Diabetologia (2004) 47:357–366
DOI 10.1007/s00125-004-1342-6

Diabetologia

Review

Incretins, insulin secretion and Type 2 diabetes mellitus

T. Vilsbøll[1, 3] · **J. J. Holst**[2]

[1] Department of Internal Medicine F, Gentofte University Hospital, Gentofte, Denmark
[2] Department of Medical Physiology, The Panum Institute, University of Copenhagen, Copenhagen N, Denmark
[3] Department of Internal Medicine F, Gentofte University Hospital, Hellerup, Denmark

Abstract

When glucose is taken orally, insulin secretion is stimulated much more than it is when glucose is infused intravenously so as to result in similar glucose concentrations. This effect, which is called the incretin effect and is estimated to be responsible for 50 to 70% of the insulin response to glucose, is caused mainly by the two intestinal insulin-stimulating hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Their contributions have been confirmed in mimicry experiments, in experiments with antagonists of their actions, and in experiments where the genes encoding their receptors have been deleted. In patients with Type 2 diabetes, the incretin effect is either greatly impaired or absent, and it is assumed that this could contribute to the inability of these patients to adjust their insulin secretion to their needs. In studies of the mechanism of the impaired incretin effect in Type 2 diabetic patients, it has been found that the secretion of GIP is generally normal, whereas the secretion of GLP-1 is reduced, presumably as a consequence of the diabetic state. It might be of even greater importance that the effect of GLP-1 is preserved whereas the effect of GIP is severely impaired. The impaired GIP effect seems to have a genetic background, but could be aggravated by the diabetic state. The preserved effect of GLP-1 has inspired attempts to treat Type 2 diabetes with GLP-1 or analogues thereof, and intravenous GLP-1 administration has been shown to be able to near-normalize both fasting and postprandial glycaemic concentrations in the patients, perhaps because the treatment compensates for both the impaired secretion of GLP-1 and the impaired action of GIP. Several GLP-1 analogues are currently in clinical development and the reported results are, so far, encouraging. [Diabetologia (2004) 47:357–366]

Keywords Glucagon-like peptide-1 · Glucose-dependent insulinotropic polypeptide · Gastric inhibitory polypeptide · Incretin effect · Type 2 diabetes · Insulin secretion

Received: 23 June 2003 / Revised: 18 November 2003
Published online: 13 February 2004

T. Vilsbøll (✉)
Department of Internal Medicine F,
Gentofte University Hospital, Niels Andersensvej 65,
2900 Hellerup, Denmark
E-mail: tivi@gentoftehosp.kbhamt.dk

Abbreviations: GLP-1, Glucagon-like peptide-1 · GIP, glucose-dependent insulinotropic polypeptide · FPG, fasting plasma glucose

The incretin effect

The incretin effect seems to play a major role in the regulation of glucose metabolism in healthy subjects. "The incretin effect" implies that ingestion of carbohydrates (glucose) causes the release from the intestinal mucosa of substances that enhance insulin secretion beyond the release caused by the absorbed glucose itself [1]. The effect can be quantified by comparing insulin or C-peptide responses to oral or intravenous glucose loads, adjusted to cause identical increases of plasma glucose concentrations. The much higher responses observed after oral administration

are the result of the incretin effect [2]. Quantified in this way, it has been shown that the incretin effect normally is responsible for about 50 to 70% of the insulin response to oral glucose [3]. It has been argued that the incretin effect is unreal and merely represents a misinterpretation of data, because the same amounts of glucose elicit similar C-peptide responses when given intravenously and orally [4]. The incretin effect, estimated from the higher peripheral insulin concentrations after oral glucose, was, therefore, suggested to merely reflect differences in hepatic insulin extraction. The cited 50 to 70% is, however, based on C-peptide concentrations and, therefore, reflects true differences in secretion. Regarding measurement of the incretin effect during isoglycaemic challenges, it should also be considered that (i) insulin secretion is compared at identical (preferably arterial) plasma glucose concentrations, which means that the pancreatic islets receive identical glycaemic stimulations in the two situations (differences must therefore be due to something else) and (ii) that the larger amounts of oral glucose required to copy the intravenous profiles actually reflect the correspondingly enhanced uptake of glucose in the liver and the peripheral tissues. Thus, it could be concluded that the incretin effect is not only responsible for two thirds of the carbohydrate meal-induced insulin secretion, but actually (albeit indirectly) for the deposition of up to two thirds of the amount of glucose ingested. A defective incretin function would, therefore, be expected to cause severe postprandial hyperglycaemia. There are, at present, no known experimental strategies whereby this assumption could be tested, mainly because several hormones are thought to contribute to the incretin effect [5]. However, it is the fundamental hypothesis of this review that incretin deficiency, along with other factors, is an important factor in the pathophysiology of Type 2 diabetes in its most frequent form, as observed in obese middle-aged people. Thus, several studies have shown that the incretin effect, as studied by comparing the insulin or C-peptide responses to isoglycaemic oral and intravenous glucose challenges, is abolished or severely reduced in these patients [6, 7]. Clearly, in fully developed Type 2 diabetes, a fundamental defect of the beta cell is its insensitivity to glucose. If, in contrast, the amplification by the incretin hormones is also lost, this must result in a further aggravation of insulin deficiency. Indirect evidence for the importance of an incretin defect as a major contributor to the insulin deficiency in Type 2 diabetes is the observation, as we shall see below, that experimental amplification of the effect, by administration of exogenous incretin hormone, could restore insulin secretion to near normal levels. Furthermore, the incretin defect in Type 2 diabetes might have a genetic component. This means that a deficient amplification of insulin secretion could have been present even before the onset of overt diabetes, and therefore might contribute to the development of the disease prior to the diagnosis of overt diabetes. We conclude that deficient incretin function is an important factor in the pathophysiology of Type 2 diabetes.

The incretin hormones

Although there are probably many postprandially released hormones with an effect on insulin secretion [5], the available experimental evidence suggests that the two most important ones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 [8].

Glucose-dependent insulinotropic polypeptide (GIP)

GIP is a peptide of 42 amino acids belonging to the glucagon-secretin family of peptides. The members of this family show pronounced sequence homology, particularly in the N-terminal part of the molecule. GIP is processed from a precursor of 153 amino acids [9], but specific functions for the other fragments of the precursor have not been identified. Most antisera raised against GIP cross-react to some extent with a larger molecule, designated GIP 8000, but the relation of the latter to GIP is not established [10]. It does not seem to be a product of the GIP precursor. In some instances, “GIP 8000” could have been due to the presence of the related peptide, glicentin (a proglucagon-derived peptide), which might cross-react with some GIP antisera. Preferably, GIP assays should not show a cross-reaction with GIP 8000. The GIP receptor has been cloned and is related to the receptors for the other members of the glucagon-secretin family of peptides. It is expressed in the pancreatic islets and also in the gut, adipose tissue, heart, pituitary, in the adrenal cortex and in several regions of the brain [11].

GIP is secreted from specific endocrine cells, the so-called K cells, which exhibit the highest density in the duodenum, but recent studies have indicated that GIP cells are found in the entire small intestinal mucosa [12]. Secretion is stimulated by absorbable carbohydrates and by lipids. GIP secretion is, therefore, greatly increased in response to meal ingestion, resulting in a 10 to 20-fold increase in the plasma concentration [13].

Interaction of GIP with its receptor on the pancreatic beta cells causes an increase of cAMP levels, which in turn increases the intracellular calcium concentration and enhances the exocytosis of insulin-containing granules by a mechanism distal to the increase of calcium [14]. A number of other signalling pathways could also be activated (presumably secondary to the rise in cAMP), including the MAP kinase as well as the PI3-kinase/protein kinase B pathways [15, 16, 17, 18].

The incretin function of GIP was first suggested by one study [19] and was confirmed in detailed clamp-studies by another study [20]. Its function has been probed in immunoneutralization studies [21, 22] and, more recently, in studies using a fragment, GIP 7–30amide, which turns out to be a GIP receptor antagonist [23], or antibodies to the GIP receptor [24]. All treatments reduced insulin responses to oral glucose and impaired glucose tolerance. Mice with a targeted deletion of the GIP receptor gene become glucose intolerant [25]. Using the Pro(3)GIP antagonist in *ob/ob* mice, one study [26] found that GIP might be responsible for as much as 80% of the incretin effect in these animals. Using the mimicry approach, where endogenous concentrations are mimicked by intravenous infusion (in this case infusions of both GIP and glucose), one study [27] showed that the increased GIP concentrations elicited by oral glucose can completely account for the accompanying augmented insulin release. The glucose intolerance of the GIP receptor knockout mice is not severe, but these mice could compensate by hypersecretion of other insulinotropic factors. Nevertheless, from other experiments, it is evident that GIP is not the only incretin hormone. Immunoneutralization experiments showed that intestinal extracts contain potent insulinotropic agents in addition to GIP [28]. Furthermore, investigations by a study in patients with resections of different parts of the small intestine, as well as in patients with celiac disease, showed that the incretin effect does not correlate to the secretion of GIP, and that the distal small intestine releases an additional incretin hormone [29, 30].

Glucagon-like peptide-1 (GLP-1)

This additional hormone could be glucagon-like peptide-1 (GLP-1). GLP-1 is a product of the glucagon gene [31]. This gene is expressed not only in the pancreatic alpha-cells, but also in the L-cells of the intestinal mucosa, one of the most abundant endocrine cells of the gut [32]. Here the primary translation product, proglucagon, is cleaved, not to produce glucagon as in the islets, but to release from its C-terminal part the two glucagon-like peptides GLP-1 and GLP-2 [33], both showing about 50% sequence homology with glucagon. The N-terminal part of the precursor, which includes the glucagon-sequence, is secreted as a single, rather large, peptide, designated glicentin (formerly gut glucagon or GLI) which, most likely, is biologically inactive. Some of the glicentin moieties are cleaved further to release the peptide, oxyntomodulin, which corresponds to the glucagon sequence and the additional C-terminal octapeptide of glicentin. This peptide is insulinotropic [34], and probably explains the insulinotropic activity of some preparations of "gut glucagon", described in earlier publications. However, as a circulating hormone in humans, its concentration is probably too low to influence insulin secretion under physiological circumstances [35]. GLP-1 secretion is stimulated by the presence of nutrients in the lumen of the gut (but additional neural or endocrine mechanisms could also operate) [36], and the secretion of GLP-1 throughout the day is highly correlated to the release of insulin [37]. GLP-1 is one of the most potent insulin-releasing substances known. It is strongly insulinotropic in mimicry experiments [38], and animal experiments involving an antagonist of the GLP-1 receptor have shown that GLP-1 is responsible for a substantial part of the insulin response to oral glucose [39, 40]. Furthermore, experiments with the same antagonist in humans have suggested that GLP-1 might be essential for normal glucose tolerance [41]. In agreement with these observations, mice with a targeted deletion of the GLP-1 receptor become glucose intolerant and might develop fasting hyperglycaemia [42]. It has been shown that GIP secretion and pancreatic sensitivity to GIP are augmented in these knockout mice [43], perhaps as part a compensatory response. This might suggest that acute ablation of the GLP-1 activity could have even more extensive effects.

Interactions between GIP and GLP-1

Thus, there is strong evidence that these two hormones both act as incretin hormones. Why do we have two hormones? Firstly, GIP is probably predominantly secreted from the upper small intestine, whereas the density of the L-cells, responsible for the secretion of GLP-1, is highest in the lower small intestine. Therefore, smaller loads of rapidly absorbable nutrients would preferentially activate the upper incretin hormone, i.e. GIP, whereas ingestion of larger meals containing more complex nutrients requiring more extensive digestive processing, would also activate the distal incretin, i.e. GLP-1. Experiments with alpha-glycosidase inhibitors such as acarbose, which delay upper intestinal digestion and absorption of carbohydrates and cause a transfer of nutrients to distal segments of the gut, are consistent with this. Acarbose reduces GIP secretion, but augments GLP-1 secretion [44] and could, partly because of this, improve glucose tolerance in diabetic subjects. In our laboratory, volunteers were intubated with long (ileal) or short (duodenal) catheters and small amounts of glucose were instilled to produce a selective response of either of the incretin hormones. Surprisingly, however, the glucose instillation resulted in almost equal GIP and GLP-1 responses whether introduced proximally or distally (unpublished studies). This could be explained by the fact that both GLP-1 and GIP producing cells are found throughout the small intestine and, perhaps, also by the recent finding that a significant number of

gut endocrine cells in several mammals, including humans, produce both GIP and GLP-1 [45]. In agreement with this, a mixed meal will normally cause a release of both peptides, but whereas the GIP concentrations might increase to several hundred picomoles per litre, GLP-1 concentrations rarely exceed 50 pmol/l [37].

Most published studies regarding postprandial GIP and GLP-1 concentrations, however, do not report the concentrations of the biologically active hormones. Recent research has established that both GIP and GLP-1 are extensively and rapidly metabolised by the ubiquitous enzyme dipeptidyl-peptidase IV, DPP-IV [46, 47, 48]. This enzyme cleaves a dipeptide from the N-terminus of the molecule, which thereby is inactivated. In fact, the metabolites (GIP 3–42 and GLP-1 9–36 amide), could act as antagonists of their own receptors [26, 49]. The enzyme occurs both in a soluble form in plasma and attached to the endothelial surfaces [50], so that the conversion might occur intravascularly as well as upon organ and tissue passage. It follows that GLP-1 and GIP assays should be sensitive to N-terminal degradation of the peptides, but most published data show results from assays that do not discriminate between the intact and degraded forms and, therefore, do not reflect the concentrations of bioactive hormones. Furthermore, the two hormones differ markedly with respect to their sensitivity to DPP-IV. Whereas as little as 10 to 20% of exogenous GLP-1 survives in intact form, about half of infused GIP survives [48, 51]. Similarly, while the half life of intact GIP is about 7 min, intact GLP-1 is cleared from plasma at a rate that exceeds cardiac output [48, 52, 53] indicating that the peptide is degraded at a rate that precludes steady state calculations of its metabolism. In agreement with this, the postprandial plasma concentrations of both hormones in their intact form are much lower than those previously reported with the use of non-discriminating assays [54, 55]. Again, intact GLP-1 concentrations (10–20 pmol/l) are much lower than intact GIP concentrations (up to 100 pmol/l). Therefore, postprandially, plasma contains much more biologically active GIP than GLP-1. It should be noted however, that the rate of secretion of the hormones is best estimated using assays that react with both the intact hormones and the metabolites of DPP-IV degradation. This is because the clearly variable fraction of the hormone molecules secreted from the gut that are degraded will escape detection by the assays for the intact hormones, whereas the non-discriminating assays will pick up both forms and, therefore, reflect the total rate of secretion. The metabolites of the two hormones are also eliminated rapidly, particularly in the kidneys, resulting in half-lives of about 17 min and 4 to 5 min for GIP and GLP-1 metabolites, respectively [48, 56]. The liver is responsible for a large part of the DPP-IV mediated metabolism of the hormones, but plays a minor role in the elimination of the metabolites [53, 57].

The question then arises as to which hormone is the most potent with respect to stimulation of insulin secretion both at the start of the meal and post prandially with increasing plasma glucose concentrations. Some investigators reported that the two hormones were equipotent [58], while others found GLP-1 to be three to five times more potent than GIP [59, 60, 61, 62]. In many reports GIP was found incapable of stimulating insulin secretion at fasting glucose concentrations and was even reported to have little effect at glucose concentrations below 8 mmol/l [63]. We, therefore, recently decided to study the insulinotropic effects of the two hormones infused at rates that would increase their physiological concentrations in the intact form. The infusions were carried out while glucose concentrations were clamped at fasting or slightly increased concentrations in order to mimic as accurately as possible the prandial situation [64]. In their physiological concentrations, the two hormones had similar and highly significant insulinotropic effects at fasting glucose concentrations as well as at 6 mmol/l, whereas at 7 mmol/l, GLP-1 was somewhat more effective. It was concluded that both hormones normally contribute to the incretin effect in humans and do so nearly from the beginning of the meal (because increases in their concentrations are seen already after 5–10 min). Together, the two hormones seem to act in an additive manner. Thus, when GIP and GLP-1 infusions, which separately provided about the same insulin response, were combined, the resulting response amounted to approximately the sum of the two individual responses [61]. Recently mice with a double knockout of the GIP and GLP-1 receptors have been generated. Preliminary results obtained in these animals are also consistent with an additive effects of the two hormones, with additive effects on glucose tolerance of the double knockout compared to each of the single receptor knockouts [65].

Incretin function in diabetes

Given that GIP and GLP-1 together are responsible for the incretin effect in healthy subjects, it is now possible to analyse the incretin defect in patients with Type 2 diabetes. Theoretically, the defect could be due to impaired secretion or accelerated metabolism of the incretin hormones; alternatively, the effect of the hormones could be compromised.

There are many publications on the secretion of GIP in Type 2 diabetes, and both increased, normal and decreased secretion have been reported [10]. As mentioned above, it is probably important that the assay used does not cross-react with the poorly characterized “GIP 8000” component in plasma. If the results obtained with such assays are disregarded, the

impression is that GIP secretion is normal or slightly impaired. A recent study in patients with Type 2 diabetes, covering a very wide clinical spectrum of the disease [66], near normal fasting concentrations and meal responses were found, with no correlations between metabolic parameters and GIP responses. In the same study, a very significant impairment of the secretion of GLP-1 was observed. By multiple regression analysis, the impairment was found to be related to impaired cell function. In a previous study in a small group of identical twins discordant for Type 2 diabetes, the GLP-1 response was lower in the diabetic twins [67]. Furthermore, in first degree relatives of diabetic patients, 24-h GLP-1 profiles were normal [68]. These observations probably indicate that the impaired secretion is a consequence rather than a cause of diabetes. The GLP-1 secretion defect is evident whether one measures the concentrations of intact GLP-1 [54] or the concentrations of the metabolite as discussed above.

The lower GLP-1 concentrations could also be caused by an increased elimination of GLP-1 in diabetic subjects compared to healthy subjects. However, in a study where the rates of elimination of the intact hormone as well as the metabolite were studied in both patients and healthy control subjects [56], elimination rates were nearly identical in the two groups, indicating that differences in elimination cannot explain the lower concentrations in Type 2 diabetic patients.

An impaired secretion of GLP-1, therefore, seems to contribute to the impaired incretin effect in Type 2 diabetes. But what about the effect of the hormones? Here a dramatic difference emerges. The effects of iv infusions of GIP and GLP-1 were studied [60] in moderate Type 2 diabetic patients and matched control subjects, and it was found that the insulinotropic effect of GIP was almost lost in the patients, whereas the insulin response to GLP-1 was similar to that observed in the control subjects. Similar results were obtained by another study [59]. Based on chromatography, the structure of the two hormones seems to be normal in diabetic patients, and recent studies have shown that mutations in the genes that encode GLP-1 and GIP are unlikely to be common causes for the impaired incretin effect [69, 70]. This points to an impaired effect of GIP on the beta cell as an important contributor to the incretin defect in Type 2 diabetes mellitus and raises the question of the function of GIP receptors in these patients. Loss of function mutations or impaired expression of GIP receptors could explain the impaired effect [71]. Several groups have reported polymorphisms in the coding region of the GIP receptor gene, but these were neither associated with diabetes [72] nor with defective signalling of the receptor [73]. In contrast, a defective expression of the GIP receptor has been observed in animals with experimental diabetes [74]. Studies in glucose-tolerant first-degree relatives of diabetic patients showed a reduced insulinotropic effectiveness of GIP in 50% of the subjects compared to the control subjects without a family history of diabetes, indicating that the GIP defect could be a genetically determined and possibly primary defect [75]. In an attempt to pursue this finding in more detail, we designed a test consisting of bolus injections of GIP and GLP-1 (with or without simultaneous glucose administration), based on a previous observation that the beta-cell secretory capacity could be quantified with GLP-1 [76]. By comparing the response to GIP with that obtained with GLP-1, one would obtain a quantitative measure of the inheritable incretin defect of the investigated subject. Surprisingly, however, it turned out that the ratio between the insulin secretory responses (as judged by C-peptide secretion) to these bolus injections was the same in Type 2 diabetic patients and matched control subjects [77]. In other words, if responses to GLP-1 were low (as in poorly controlled diabetic subjects), the responses to GIP were equally impaired and vice versa. Based on these findings, it was concluded that a decreased expression of the GIP receptor was unlikely to occur in the patients – rather, low responses would be compatible with a reduced number of cells, as frequently found in Type 2 diabetic patients [78]. Furthermore, a defective response to GIP could not be reproduced with this technique. We, however, went on to study the differential effects of high doses of GIP and GLP-1 in Type 2 diabetic patients during the conditions of 15 mmol/l hyperglycaemic clamp [77]. In these studies, the GLP-1 infusion was capable of restoring the late phase (30–120 min) insulin response to glucose (which was nearly absent in these patients) to values indistinguishable from those observed in the healthy control subjects. In other words, with GLP-1 the subjects showed a completely normal insulin response to glucose. A similar observation (that GLP-1 can restore beta-cell responsiveness glucose in patients with Type 2 diabetes) was made by a study using an entirely different approach [79]. Moreover, the normal glucose-induced inhibition of glucagon secretion was completely restored. GIP, however, regardless of dose, had neither effect on insulin secretion nor on glucose turnover. It was concluded that the GIP defect in Type 2 diabetes is very severe indeed, but restricted to "late phase" insulin secretion, which could be particularly relevant for postprandial insulin secretion. However, these findings obviously did not provide insight into the cellular or molecular mechanisms involved, except for suggesting that a defective expression of the receptor was unlikely to be involved. In further studies using the same technique, we investigated groups of diabetic patients known or suspected to have diabetic aetiologies different from those of the classic obese elderly Type 2 diabetic patients [80]. The groups included patients with Type 1 diabetes, diabetes secondary to pancreatitis, monogenic diabetes (MODY3), lean

Type 2 diabetic patients and patients with LADA. It was the underlying hypothesis that these patients would not exhibit a comparable GIP defect, based on the assumption that the GIP defect was a genetic defect contributing to the phenotype of the typical Type 2 diabetic patient. Again, however, the results were unexpected. The different groups had clearly lower relative responses to GIP than the non-diabetic control group, and for example, the patients with secondary diabetes had virtually absent late response to GIP and no effect on glucose turnover. It was concluded that the observed GIP defect is a consequence of the diabetic state, and although a genetic component might also be involved in Type 2 diabetic patients, as shown in the study of the first degree relatives [75], the defect induced by diabetes is very severe. The differential responsiveness of the cells to GIP and GLP-1 is surprising because of the many similarities between the two hormones, their receptors and their signal transduction mechanisms [8, 15, 81]. Apparently, however, the interaction between glucose stimulation of insulin secretion and the potentiating actions of the two hormones differ in spite of the fact that both seem to depend on an initial accumulation of cAMP.

Incretin hormones as therapeutic agents

Whereas lost efficacy of GIP seems to contribute to the insufficient insulin secretion in diabetes and, therefore, could preclude its application as a therapeutic agent, the preserved effect of GLP-1 has inspired attempts to treat Type 2 diabetes with GLP-1 [82]. Indeed, in 1993 one study could show that an iv infusion of GLP-1 could completely normalise plasma glucose concentrations, even in patients with advanced Type 2 diabetes [83]. As mentioned above, addition of GLP-1 might restore glucose-induced insulin secretion to normal values in the patients [77, 79]. However, it should be noted that GLP-1 not only potentiates glucose induced insulin secretion, but also has numerous other effects, all of which seem to be desirable in the context of treating Type 2 diabetic patients (Table 1).

Firstly, its insulinotropic effect is strictly glucose dependent, which implies that it is unlikely to cause lasting and profound hypoglycaemia in normal subjects, and in particular, in patients with Type 2 diabetes [84, 85]. Secondly, it stimulates all steps of insulin biosynthesis as well as insulin gene transcription [86], thereby providing continued supplies of insulin for secretion. In addition, it up-regulates the genes for the cellular machinery involved in insulin secretion [87]. Finally and most importantly, GLP-1 has been shown to have trophic effects on beta cells in rodents. Not only does it stimulate beta-cell proliferation [88, 89], it also enhances the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium [90] and has now been shown to also inhibit apoptosis induced by e.g. cytokines or free fatty acids [91]. This raises the hope that GLP-1 could be capable of providing new beta cells in individuals with an insufficient number of functioning cell [92], such as Type 2 diabetic patients (although it is not yet established to what extent this process could occur in humans).

Table 1. Actions of GLP-1

1. Insulin secretion
   a) potentiates glucose induced insulin secretion
   b) enhances all steps of insulin biosynthesis
   c) up regulates insulin gene expression
   d) up regulates expression of genes essential for beta cell function (glucokinase, GLUT 2 etc)
   e) mitotic for beta cells
   f) promotes differentiation of duct progenitor cells to beta cells inhibits apoptosis of beta cells
2. Inhibits glucagon secretion
3. Inhibits gastrointestinal secretion and motility
4. Inhibits appetite and food intake

In addition to its effects on the beta cells, GLP-1 also strongly inhibits glucagon secretion. The importance of this with respect to diabetes treatment is perhaps best illustrated in studies of GLP-1 infusion in patients with insulin-requiring diabetes and no residual beta-cell secretory capacity [93]. In these patients, GLP-1 retains substantial glucose lowering activity, in spite of undetectable C-peptide responses, while glucagon secretion is strongly inhibited. The glucose-lowering effect is likely to be a consequence of the inhibition of glucagon secretion, because in these patients GLP-1 appears to act mainly as a glucagon antagonist. Glucagon antagonists have been shown, at least experimentally, to be able to improve diabetic hyperglycaemia [94, 95].

Further important effects of GLP-1 include inhibition of gastrointestinal secretion and motility, notably gastric emptying [96, 97]. This effect is also desirable in patients with diabetes, because the slower gastric emptying rate reduces postprandial glucose excursions as is evident from the use of another potent gastric inhibitor, amylin, for diabetes treatment [98]; finally, GLP-1 inhibits appetite and food intake. This has been shown in both normal subjects, obese subjects and subjects with Type 2 diabetes mellitus [99, 100, 101]. The latter effect would support attempts at weight reduction in patients with Type 2 diabetes and, if effective, would be considered most desirable. It should be noted, though, that GLP-1 receptor knockout mice do not become obese [42], indicating that GLP-1 might not be indispensable for normal appetite regulation or that additional regulatory mechanisms could compensate for the lack of GLP-1 effect.

Taken together, all of these effects render GLP-1 interesting as a candidate for diabetes therapy. Indeed, others [102] were able to show near normalisation of diurnal plasma glucose concentrations during continu-

ous intravenous infusion of GLP-1 in a group of Type 2 diabetic patients. However, it turns out that simple subcutaneous injections of GLP-1 are ineffective [103]. As already discussed, the reason is that GLP-1 is degraded extremely rapidly and less than 10% of the peptide survives in the intact bioactive form after subcutaneous injection [51]. Thus, it is clear that GLP-1 cannot be immediately used for clinical treatment of Type 2 diabetes. Recent clinical experiments involving continuous subcutaneous infusion of native GLP-1 with conventional insulin pumps have provided an indication of the likely effects of a GLP-1 based therapy of Type 2 diabetes [104]. After a 3-week wash-out period, 20 patients were allocated to continuous infusion of either saline or GLP-1 at a rate of 4.8 pmol/kg/min using Minimed pumps. The patients were evaluated before, after 1 week and after 6 weeks of treatment. No changes were observed in the saline treated group, whereas in the GLP-1 group, fasting and average plasma glucose concentrations were lowered by approximately 5 mmol/l, HbA_{1c} decreased by 1.2%, NEFA were lowered, and the patients had a significant weight loss of approximately 2 kg. In addition, insulin sensitivity as determined by a hyperinsulinaemic euglycaemic clamp, almost doubled, and insulin secretion capacity (measured using a 30 mmol/l glucose clamp and arginine) greatly improved. There was no significant difference between results obtained after 1 and 6 weeks treatment, but there was a tendency towards further improvement of plasma glucose as well as insulin secretion. There were very few side effects and no differences between saline and GLP-1 treated patients in this respect. Given that treatment of Type 2 diabetes will be chronic, if not life-long, 6 weeks of therapy must be considered short-term. In addition, continuous subcutaneous infusion might not be the optimal mode of administration of an activator of GLP-1 receptors. Currently, however, several DPP-IV resistant and long acting analogues of GLP-1 are undergoing clinical development for diabetes therapy [105]. Generally these agents have shown efficacy similar to that of the subcutaneously administered native peptide. Recently, results obtained over 5 months with the GLP-1 receptor activator, exendin-4, were reported and again, the results included improvements of glucose concentrations, lowering of HbA_{1c} values and weight loss [106]. The most exciting aspect of GLP-1 treatment is the possibility that it (perhaps especially because of its trophic effects on the pancreas) might halt the progression of disease that inevitably seems to accompany conventional treatment [107] and has not yet been elucidated in any of the trials. However, adaptive turnover of human cells is probably a limited and slow process [78] compared to rodents, and it might be that detection of effects of GLP-1 or its analogues on beta-cell's mass will require observation periods of more than a year. The trophic effects of GLP-1 also raise the question as to whether or not a prolonged therapy will be associated with an increased risk of islet-cell nesidioblastosis or tumour formation. So far, there are no reports of neoplastic reactions in animals exposed to chronic treatment with GLP-1 analogues.

Conflict of interest statement

In 2003, T. Vilsbøll was employed for one year in an educational position as part of her training as a clinical pharmacologist at Novo Nordisk. All of Dr. Vilsbøll's studies cited in this review were carried out before this employment. During this research period Dr. Vilsbøll had no interest in any pharmaceutical company, but served as research assistant, financed by the University of Copenhagen, at the Department of Internal Medicine at Gentofte Hospital, associated with the Department of Medical Physiology, University of Copenhagen. Dr. Holst has been on advisory boards of several companies that are developing GLP-1 based therapies for diabetes (including NovoNordisk, Bionebraska (later Restoragen, now closed down) and Amylin Corporation), but otherwise has no conflict of interest regarding GLP-1.

Acknowledgements. The studies included have been supported by the Danish Diabetes Association, the Danish Research Council and the Novo Nordisk Foundation.

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