weight. Exenatide is efficient in improving metabolic control in animal models of Type 2 diabetes as well as in subjects with Type 2 diabetes. It shows durability with a persistent reduction in HbA<sub>1c</sub> by approximately 1% after 30 weeks of treatment in association with reduced body weight. Exenatide treatment is safe and tolerable. It is not associated severe hypoglycemia, although mild hypoglycemia has been observed, particularly when given together with sulfonylureas. Furthermore, mild-to-moderate nausea are usually seen in the beginning of the treatment.

### Expert opinion

It is clear that GLP-1-based therapy offers improvement of pathophysiologically important processes in Type 2 diabetes and that the experience with this treatment is that it improves glycemic control in Type 2 diabetes. Thus, GLP-1-based therapy increases insulin secretion and inhibits glucagon secretion in association with delay in gastric emptying and reduction in body weight. GLP-1-based therapy in addition seems to increase  $\beta$ -cell mass and thereby has the potential of preventing the progression of the disease. GLP-1-based therapy also offers a safe and tolerable treatment and is therefore a potential breakthrough in the treatment of Type 2 diabetes, and therefore also for the prevention of complications to the disease. The GLP-1 receptor agonist, exenatide, represents a first generation GLP-1 mimetic. It activates GLP-1 receptors and has a longer half-life than GLP-1 and can therefore be given subcutaneously twice daily. Its efficiency seems high with reported reduction of HbA<sub>1c</sub> levels by 1% unit and it reduces body weight. Nevertheless, limitations have been observed and therefore several issues remain to be solved before a clear position of exenatide is available regarding its potential and place in therapy of Type 2 diabetes. An important aspect is that even though exenatide clearly improves glycemic control, normalization of glycemic control has not been achieved in long-term studies. This may be explained by incomplete normalization of islet function by

exenatide. This in turn may suggest that the islet dysfunction in Type 2 diabetes involves also mechanisms, which are not sensitive to activation of the GLP-1 receptors. It may also, however, be explained by the pharmacokinetic of exenatide, since its comparable short duration of action does not result in full coverage throughout the 24 h period. Another aspect is that although exenatide is tolerable, nausea and vomiting are common and mild hypoglycemia has been frequently reported, particularly in subjects also treated with sulfonylurea. These limitations need to be overcome during development of second generation GLP-1 mimetics.

Exenatide might be used in the early stages of Type 2 diabetes, when it may improve glycemic control by its action to stimulate insulin secretion, reduce glucagon secretion and delay gastric emptying. Due to the potential action of exenatide on  $\beta$ -cell mass, mainly through inhibition of apoptosis, it is also possible that it may have clinical effects also in later stages of the disease. Furthermore, since a weak target (if any) of exenatide is insulin action, exenatide be used combination with metformin or TZDs. However, it should be emphasized that the long-term effect of exenatide, beyond 1 year of treatment, still remains to be established. An important comparison would be between exenatide on one hand and other GLP-1 receptor agonists (liraglutide and CJC-1131) on the other hand. They show different pharmacokinetic properties (exenatide requiring twice daily administration, liraglutide once daily administration and CJC-1131 once weekly administration) [For review see 7]. However, at present no head-to-head comparison is available on these compounds. Finally, a most important comparison for the future is that between GLP-1 receptor agonists, such as exenatide, and the DPP-4 inhibitors. These two classes of compounds show many similarities, since they are based on activation of GLP-1 receptors or increasing incretin hormone concentrations. However, differences exist since GLP-1 receptor agonists are injectables, are associated with nausea and reduce body-weight, whereas DPP-4 inhibitors are orally-active, are not associated with nausea and are body weight neutral [for review see 74]. The final comparison between exenatide and other GLP-1 receptor agonists and between GLP-1 receptor agonists and DPP-4-inhibitors, particularly in regard to efficiency and durability, remain to be examined in studies with direct comparisons.

### Executive Summary

- Glucagon-like peptide (GLP)-1 is an incretin hormone which is antidiabetic due to stimulation of insulin secretion, inhibition of glucagon secretion, increase in  $\beta$ -cell mass, delay in gastric emptying and induction of satiety with reduction in body weight.
- Due to the combined antidiabetic actions of GLP-1, the hormone is developed as a novel treatment of Type 2 diabetes.
- However, a problem is that GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase (DPP)-4, resulting in a short half-life (<2 min) of the native hormone. Hence, native GLP-1 is unattractive as a treatment.
- To overcome the problem with the rapid inactivation of native GLP-1, two strategies have evolved: the use of DPP-4-resistant GLP-1 receptor agonists (GLP-1 mimetics) and the use of DPP-4 inhibitors.
- Exenatide is a DPP-4 resistant GLP-1 receptor agonist (GLP-1 mimetic), which originally was isolated as exendin-4 from the lizard Gila monster.
- Exenatide has proven to be antidiabetic in animal models of diabetes and in subjects with Type 2 diabetes by executing the same effects as GLP-1.
- In long-term studies (up to 30 weeks), exenatide improves the metabolic control, as verified by reduction in HbA1c by approximately 1% in association with a reduction in body weight.
- Exenatide is not associated with severe hypoglycemic events, which may be explained by the glucose-dependency of the GLP-1 action.
- Exenatide is tolerable. Nevertheless, mild-to-moderate nausea is common and observed in approximately 30% of subjects treated with exenatide, although it is usually transient and seen only during the initial phase of treatment. Furthermore, antibodies to exenatide develop in 20 to 40% of patients. However, these are reported to lack significance on glucose metabolism.
- Exenatide offers a novel and efficient treatment of Type 2 diabetes and represents the first generation of GLP-1 mimetics.

In summary, exenatide offers a new treatment of Type 2 diabetes, and ongoing studies in Phase III program will position this compound as an important treatment in Type 2 diabetes. Its advantages are the efficacy and the concomitant reduction in body weight, whereas its advantages are the requirement to be administered parenteral and its association with nausea, hypoglycemia when used with sulfonylureas, and antibody formation.

### Outlook

It is known that the degree of complications with Type 2 diabetes is dependent on the long-term metabolic control of the disease [8,9]. It is also known that stages preceding the onset of Type 2 diabetes, for example impaired glucose tolerance and impaired fasting glycemia, are risk factors for development of complications such as cardiovascular diseases as well [115]. This knowledge will in the future lead to more aggressive treatment and to start of treatment earlier than what is undertaken today. This in turn requires that tools for such treatment are efficient, are directed at the pathophysiologically important factors for the disease, and are safe. GLP-1-based therapy offers such treatment, which in the longer run may prevent the progression of the disease by increasing  $\beta$ -cell mass and that such treatment is safe and, as for

exenatide, also associated with weight loss. Based on existing knowledge and prediction of the future, therefore, it is highly likely that GLP-1-based therapy will be a first-line choice for future physicians in the treatment of Type 2 diabetes.

The combination of efficacy and durability, the glucose dependent mechanism of action and the tolerability makes exenatide suited for development of a sustained release formulation. This has been developed by Amylin Pharmaceuticals in association with Alkermes Inc. (MA, USA). An injectable sustained-release form of exenatide has thereby been produced, named exenatide LAR. The goal has been to develop a formulation that might allow once-a-week to once-a-month administration of exenatide. Initial preclinical work with exenatide LAR has been successful and a first clinical trial, completed in 2001, showed that the subcutaneous administration of exenatide LAR releases exenatide for over 30 days. Exenatide LAR was well-tolerated with no significant adverse effects. Based on these and similar data and previous clinical results, Amylin (together with Eli Lilly and Alkermes) is now undertaking an independent development program for exenatide LAR. However, no data have as yet been reported.

Two studies from the 1990s demonstrated that GLP-1 is also antidiabetic in subjects with Type 1 diabetes [64,116]. This would suggest that

exenatide would have a potential to be also used in the treatment of Type 1 diabetes. The rationale for such a treatment is that exenatide delays gastric emptying and inhibits glucagon secretion, which are events tentatively improving glycemic control in subjects with complete loss of  $\beta$ -cell function. It may also be speculated that the inhibition of apoptosis may be a target for treatment in Type 1 diabetes. In a first study examining this, exenatide was given subcutaneously 15 min before breakfast to nine subjects with Type 1 diabetes at doses of 0.01 to 0.06  $\mu\text{g}/\text{kg}$ . It was found that exenatide reduced the prandial glucose excursion by 90%, suggesting that exenatide may be further developed along this line [117].

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**Affiliation**

Bo Ahrén  
 Lund University, Department of Medicine,  
 B11 BMC, SE-221 84 LUND, Sweden  
 Tel.: +46 462 220 758  
 Bo.Ahren@med.lu.se