Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes

JF Gautier1, 2, S Fetita1, E Sobngwi1, 2, C Salaün-Martin3

SUMMARY
Incretin hormones are defined as intestinal hormones released in response to nutrient ingestion, which potentiate the glucose-induced insulin response. In humans, the incretin effect is mainly caused by two peptide hormones, glucose-dependent insulin releasing polypeptide GIP, and glucagon-like peptide-1 GLP-1. GIP is secreted by K cells from the upper small intestine while GLP-1 is mainly produced in the enteroendocrine L cells located in the distal intestine. Their effect is mediated through their binding with specific receptors, though part of their biological action may also involve neural modulation. GIP and GLP-1 are both rapidly degraded into inactive metabolites by the enzyme dipeptidyl-peptidase-IV (DPP-IV). In addition to its effects on insulin secretion, GLP-1 exerts other significant actions, including stimulation of insulin biosynthesis, inhibition of glucagon secretion, inhibition of gastric emptying and acid secretion, reduction of food intake, and trophic effects on the pancreas. As the insulinotropic action of GLP-1 is preserved in type 2 diabetic patients, this peptide was a candidate as a therapeutic agent for this disease.

A number of pharmacological strategies have been developed to provide continuous delivery of GLP-1 and to prevent degradation of GLP-1, including continuous intravenous administration of GLP-1, DPP-IV inhibitors and DPP-IV resistant GLP-1 analogues. Recent results of the most clinically advanced incretin mimetics confirmed their efficacy to improve glycemic control in type 2 diabetic patients. Further results are expected to confirm the efficacy/safety profile of these compounds, and to find their place in the therapeutic strategy of type 2 diabetes.

Key-words: Incretin hormones · Glucagon-like peptide-1 · Insulin · Type 2 diabetes.


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REVIEW

Action biologique des incrétines GIP et GLP-1 et perspectives thérapeutiques chez les diabétiques de type 2


Plusieurs stratégies pharmacologiques sont actuellement explorées. Les molécules en cours de développement clinique sont les analogues du GLP-1 résistant à la DPP-IV et les inhibiteurs de la DPP-IV. Les résultats des essais randomisés contrôlés contre placebo avec les agents les plus avancés dans leur développement, confirment leur efficacité sur le contrôle de l’équilibre glycémique chez les diabétiques de type 2. D’autres résultats sont attendus pour en préciser le rapport bénéfice/risque et définir leur place dans l’arsenal thérapeutique du diabète de type 2.

Mots-clés: Incrétines · Glucagon-Like Peptide-1 GLP-1 · Insuline · Diabète de type 2 · Analogues du GLP1.
Introduction

The idea that factors secreted from the gut participate in the regulation of endocrine secretion was raised as early as the beginning of the XXth century [1]. The term “secretin” was first used to define factors regulating pancreas secretion and the term “incretin” was later introduced in the 1920's to describe these potential mediators [2]. The connection between the gastrointestinal tract and the endocrine pancreas was confirmed in the 1960s, when insulin became measurable in plasma. Clinical studies showed that for an oral and an intravenous load of glucose producing identical increases in plasma glucose levels, the insulin secretory response was greater when glucose was administered orally. These findings suggested that not only glucose interacted with beta cells in the islets of Langerhans, but also gut factors were released, that stimulated insulin secretion [3].

The incretin effect was finally defined as the phenomenon of oral glucose eliciting a greater insulin response than intravenous glucose infusions, irrespective of whether the same amount of glucose is infused or an equivalent rise in glycaemia is produced by the parenteral route [4]. In humans, two peptide hormones have been identified as being responsible for the incretin effect, namely glucose-dependent insulin releasing polypeptide, GIP (formerly called gastric inhibitory polypeptide) and glucagon-like peptide-1, GLP-1. GIP and GLP-1 are both secreted in response to food ingestion and both potentiate the glucose-induced insulin response.

GLP-1 previously demonstrated a promising potential in the treatment of diabetes mellitus, showing near normalized glucose levels following intravenous infusions in patients with type 2 diabetes [5-7]. It is now recognized that the biological effects of GLP-1 comprise not only an effect on insulin-secreting cells but also on other pancreatic cells, as well as effects on several extrapancreatic sites. Additionally, trophic effects on the pancreatic islets have been recently discovered in animal models, which make GLP-1 and GLP-1 analogues exciting candidates for diabetes therapy [8].

The aim of the present article is to review the current knowledge on the effects of the two incretin peptides GIP and GLP-1, to describe their interactions in the diabetic state, and to delineate therapeutic perspectives that can be derived from their spectrum of actions in patients diagnosed with type 2 diabetes.

Incretin synthesis, release, degradation and effectors

GIP and GLP-1 are both members of the glucagon peptide superfamily, sharing a close amino acid homology.

GIP is a single 42 amino acid peptide derived from the processing of a 153 amino acid precursor, whose 10 kilobase-spanning gene is located on chromosome 17 in humans (reviewed in [9]) (Fig 1). In humans, two peptide hormones have been identified as being responsible for the incretin effect, namely glucose-dependent insulin releasing polypeptide, GIP (formerly called gastric inhibitory polypeptide) and glucagon-like peptide-1, GLP-1. GIP and GLP-1 are both secreted in response to food ingestion and both potentiate the glucose-induced insulin response.

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GIP is a single 42 amino acid peptide derived from the processing of a 153 amino acid precursor, whose 10 kilobase-spanning gene is located on chromosome 17 in humans (reviewed in [9]) (Fig 1). GIP is secreted in a single bioactive form by K cells and released from the upper small intestine (duodenum and proximal jejunum), in response to the oral ingestion of carbohydrates and lipids.

GLP-1 is a product of the proglucagon gene, spanning 10 kilobases and located on the long arm of chromosome 2,
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that encodes not only GLP-1 but also glucagon, GLP-2 and other proglucagon-derived peptides [9] (Fig 1). Glucagon is the main product of post transcriptional processing of proglucagon in the endocrine pancreas. GLP-1 is produced together with GLP-2 and glicentin (enteroglucagon) as the main products in the enteroendocrine L cells. Despite close structural homology, GLP-2 does not share the same biological action as GLP-1, but rather acts as a regulator of growth in the intestinal tract (reviewed in 10).

GLP-1 is mainly expressed in mucosal L cells located predominantly in the distal intestine (ileum and colon), and is also expressed in pancreatic alpha cells, as well as in neurons from several brain areas (hypothalamus, pituitary, nucleus of the tractus solitarius, reticular nucleus). GLP-1 is secreted from L cells in two bioactive forms, GLP-1(7-37) and the predominant circulating active form GLP-1(7-36) amid, also called “truncated” GLP-1. Both peptides are equipotent, with a same plasma half-life and identical activity through the same receptor.

Despite the distal location of L cells in the gastrointestinal tract, GLP-1 is released into the circulation within minutes following oral ingestion of nutrients, suggesting that this prompt release is more indirectly controlled by neural and endocrine factors initiated by nutrient entry in the proximal gastrointestinal tract, rather than directly stimulated by contact of L cells with nutrients. Although these factors remain largely unknown in humans, experimental studies in rodents suggest that the vagal nerve, through muscarinic receptors, is a contributing factor.

Circulating levels of GIP and GLP-1 are very low in the fasting state, and rapidly increase following food ingestion. Both GIP and GLP-1 are extensively and rapidly degraded by the enzyme dipeptidyl-peptidase IV (DPP-IV), which cleaves the biologically active forms at the position 2 alanine, resulting in inactive or weak antagonist peptide fragments. The enzyme DPP-IV is widely expressed, including in the vascular endothelium of the capillaries of the villi. These findings suggest that the majority of GIP and GLP-1 arriving in the portal circulation is already inactivated by DPP-IV upon entry into the capillaries. Independently of this action, it is likely that the activity of endogenous GLP-1 is also exerted through interaction with sensory afferent nerve fibres relaying in the brain and modulating efferent vagal fibres that, in turn, regulate a number of its biological actions (gastrointestinal secretion and motility, pancreatic secretion).

Physiological actions of GIP (Tab I)

Action on insulin secretion

GIP exerts glucose-dependent stimulatory effects on insulin secretion in animals and humans [14-15]. The incretin function of GIP was first studied in dogs and rodents, using GIP antagonists and GIP receptor antisera (“neutralization studies”). When given alone, these compounds induced a reduction in the insulin response to oral glucose; when given concomitantly with exogenous GIP, they attenuated its insulinotropic effects [16]. In other experimental studies, it was shown that knockout mice lacking the GIP receptor exhibited glucose intolerance after an oral glucose load [17]. As the glucose intolerance found in this experimental model was not very severe, it was concluded that GIP is not the only incretin hormone and that other insulinotropic agents are secreted, which compensate the lack of GIP receptor activation [11]. Results of studies in humans as well as studies in mice with double knockout of the GIP and GLP-1 receptors consistently showed an additive effect of the two hormones GIP and GLP-1 in the incretin effect [16]. In physiological conditions, it appears that smaller loads of rapidly absorbable nutrients would preferentially activate the upper incretin hormone GIP, whereas ingestion of larger meal containing more complex nutrients would also activate the distal incretin GLP-1.

Effect on fat metabolism

There is experimental evidence indicating that GIP regulates fat metabolism in adipocytes, including enhanced insulin-stimulated incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, stimulation
of fatty acids synthesis. At present, the exact signalling mechanisms mediating the effects of GIP on fat cells are unknown [12].

Other actions

GIP has been shown to promote beta cell proliferation and cell survival in islet cell line studies [18]. In contrast with GLP-1, GIP does not influence pancreatic alpha cell secretion of glucagon in humans, nor does it affect gastric emptying.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>42 amino acids</th>
<th>30 amino acids</th>
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<tbody>
<tr>
<td>Released from</td>
<td>K cells - duodenum</td>
<td>L cells - ileum and colon</td>
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<tr>
<td>Active form</td>
<td>Single bioactive form</td>
<td>Two bioactive forms: (7-37) and (7-36)amide</td>
</tr>
<tr>
<td>Inactivated by</td>
<td>DPP-IV</td>
<td>DPP-IV</td>
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**Physiological actions**

<table>
<thead>
<tr>
<th>Insulin secretion</th>
<th>Stimulated</th>
<th>Stimulated</th>
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<tr>
<td>Glucagon secretion</td>
<td>-</td>
<td>Inhibited</td>
</tr>
<tr>
<td>Food intake</td>
<td>-</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastrointestinal motility</td>
<td>-</td>
<td>Participates in the ileal brake</td>
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<tr>
<td>Insulin biosynthesis</td>
<td>-</td>
<td>Stimulated</td>
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<td>Beta cell proliferation</td>
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<th>In type 2 diabetes</th>
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<tr>
<td>Secretion</td>
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<td>Response</td>
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**Physiological actions of GLP-1**

*(Tab I, Fig 3)*

**Effects on insulin secretion**

GLP-1 stimulates glucose-induced insulin secretion in isolated islets of Langerhans, in the perfused pancreas and in whole organisms, in animals and humans.

It has been demonstrated in rats, that insulin secretory responses to oral intake of nutrients and to intraduodenal glucose were suppressed when using the GLP-1 receptor.
antagonist exendin 9-39 [9]. In addition, GLP-1 knockout mice showed fasting hyperglycaemia and abnormal glucose excursion with significantly reduced insulin response after a glucose load [19].

In humans, secretion of GLP-1 throughout the day is strongly correlated to the release of insulin [20]. The effect of GLP-1 on insulin secretion is strictly glucose-dependent and there is no effect of GLP-1 on insulin secretion for glucose concentrations below a certain threshold (approximately 4.5 mmol/l).

The incretin activity of GLP-1 has been recognized from studies performed in healthy subjects, using exogenous GLP-1 [21-22]. However, the contribution of the incretin effect in normal subjects is a matter of debate. A number of experimental data suggest that GLP-1 is responsible for a substantial part of the insulin response to oral glucose [16], whereas other experiments suggest that the contribution might be rather small in normal conditions [23].

**Effects on insulin biosynthesis**

Additionally to its effects on insulin secretion, GLP-1 has been shown to stimulate insulin gene transcription and all steps of insulin biosynthesis in isolated beta cells, thereby providing continual supplies of insulin for secretion (reviewed in 24). This may be important for maintaining insulin levels during secretion which tends to deplete them.

**Effect on somatostatin secretion**

GLP-1 is a potent stimulator of somatostatin secretion from isolated human islets. This effect is not dependent on glucose concentrations [9].

**Inhibitory effects on glucagon secretion**

GLP-1 is able to suppress glucagon secretion in pancreatic islets, in perfused pancreas and in whole organisms. The mechanism by which GLP-1 inhibits glucagon secretion remains to be elucidated. The inhibitory effect is probably indirectly mediated via insulin release and via somatostatin secretion. However, a direct effect of GLP-1 is not completely excluded since GLP-1 receptors are expressed on pancreatic glucagon cells [24].

The inhibitory effects of GLP-1 on glucagon secretion seem to represent an important mechanism for regulating elevated levels of blood glucose. In patients with type 1 diabetes (i.e. who had no insulin effect), administration of GLP-1 decreased blood glucose levels while the secretion of glucagon was strongly inhibited, suggesting that GLP-1 suppressed the hepatic production of glucose induced by glucagon [25].

The inhibition of glucagon secretion by GLP-1 is glucose dependent, meaning that GLP-1 administration is unlikely to impair the glucagon counter regulatory response to hypoglycaemia [26].

**Effects on the gastrointestinal tract**

GLP-1 exerts inhibitory effects on gastrointestinal secretion and motility, particularly on gastric emptying [23, 24]. Administration of GLP-1 at physiological doses in healthy volunteers results in a dose-dependent slowing of gastric emptying and of glucose absorption, which participate in a subsequent reduction of postprandial plasma glucose concentration [23]. These effects suggest the participation of GLP-1 in the “ileal brake” phenomenon, by which nutrients present in the distal part of the small intestine induce a reduction in upper intestinal motility and secretory activity. The actions of GLP-1 on gastrointestinal motility and secretion probably involve neurally mediated mechanisms, including vago-vagal pathways.

The physiological role of GLP-1 may be to adjust the absorptive capacity of the gut and to adjust the amount of chyme, by slowing gastrointestinal transit and decreasing secretion of digestive enzymes. In physiological conditions, it is likely that the gastrointestinal effects of GLP-1, (i.e. reduction of gastric secretion and slowing of gastric emptying) are more important than its insulinotropic action [23]. In pathological conditions such as diabetes, the inhibitory effects of GLP-1 on gastrointestinal motility, particularly gastric emptying, are of special interest because they potentially reduce postprandial glucose excursions.

**Effects on food intake**

GLP-1 has been shown to reduce caloric intake and to enhance satiety, these effects being probably related to central mechanisms. In experimental studies with rodents, intracerebroventricular administration of GLP-1 significantly reduced food ingestion, whereas concomitant injection of the GLP-1 receptor antagonist exendin-9-39 abolished this effect [27]. Significant reduction of food intake and consequently lower weight gain was also observed with the systemic administration of a GLP-1 analogue in rhesus monkeys, in diabetic db/db mice and in Zucker diabetic fatty rats (reviewed in 28). In normal subjects, the intravenous administration of GLP-1 above physiological levels induced increased feelings of satiety as well as a reduction of food intake [29]. Similar effects were observed in obese subjects, as well as in patients with type 2 diabetes [30-31]. In type 2 diabetic patients treated with a subcutaneous infusion of GLP-1 for up to 6 weeks, the reduction of food intake was sustained and associated with a reduction of body weight [32].

The exact mechanism by which peripheral GLP-1 is able to modulate food intake behaviour is not completely elucidated [28]. One possibility is that peripheral GLP-1 acts on vagal afferent fibers, where it may modulate GLP-1 neuronal transmission in CNS. This hypothesis is supported by the localization of GLP-1 containing neurons in the nucleus of the tractus solitarius, which projects into thalamic and hypothalamic regions implicated in the control of
food intake. Another possibility is that circulating GLP-1 directly reaches accessible receptors located in blood brain barrier-free areas (such as the area postrema and subfornical organ) that in turn, relay to brain nuclei involved in nutrient homeostasis. It is also likely that gastric emptying mediated by GLP-1 increases the sensation of fullness and leads to the termination of meal ingestion, thereby participating in the regulation of food intake. Finally, nausea, a side effect often observed after administration of exogenous GLP-1, may also be a contributing factor, though the decrease of food intake was observed even in subjects who did not report nausea.

**Trophic effects on pancreas**

GLP-1 has been shown to exert trophic effects on pancreatic beta cell mass (reviewed in 33). When given for prolonged periods to normal rodents or to animals with impaired glucose tolerance or diabetes, GLP-1 and its long acting analogue Exendin 4 increased beta cell mass. GLP-1 promoted beta cell replication in mice, and stimulated DNA synthesis in cell lines in vitro. GLP-1 also promoted the differentiation of beta precursor cells in the pancreatic duct epithelium. In addition, GLP-1 exhibited antiapoptotic effects in beta cells of rodent models (Zucker diabetic fatty rats). Recent data indicate that the antiapoptotic effects were also observed in freshly isolated human islets cultures in vitro [34]. Unlike insulinotropic effects dependent on Protein Kinase A (PKA) pathways, the trophic and survival effects of GLP-1 are probably mediated through different signalling pathways. Whether GLP-1 also expresses pancreatic trophic properties in vivo in human remains to be confirmed. Nevertheless, these findings raise considerable interest from a clinical perspective, as GLP-1 and GLP-1 analogues could be potentially useful in preserving functional beta cell mass in patients with type 2 diabetes.

**Incretin function in type 2 diabetes**

The secretion of GIP and GLP-1 in patients with type 2 diabetes have been largely studied [35, 36]. In these patients, circulating levels of GIP are normal or slightly increased in basal and in postprandial conditions. In contrast, plasma levels of GLP-1 are reduced in type 2 diabetic patients or in patients with impaired glucose tolerance, as compared to normal subjects. The mechanism of the impaired secretion of GLP-1 is unknown, but several factors such as the severity of diabetes or the Body Mass Index have been suggested to influence GLP-1 secretion, consistent with previous findings that secretion of GLP-1 is decreased in morbid obesity [24].

The response to exogenous incretin hormones has also been studied in type 2 diabetic patients, with significant differential results between GIP and GLP-1. The insulinotropic response to GIP administration is defective in diabetic patients, i.e. the insulin response to oral glucose alone and to glucose plus GIP is unchanged. The precise cellular mechanisms contributing to impaired GIP function in diabetes remain to be elucidated. In contrast to GIP, GLP-1 has a well preserved insulinotropic and glucagonostatic activity in type 2 diabetic patients [11, 37] and a preserved ability to decelerate gastric emptying [38]. The different responsiveness is somewhat surprising since both hormones GIP and GLP-1 are very similar (close structural homology, same family of receptors, same signal transduction mechanisms).

In summary, these findings suggest that in patients with type 2 diabetes: 1) the secretion of GLP-1 is impaired while the secretion of GIP is unaffected, 2) GIP administration has very little insulinotropic activity whereas GLP-1 maintains its ability to stimulate glucose-dependent insulin secretion. Because the insulinotropic action of GLP-1 is preserved in diabetes, this peptide as well as GLP-1 receptor agonists were interesting potential therapeutic agents for this disease [24].

**From a spectrum of actions to therapeutic perspectives in type 2 diabetes**

Type 2 diabetes is characterized by a failure of beta-cells to secrete adequate amounts of insulin to compensate for insulin resistance in peripheral tissues and by an increased endogenous glucose production [39].

The therapeutic strategy recommended for patients diagnosed with type 2 diabetes is stepwise, that includes firstly lifestyle intervention (exercise, diet, weight control), then oral treatment with antidiabetic agents, followed by insulin therapy, in order to achieve adequate glycemic control [40]. A number of antidiabetic agents are effective and their mechanism of action is rather well established (Fig 2). First line antidiabetic agents include metformin and sulfonylureas [41]. Treatments with the three main antidiabetic agents, i.e. sulfonylurea, metformin and insulin, have proven to be equally effective in reducing fasting plasma glucose concentrations in patients with newly diagnosed type 2 diabetes. However, despite adequate drug treatment, glucose and HbA1c measurements steadily increase with time, reflecting the ongoing deterioration of beta-cell function [42].

Recently, new antidiabetic agents have become available (Fig 2). Meglitinides are insulin secretagogues with short action, whose mechanism of action is related to the regulation of K+ efflux from pancreatic beta cells. Alpha-glucosidase inhibitors reduce the rate of absorption of carbohydrates in the intestinal tract, thereby limiting postprandial glucose excursions. The most recently approved thiazolidinediones are insulin sensitizing agents that enhance the muscular and adipose tissue response to insu-
lin, thereby reducing the insulin resistance implicated in the pathophysiology of type 2 diabetes.

Although the armamentarium now includes a variety of antidiabetic agents, new therapies are still needed in type 2 diabetes, to control metabolic abnormalities, and also to preserve beta cell mass and to prevent the loss of beta cell function. GLP-1 is a drug candidate that potentially fulfills these conditions. GLP-1 glucoregulatory actions include glucose dependent enhancement of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying and reduction of food intake (Fig 3). Combined insulinotropic and anorectic effects make it a very attractive agent for the therapy of obese patients with type 2 diabetes. In addition, severe hypoglycemic episodes should not occur, given the strictly glucose dependent insulinotropic effects of GLP-1. Finally, another exciting aspect of GLP-1 is that it may prevent the progression of the disease because of its trophic effects on the pancreas.

As a peptide, GLP-1 cannot be administered orally because it is immediately denatured and inactivated by gastric acid. Subcutaneous or intravenous administration is required for GLP-1 to reach the circulation. Nevertheless, the peptide cannot be immediately employed because of its extensive and rapid degradation by the ubiquitous DPP-IV enzyme. A number of pharmacological strategies have been developed in order to provide continuous delivery of GLP-1 and prevent its degradation, including: 1) continuous administration of GLP-1, 2) DDP-IV resistant GLP-1 analogues, and 3) inhibition of DPP-IV.

Continuous administration of GLP-1

One approach is the continuous subcutaneous infusion of GLP-1 via a portable minipump [16]. This method has been proven to provide stable plasma concentrations. But it is costly and associated with an increased risk of catheter infection. Its application may be limited by patients’ preference for less invasive methods.

DDP-IV resistant analogues

The generation of DPP-IV resistant analogues consists of substituting alanine by another amino acid at the N-terminal position of the native molecule. This substituted analogue is more resistant analogue to the action of DDP-IV and has an extended half-life. Several companies are presently assessing the efficacy and safety of various analogues in clinical studies.

Exenatide

Exenatide is the most advanced candidate drug in the clinical development of GLP-1 analogues. Exenatide is the synthetic version of exendin-4, a peptide originally isolated from the saliva of the lizard Heloderma suspectum (Gila monster), showing a 53% amino acid homology with mammalian GLP-1. Exendin-4 acts as a full agonist at the GLP-1 receptor. This new compound exhibited glucoregulatory actions in a large number of preclinical experiments (glucose-dependent enhancement of insulin secretion, glucose-dependent inhibition of glucagon secretion), as well as slowing gastric emptying and reducing food intake. Additionally, exendin-4 has been shown to promote beta-cell proliferation and islet neogenesis from precursor cells in vitro and in vivo [43]. In human studies, exenatide is commonly administered as a twice-daily subcutaneous injection (SC), the plasma half life being estimated at 2-4 hours. In preliminary clinical studies performed in healthy volunteers and in type 2 diabetic patients, exenatide reduced both fast-
ing and postprandial glucose excursions [44-46]. Data of a 28-day phase II controlled study indicated that exenatide caused a marked reduction in HbA1c compared to baseline, in type 2 diabetic patients not achieving optimal glucose control with diet and oral drug therapy [47]. Additionally, glucose profiles during ingestion of mixed meals demonstrated a marked acute effect of exenatide to reduce postprandial glycaemia, which was sustained over the 28-day period.

Phase III placebo-controlled studies evaluating the effects of exenatide in approximately 1100 patients have been completed [48-50]. Over 30 weeks of treatment, exenatide significantly reduced HbA1c by approximately 1% point, decreased both fasting and postprandial plasma glucose levels, and was associated with weight loss of approximately 2 kg, in patients inadequately controlled with maximally effective doses of metformin [48] or sulfonylurea [50] or with combined metformin-sulfonylurea therapy [49]. There was evidence of an improved D-cell function (derived from increases in HOMA-B Homeostasis Model Assessment, and from a reduction in the proinsulin/insulin ratio) resulting from treatment with exenatide. Exenatide was generally well tolerated, the most frequent adverse events being gastrointestinal (nausea). Mild or moderate hypoglycaemia was noted in two studies in patients treated with a sulfonylurea alone [50] or associated with metformin [49], while the incidence of hypoglycaemia was not increased in patients not treated with sulfonylurea [48].

Liraglutide

Liraglutide is a long-acting acylated GLP-1 analogue, acting as a full agonist toward the GLP-1 receptor [51]. The compound is administered as a once-daily subcutaneous injection (SC) in humans (half-life of approximately 12 hours). Animal and human studies have demonstrated blood glucose-lowering effects. In a recent comparative phase II trial (12-week duration) in type 2 diabetic patients, liraglutide provided effective glycemic control (i.e. HbA1c and fasting serum glucose being significantly lower than with placebo) and was not associated with weight gain [52]. The results of a 5-week study performed in 144 type 2 diabetic patients demonstrated that liraglutide, used alone or combined with metformin, significantly reduced levels of fasting plasma glucose in diabetic patients compared to metformin treatment alone or to combined metformine and glimepiride therapy. When used with metformin, liraglutide significantly decreased both fasting plasma glucose and body weight, compared with combined metformin and glimepiride therapy. After 5 weeks of treatment, the mean decrease in HbA1c in this group was superior to 1% (-1.1%, 95%CI:-1.3;-0.8%) [53]. Reported side effects were mild or moderate nausea.

CJC-1131

CJC-1131 is a GLP-1 analogue with an extended half-life of approximately 10 days in humans. Preliminary results of a phase II study performed in type 2 diabetic patients, previously treated with oral hypoglycemic agents, showed a 0.6% reduction in HbA1c and a ~2.3 kg reduction in body weight after 4 weeks of a once-daily subcutaneous injection (SC) of CJC-1131 monotherapy treatment. The most frequently reported adverse events were gastrointestinal (mild nausea, stomach discomfort) [54].

DPP-IV inhibitors

A number of DPP-IV inhibitors are undergoing clinical development for diabetes therapy (LAF-237, MK-0431, P93/01). They have been shown to prevent the degradation of endogenous incretins, resulting in an enhanced insulin response and improved glycemic control. DPP-IV inhibitors offer the advantage of an oral administration. Their potential limitation is that DPP-IV is a ubiquitous enzyme. Thus, nonspecific inhibition may result in increased levels of other peptides that are also cleaved by DPP-IV, such as neuropeptide Y, endomorphin, growth hormone releasing hormone GH-RH, GLP-2, with potential unknown adverse effects.

LAF-237

The effectiveness of the DPP-IV inhibitor LAF-237 in type 2 diabetic patients was examined either in monotherapy or in combination with oral antidiabetic agents in 12-week placebo-controlled studies [55, 56]. Administration of LAF-237 (oral dose, twice daily) in monotherapy of 72 patients with type 2 diabetes led to significant reductions in HbA1c values of 0.6%, particularly in patients having higher baseline HbA1c levels, to reduced fasting and postprandial plasma glucose concentrations, and to increased mean 4-hour postprandial C-peptide and insulin levels. When assessed in combination with metformin in type 2 diabetics not well controlled with metformin alone, LAF-237 treatment reduced HbA1c by 0.6% and fasting and postprandial plasma glucose levels.

MK-0431

MK-0431 is a competitive reversible inhibitor of DPP-IV currently undergoing clinical development. The efficacy and safety of a single dose of MK-0431 has been evaluated in a placebo-controlled, crossover study in type 2 diabetic patients who were previously treated with diet and exercise [57]. Following oral glucose administration, MK-0431 significantly reduced the glycemic excursion and increased the levels of bioactive GLP-1 by approximately 2-fold. MK-0431 treatment was also associated with reduced plasma glucagon and increased plasma insulin and C-peptide levels.

P93/01

P93/01 is another DPP-IV inhibitor that was evaluated in a preliminary single dose study to drug naive mild diabe-
tic patients and demonstrated a reduction of the prandial glucose peak as well as a reduction of glucose AUC (Area under the curve) in the group of patients who had the most elevated HbA1c levels [58].

Finally, at this stage of clinical development, the primary efficacy endpoint of candidate drugs in type 2 diabetic patients is the improvement of plasma glucose and HbA1c levels. GLP-1 analogues have provided promising results in phase III clinical studies. Long term studies are needed to complete the efficacy/safety profile of GLP-1 analogues and to test whether these compounds are able to preserve beta cell function over time as compared to available antidiabetic agents.

Conclusion

GIP and GLP-1 are both incretin hormones secreted in response to meal ingestion that potentiate the glucose-induced insulin response. In addition, GLP-1 plays an important role in inhibiting glucagon secretion. Trophic effects of GLP-1 on pancreatic beta cells were also demonstrated in animal models. Other physiological actions of GLP-1 include the inhibition of gastrointestinal secretion and gastric emptying, and the reduction of food intake. In contrast with GIP, the insulinotropic action of GLP-1 has been shown to be preserved in type 2 diabetic patients. All these findings support GLP-1 as an alternative attractive therapy to conventional antidiabetic agents.

Data from clinical trials with various DPP-IV inhibitors and GLP-1 analogues are promising. Results of phase III trials with exenatide, the most advanced GLP-1 analogue in clinical development, demonstrated a sustained effect in improving glycemic control in type 2 diabetic patients with failure of oral treatment, without inducing weight gain. Further results are expected to complete the efficacy/safety profile of these agents, and to define their role in the therapeutic strategy of type 2 diabetes.

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