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REVIEW

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Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005

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Abstract The incretin hormones are intestinal polypeptides that enhance postprandial insulin secretion. Gastric inhibitory polypeptide (GIP) was initially thought to regulate gastric acid secretion, whereas glucagon-like peptide-1 (GLP-1) was discovered as a result of a systematic search for intestinal insulinotropic products of proglucagon gene expression. The incretin effect is markedly impaired or absent in patients with type 2 diabetes because of decreased secretion of GLP-1 and a loss of the insulinotropic effects of GIP. Metabolic control can be restored or greatly improved by administration of exogenous GLP-1, but this peptide is almost immediately degraded by dipeptidyl peptidase IV (DPP-IV), and therefore has little clinical value. DPP-IV-resistant analogues (incretin mimetics) have been identified or developed, and inhibitors of DPP-IV have also proved effective in protecting endogenous GLP-1 (and GIP) from degradation. Both principles have been tested in clinical studies. The incretin mimetics, administered by sc injection, have demonstrated lasting improvement in HbA_1c in patients insufficiently treated with conventional oral therapy, and their use has been associated with steady weight loss for up to 2 years. The DPP-IV inhibitors, given once or twice daily by mouth, also appear to provide lasting improvement in HbA_1c, but are weight-neutral. The first incretin mimetic has reached the market in the US, and applications for approval of the first inhibitors are expected to be filed early in 2006.

Keywords Byetta · DPP-IV · Exendin · GIP · Glucagon-like · Incretin · Liraglutide · Proglucagon · Vildagliptin

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Abbreviations DPP-IV: dipeptidyl peptidase IV · GIP: gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide · GLP: glucagon-like peptide

Discovery of glucagon-like peptide-1

Diabetologists have been interested in two aspects of the gut for the past 30 years. The first is the incretin effect, i.e. the amplification of nutrient-induced insulin secretion by hormones from the gut [1], and the second has been the occurrence of glucagon-producing L-cells in the gut. Could the two have anything to do with each other? Glucagon from the pancreas was known to be able to stimulate insulin secretion in man [2], but the intestinal glucagon immunoreactive cells did not appear to produce real glucagon, but substances that could only be measured by certain glucagon radioimmunoassays directed against the mid region of the molecule. This was because the 'gut glucagons' contained the entire glucagon sequence [3, 4]. Indeed, as early as 1973 we found that individuals who suffered from postprandial reactive hypoglycaemia had exaggerated secretion of 'gut glucagon' [5, 6]. The predominant molecule of the 'gut glucagons' turned out to be a peptide of 69 amino acids, designated glicentin, which, as predicted [3], contained the full glucagon sequence (residues 33–61), but this molecule had no effect on insulin secretion. A truncated form, corresponding to residues 33–69 [4], today referred to as oxyntomodulin [7], was quite effective in stimulating insulin secretion [8], as would be expected of a peptide in which the full glucagon sequence occupies its N-terminus. Nevertheless, it was not as potent as glucagon. It was therefore questionable whether this molecule, which circulates in low concentrations [9], would contribute to the incretin effect.

Around 1973, the peptide gastric inhibitory polypeptide (GIP) had been shown to stimulate insulin secretion [10, 11] and was henceforth called glucose-dependent insulinotropic polypeptide, thus preserving the acronym. It was also shown to be likely to function as an important incretin hormone in mimicry experiments [12], in which

endogenous hormone concentrations are mimicked by infusion of exogenous hormone. But it was clear that there had to be another incretin hormone. Immunoneutralisation studies, carried out in vitro and in vivo in rats, demonstrated that removal of GIP did not eliminate the incretin effect [13, 14], while in patients with intestinal resections, the incretin effect correlated not with GIP secretion, but with the residual length of ileum, in which the density of L-cells is highest. Again, the L-cell came under scrutiny.

Because of the presence of the full glucagon sequence in glicentin, we reasoned at that time that this molecule might represent proglucagon, the biosynthetic precursor of glucagon, and this belief was strengthened when we found small amounts of glicentin to be present in the pancreas [15], and were able to demonstrate parallel secretion of glucagon and the N-terminal part of glicentin after glucagon had been cleaved off [16]. However, translation studies in cell-free systems indicated that proglucagon had more than 69 amino acids, and in 1982 K. Lund, working in J. Habener's laboratory, managed to deduce the sequence of proglucagon from anglerfish (chosen for the ease of isolating pancreatic endocrine tissue contained in the so-called Brockmann bodies) [17]. This molecule contained a glucagon-like peptide (GLP) in addition to anglerfish glucagon, and therefore nurtured the notion that the proglucagon gene might encode more than one bioactive peptide. Finally, in 1983, G. Bell and co-workers cloned the hamster and human proglucagon genes [18, 19] and were thereby able to deduce the human proglucagon sequence. In agreement with the prediction, its N-terminus consisted of the full sequence of glicentin, containing also the glucagon sequence. But surprisingly, the molecule contained not one, but two additional glucagon like-sequences, henceforth designated GLP-1 and GLP-2. These sequences were flanked by pairs of basic amino acids, predicted posttranslational processing sites, suggesting that the two peptides might be cleaved out of the precursor to be released to the blood stream. This turned out to be the case for proglucagon produced in the intestinal L-cells, whereas proglucagon produced in the pancreatic alpha cells was cleaved into glucagon and a large C-terminal fragment, the so-called major proglucagon fragment [20, 21].

The problem was that, as demonstrated in experiments using the isolated perfused pancreas, neither of the GLPs stimulated insulin secretion. GLP-2 has since been shown to function as an important growth factor for the gut [22], and is currently being evaluated as a therapeutic agent for intestinal insufficiency [23]. Having established radioimmunoassays for the glucagon-like peptides, we were now able to study the insulin-stimulating effect of a peptide that we isolated from gut extracts on the basis of its GLP-1 immunoreactivity. This peptide was strongly insulinotropic. When sequenced, we found that it represented a truncated form of GLP-1, corresponding to residues 7–37 [24] of the predicted molecule. Clearly, natural GLP-1 was not processed at the dibasic site in proglucagon, but at a monobasic site corresponding to residue no. 77 in proglucagon [24]. In addition, natural GLP-1 turned out to be C-terminally amidated [25], hence the designation 'GLP-1 (7–36) amide.' There was no doubt that a new potent insulinotropic molecule had been identified [26, 27]. S. Bloom and co-workers [28] quickly performed mimicry experiments in human volunteers, and showed that apparently physiological concentrations of the new peptide powerfully stimulated glucose-induced insulin secretion: the missing incretin hormone had been found.

GLP-1 and diabetes treatment

Initially, no attempt was made to use GLP-1 for diabetes treatment: the disappointing attempts to stimulate insulin secretion in type 2 diabetic subjects with GIP had not been forgotten [29]. It was, however, soon realised that GLP-1 was different, for unlike GIP, GLP-1 powerfully inhibited glucagon secretion [30]. Furthermore, GLP-1 not only stimulated glucose-induced insulin secretion, but also all steps of insulin biosynthesis and insulin gene expression [31]. GLP-1 also turned out to have powerful effects on gastrointestinal secretion and motility [32, 33], and it was shown that inhibition of gastric emptying had strong effects on postprandial glucose excursions [34] in healthy subjects and patients with type 2 diabetes [35]. In addition, GLP-1 was shown to inhibit appetite and food intake, both in healthy individuals [36], and in patients with type 2 diabetes [37]. These gastrointestinal 'ileal brake' effects of GLP-1 may in fact be the most important actions of the hormone under physiological conditions [38]. It was eventually demonstrated that, unlike GIP, intravenous infusion of GLP-1 had dramatic effects on insulin secretion and blood glucose in patients with type 2 diabetes and was capable of completely normalising fasting blood glucose levels, even in patients with long-standing type 2 diabetes and HbA_{1c} levels of 11% [39–42].

From this point on, laboratories in academia and industry strove to turn this molecule into a suitable pharmaceutical agent. It soon emerged that simple subcutaneous injections were ineffective. There was an effect on insulin and blood glucose, but this was both transient and weak [43, 44]. The explanation for this was that the molecule is broken down extremely rapidly after both subcutaneous and intravenous administration [45–47]. This mechanism involved the ubiquitous enzyme, dipeptidyl peptidase IV (DPP-IV) [45], as predicted by R. Mentlein in Kiel [48], who went on to show that GLP-1 is a substrate for this enzyme. The degradation is truly extensive, which means that the peptide has a plasma half-life of 1 to 2 min and a clearance of 5 to 10 l/min, two to three times cardiac output [49]. For practical diabetes treatment, there were now three possibilities: (1) to provide GLP-1 continuously; (2) to develop stable analogues of GLP-1 or agonists of the GLP-1 receptors; and (3) to try to inhibit the enzyme, DPP-IV.

The effect of continuously administered GLP-1

In early, rather heroic studies, GLP-1 was given as continuous intravenous infusion to a relatively large number of

people with type 2 diabetes [50, 51]. Administration was at four different infusion rates: 4, 8, 16 and 24 ng kg^{-1} min^{-1} (approximately: 1.2, 2.4, 4.8 and 9.6 pmol kg^{-1} min^{-1}). Infusion rates of 4.8 pmol kg^{-1} min^{-1} and above caused nausea and vomiting, and were therefore abandoned. The two lower infusion rates were practically free from side effects and effective in reducing diurnal blood glucose levels, with similar efficacy on the 1st and the 7th day. Termination of the infusion resulted in an immediate return of blood glucose concentrations to pre-infusion levels. Another study showed that overnight intravenous infusion of GLP-1 not only returned fasting glucose values towards normal, but had the same effect upon postprandial plasma glucose concentrations when the infusion was continued [52].

Intravenous infusions are clearly not of any clinical utility, and M. Zander in our laboratory [53] therefore carried out a clinical study, in which a group of patients with type 2 diabetes received GLP-1 or saline as a continuous subcutaneous infusion (using insulin pumps) for 6 weeks. These patients were assessed before, after 1 week and after 6 weeks of treatment. No changes were observed in the saline-treated control group, whereas fasting and average plasma glucose concentrations were lowered by approximately 5 mmol/l in the GLP-1 group. In this group HbA_1c fell by 1.2%, free fatty acids were significantly lowered, and the patients lost 2 kg in weight. Furthermore, insulin sensitivity, as determined by a hyperinsulinaemic–euglycaemic clamp, almost doubled, insulin secretion capacity (measured using a 30 mmol/l glucose clamp + arginine) greatly improved, and a first-phase response was restored. 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. The treatment was free from side effects, which did not differ between saline and GLP-1 treated patients. Despite the marked metabolic improvement, plasma glucose levels were not completely normalised, but the dose given (4.8 pmol kg^{-1} min^{-1}) may not have been optimal. A further study showed that higher infusion rates were even more efficacious and side effects were not prohibitive [54]. This work, confirmed by others [55], provided 'proof-of-concept' for the principle of GLP-1-based therapy of type 2 diabetes mellitus. However, as with continuous subcutaneous infusion of insulin, this therapeutic approach was limited in its application, and alternative approaches were therefore explored.

Stable analogues and GLP-1 receptor activators

Initial studies showed that GLP-1 could be protected from degradation by DPP-IV, without loss of biological activity, simply by substituting amino acid residue no. 2 (Ala) with other amino acids with short side chains, e.g. glycine, serine, threonine or alpha-amino-isobutyric acid [56]. As predicted [57], however, this only extended the half life of the molecule by a few minutes, too short for single subcutaneous injections. The explanation for this is the dramatic renal clearance of GLP-1, with extraction ratios up to 70%.

Meanwhile a molecule had been discovered, which is a full agonist for the GLP-1 receptor, is resistant to DPP-IV, and is apparently cleared in the kidneys only by glomerular filtration [58]. Its name: exendin-4. In the 1970s many biologists were searching for new biologically active peptides, inspired by the success of the Italian pharmacologists, Erspamer and Melchiorri, who found numerous new active peptides in the skin of amphibia [59], many of which had mammalian counterparts. A particularly successful approach was adopted by K. Tatemoto and V. Mutt who, noting that many biologically active peptides carry a C-terminal amidation, developed an assay for C-terminally amidated peptides, and identified several new important peptides, including vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY) [60]. Using a similar approach, J. Raufman and J. Eng noted the importance of the N-terminal histidine in peptides of the secretin–glucagon family, and developed an assay for peptides with this N-terminus, which they applied to the venom of the Heloderma lizards, *Heloderma suspectum* (the Gila monster; Fig. 1) and *Heloderma horridum*, which had already been shown to contain the biologically active peptides helospectin and helodermin. In *H. horridum*, they identified a new peptide, which they named exendin-3, in order to identify it as the third peptide with endocrine activity (on pancreatic acinar tissue) to be found in an exocrine secretion of Heloderma lizards [61]. In venom from *H. suspectum*, a similar peptide, differing from exendin-3 by only two amino acids near the N-terminus, was identified and named exendin-4 [62]. This peptide, although also capable of activating adenylate cyclase activity in pancreatic acini, clearly differed from exendin-3 in its actions. In a search for mammalian counterparts of exendin-4, it was noted that GLP-1 had similar activities and appears to compete with exendin-4 for binding to the acini [63]. In a subsequent collaboration with R. Goke et al. from Marburg,

Fig. 1 The Gila monster (*Heloderma suspectum*), a poisonous lizard from the deserts of Arizona. In 1992, J. Raufman and coworkers isolated exendin-4 from an exocrine secretion (the saliva) of this creature. Exendin-4 is the 4th peptide with endocrine actions (on the pancreas), and is now registered as an antidiabetic agent under the name of Byetta

Germany, it was unequivocally established that exendin-4 acts as a high potency agonist at the GLP-1 receptor of insulin-secreting beta cells [64]. It was also established that a fragment of the exendins, exendin 9–39, identified during a systematic analysis of the activities of truncated forms of exendin-3 [65], was a high potency antagonist [64], a finding that proved most valuable in later studies of the physiological role of GLP-1.

Subsequent research has established that exendin-4 is not the GLP-1 of the Gila Monster [66] (it has its own GLP-1, which is much closer to mammalian GLP-1), and that a mammalian counterpart does not seem to exist. A single subcutaneous injection of 10 μg, the recommended dose, has biological effects for some 5 to 7 h in humans [67]. Synthetic exendin-4, now known as exenatide, is therefore given twice daily. This apart, exenatide seems to share all of the effects of native GLP-1 [58]. The compound has been tested in several clinical trials, most recently in three controlled pivotal phase III studies involving 1,494 patients, in whom exenatide was given for 30 weeks as an add-on therapy to type 2 diabetic patients inadequately treated with sulfonylureas [68], metformin [69] or a combination of metformin and sulfonylureas [70]. After 30 weeks of treatment, fasting blood glucose concentrations fell, HbA_1c levels were reduced by approximately 0.8% overall and to or below 7% in 41, 46 and 34% of the patients in the three groups. Adverse effects were mild and generally gastrointestinal. Mild hypoglycaemia was noted in 28 to 36% of patients also receiving sulfonylurea. An important result was a significant, dose-dependent and progressive weight loss of 1.6 kg (patients treated with sulfonylurea and sulfonylurea + metformin) and 2.8 kg (metformin treatment) from baseline. In open-label extensions of these studies, exenatide was given for a total of 82 weeks with continued effects on HbA_1c and body weight (details: http://www.amylin.com). However, some patients (about 38% of patients after 30 weeks) appear to develop low-titre antibodies against exenatide, and 6% developed antibodies with higher titres. In about half of these, the glucose-lowering effect of exenatide appeared attenuated. The three studies provided the basis for an application for approval of exenatide as a new drug for the treatment of diabetes, and this was approved by the FDA in April 2005. Information about the new drug, named Byetta, is available from the web site of the company (http://www.BYETTA.com). Exenatide thus represents an efficacious supplement to failing conventional oral antihyperglycaemic agents, and the sustained effect observed in the extension studies and its continued weight-lowering effects must be considered very promising.

Other analogues currently in clinical development include slightly modified versions of the GLP-1 molecule that attach to albumin, thereby acquiring the pharmacokinetic profile of albumin. One such analogue is liraglutide, which consists of a slightly modified GLP-1 sequence with a palmitoyl chain attached. This confers affinity for and binding to albumin and, as a result, protects the molecule both from DPP-IV and renal elimination. The plasma half life of this compound is 12 h, and it therefore provides exposure for more than 24 h after a single injection [71]. The compound seems to possess all of the activities of native GLP-1 [72]. A recent report describes administration of increasing doses of liraglutide to patients with type 2 diabetes for 3 months [73]. Liraglutide lowered fasting blood glucose and HbA_1c dose-dependently (by up to 0.75% points from a base line level of 7.6%), and also significantly lowered body weight in some doses. There were very few side effects, and no antibody formation. The strength of this compound seems to be its attractive pharmacokinetic profile, providing a rather stable plateau of active compound in plasma upon single daily injections. In this way, side effects (nausea, vomiting) associated with large excursions in the plasma concentration of more rapidly metabolised compounds after subcutaneous injection may be avoided. In a recent study [74], liraglutide was given in doses up to 2 mg once daily in a 5-week period with weekly up-titrations to patients with high HbA_1c levels (8–10%). Particularly when given in addition to metformin, liraglutide powerfully reduced fasting glucose levels (from 13 to 9 mmol/l) and resulted in weight loss of 2.4%. Gastrointestinal side effects were transient and led to withdrawal in only 4% of the patients. A number of additional GLP-1 analogues are in clinical development, but little information is currently available for these.

Inhibitors of DPP-IV

The therapeutic use of inhibitors of DPP-IV, the enzyme responsible for inactivation of GLP-1, as an antihyperglycaemic agent was first proposed in 1995 [46], based on the finding that GLP-1 seems uniquely sensitive to cleavage by DPP-IV. Compounds of this class have now reached phase III clinical trials. A DPP-IV inhibitor can completely prevent the N-terminal degradation of GLP-1 that occurs in vivo, resulting in significant enhancement of its insulinotropic activity [75]. Studies in Vancouver diabetic fatty rats have shown that chronic oral administration of the DPP-IV inhibitor, isoleucine thiazolidide (P32/98), for 12 weeks improves glucose tolerance, insulin sensitivity and beta cell responsiveness [76]. The longer-acting inhibitor, FE 999-011 continuously inhibited plasma DPP-IV activity and not only normalised glucose excursions after oral glucose administration in insulin-resistant Zucker obese rats, but also delayed the onset of hyperglycaemia in Zucker diabetic fatty rats [77]. These effects were, at least in part, attributed to increased levels of intact GLP-1. Increased intact GLP-1 concentrations were further implicated in the improved islet function seen after chronic treatment of high-fat-fed (glucose-intolerant and insulin-resistant) mice with valine-pyrrolidide [78]. Additional support for the involvement of DPP-IV inhibition in mediating glucose tolerance comes from studies in Fischer rats, which have a catalytically inactive DPP-IV molecule, and CD26 knockout mice with a targeted disruption of the gene encoding DPP-IV. Such animals have improved glucose tolerance compared to their wild-type counterparts [79–81]. In DPP-IV-negative Fischer rats and DPP-IV inhibitor-treated control animals,

the impaired glucose tolerance that normally develops with ageing is prevented [81, 82], while the lack of DPP-IV protects both Fischer rats and CD26 knockout mice from diet (high fat)-induced insulin resistance and glucose intolerance [82–84]. Once again, these effects are believed to involve preservation of endogenous GLP-1, because intact GLP-1 concentrations are elevated.

After these promising preclinical studies, the first clinical proof-of-concept was obtained using the short-acting inhibitor, NVP-DPP728 [85]. When given twice or three times daily for 4 weeks in patients with relatively mild type 2 diabetes (mean HbA_1c 7.4%), both fasting and prandial glucose levels were lowered significantly, resulting in a 0.5% reduction in HbA_1c; despite the fall in glycaemia, fasting and post-prandial insulin levels were sustained. NVP-DPP728 appeared to be well tolerated, with only minor adverse events. Some of these symptoms (pruritis and nasopharyngitis) did, however, seem to be drug- rather than class-specific, because they were not reported for another inhibitor, LAF237, subsequently developed by the manufacturer of NVP-DPP728. NVP-DPP728 has now been dropped in favour of LAF237, which is longer-acting and suitable for once-daily administration. A recent clinical study showed LAF237 to have a pharmacodynamic profile similar to that of its predecessor [86]. The mechanism of action was suggested to be incretin-mediated, because LAF237 treatment increased baseline and prandial active GLP-1 levels. As with NVP-DPP728, insulin levels were not actually increased, but interestingly, glucagon levels were significantly suppressed. Most recently, clinical data have emerged from a 52-week study in patients already on metformin treatment [87]. LAF 237 significantly lowered HbA_1c levels from 7.7% to approximately 7% after 3 months of treatment, and this level was maintained for the remaining period, whereas a significant increase was noted in the control group, resulting in a difference between placebo- and LAF-237-treated patients of 1.1%. In addition, meal-induced insulin secretion was impaired in the placebo group and remained unaltered in the treatment group, in spite of significantly lower glucose levels. Side-effects were inconspicuous.

In contrast to the results obtained with the GLP-1 analogues, no change in body weight was seen with DPP-IV inhibition. The binding kinetics, type of inhibition and selectivity with respect to other peptidases for the inhibitor (now called vildagliptin) have been reported [88]. The inhibitor significantly increased insulin secretion rate (so-called insulin secretory tone) at 7 mmol/l glucose, and inhibited glucagon secretion, while increasing levels of active GLP-1 and GIP [89]. According to the makers' website (http://www.novartis.com), phase III clinical trials are in progress, and filing for FDA approval is expected in 2006. An inhibitor from another company, MK-0431 (sitagliptin), is also in phase III trials (details: http://www.Merck.com), but so far, little is known about this compound [90]. According to their respective websites, three other companies are now developing DPP-IV inhibitors (see: http://www.GSK.com [phase I]; http://www.BMS.com [saxagliptin; phase III]; and http://www.Prosidion.com [PSN9301; phase II]), with several other companies reportedly having a DPP-IV inhibitor programme.

Protective effects of GLP-1

Thus, both GLP-1 analogues, receptor activators and DPP-IV inhibitors have shown promising potential as antihyperglycaemic agents. The most important question, whether or not this incretin-based approach to treating type 2 diabetes will be able to slow or prevent the apparently inevitable progression of the disease, remains to be answered. But in this respect, the GLP-1-based therapies possess a unique potential: GLP-1 has trophic effects on beta cells [91]. Not only does it stimulate beta cell proliferation [92, 93], it also enhances the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium [94] and, perhaps most importantly, GLP-1 is capable of inhibiting apoptosis of beta cells including human beta cells [95]. Since the normal number of beta cells is maintained in a balance between apoptosis and proliferation, this observation is of considerable interest, and raises the possibility that GLP-1 could be useful in conditions in which beta cell apoptosis is increased. The complicated mechanisms whereby GLP-1 may exert these effects on beta cells were reviewed recently [96].

For obvious reasons, it is difficult to estimate the protective effects of GLP-1 on beta cells in humans, and it might be argued that this is irrelevant if the effect is not translated into improved glycaemic control. So is there any clinical evidence that a GLP-1-based therapy really does have protective effects on beta cells? One problem is that the rate at which beta cell proliferation occurs in humans is not known. Or said in another way: how long should one wait for such effects to unfold? Nevertheless, there are some data that may be of use. In the study where LAF 237 was administered for 52 weeks to patients inadequately treated with metformin, the LAF group showed a sustained improvement in HbA_1c levels throughout the 52-week period, whereas an increase was observed in the control group [87]. Similarly, over 82 weeks of treatment with exenatide, HbA_1c levels remained constant at approximately 7%, although—according to the UKPDS—an increase would have been expected over this time span. These sustained effects could be the first indications that GLP-1 has beta-cell-protective effects that persist after the plateau reached 3 to 4 months after initiation of therapy. The reason for this remains unclear, and it may be that continued exposure to GLP-1 (which cannot be provided with exenatide given twice daily) or higher concentrations of active GLP-1 than those achievable by DPP-IV inhibition are required for further improvements in metabolic control to occur. At any rate, these observations tell us that a GLP-1-based therapy should be started as early in the clinical course as possible, before beta cell function has deteriorated to unacceptable levels.

Conclusion

Two therapeutic principles of great promise have emerged from the finding that intestinal extracts contain an incretin hormone with insulinotropic action in type 2 diabetes. One, the DPP-IV inhibitors, involves administration of a single tablet once daily, which, so far, possesses no class-related side effects. Although apparently effective as antihyperglycaemic agents, the DPP-IV inhibitors may be of particular value for the prevention or delay of overt diabetes, and might therefore be given to individuals at risk of developing type 2 diabetes. With the other therapeutic principle, the injectables, higher levels of active substance are reached compared to the DPP-IV inhibitors, and, in addition, they promote weight loss. They might, therefore, be particularly useful for the treatment of already established disease. In any case, GLP-1-based therapies have added new colours to the palette of drugs at the diabetologist's disposal.

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