Incretins are hormones from the gut that augment the postprandial nutrient-induced insulin secretion. The incretin effect is normally quantified by comparing the insulin responses to oral and intravenous glucose administration, where the infusion is adjusted so that the plasma glucose concentrations are similar to those observed after the oral administration. The insulin response to oral glucose is normally much larger than that observed after intravenous (IV) glucose, and in healthy subjects as much as 70% of the insulin response may be attributable to the action of the incretin hormones. An illustration of the power of the incretin effect was provided by Nauck et al., who studied glucose excursions and insulin responses after increasing doses of oral glucose. It turned out that the glucose excursions were identical regardless of the amount of glucose ingested, the explanation being that incretin-induced insulin secretion was augmented progressively, thereby effectively preventing post-challenge hyperglycaemia.

The two most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP, formerly also called gastric inhibitory polypeptide) and glucagon-like peptide-1. Their insulinotropic effects are additive, and together the two hormones can fully explain the incretin effects. The secretion of the incretin hormones is also proportional to the size of the ingested nutrient load. In patients with type 2 diabetes, however, the incretin effects are severely reduced or absent and there is little doubt that the lacking incretin effect contributes significantly to the inadequate insulin secretion observed in these patients. It is therefore relevant to ask why the incretin effect is lost in type 2 diabetes.

It is clear that differences in the metabolism of the GIP and GLP-1 cannot explain the deficiency. Detailed studies of meal-induced secretion of GLP-1 and GIP in the patients revealed that GIP secretion may be slightly decreased compared to healthy controls whereas GLP-1 secretion may be reduced by as much as 50% (calculated as incremental AUCs), and the lower GLP-1 secretion is likely to contribute to the incretin deficiency. However, the most important finding is that the actions of both incretin hormones are severely compromised in type 2 diabetes. Thus, the insulinotropic effects of GIP as studied in hyperglycaemic clamp experiments are nearly completely lost, regardless of GIP dose. In contrast, GLP-1 is still capable of enhancing glucose-induced insulin secretion to completely normal levels, but the amount of GLP-1 required to normalise insulin secretion is about five times higher than that required in healthy controls. Thus, while the diabetic beta cells are almost completely unresponsive to GIP, GLP-1 is capable of completely restoring the beta cell responsiveness to glucose, but the potency of the hormones in this respect is markedly reduced.

This raises the possibility of restoring beta cell function in patients with type 2 diabetes with supraphysiological amounts of GLP-1. GIP is unlikely to be of therapeutic value, at least acutely, although GIP analogues have shown some efficacy in animal models of diabetes.

It is not known why the effect of GIP is lost in the patients, except that it seems clear that the loss is secondary to the occurrence of diabetes. Therefore, it cannot be excluded that the effect of GIP can be restored with time as metabolic control is improved by other treatment. Thus, it has recently been shown that the potency of GLP-1 with respect to enhancing beta cell responsiveness to glucose can be improved by strict glycaemic control. At any rate, GLP-1 infusions have been demonstrated to completely normalise fasting glucose concentrations in patients with severe long-standing diabetes mellitus and haemoglobin A1c levels around 11% and to virtually normalise both fasting and postprandial glucose levels in patients with moderate disease. GLP-1 is therefore of interest as a treatment for diabetes.

However, GLP-1 has many more actions than merely enhancing glucose-induced insulin secretion. It also increases the biosynthesis of new insulin molecules and upregulates all the entire machinery required for insulin synthesis in the beta cells. Furthermore, it has been demonstrated to exert tropic actions on the beta cells in rodents. Thus, GLP-1 causes proliferation of already existing beta cells and also promotes differentiation of new beta cells from progenitor cells.
in the ducts leading to the formation of small new islets. Finally and probably most important for humans, it strongly inhibits cytokine, lipid and glucose-induced apoptosis of beta cells including human beta cell. Although no data regarding this are available in humans in vivo, this trophic potential nevertheless holds great promise, since GLP-1 may be able to exert beta cell protective effects in our patients and possibly prevent progression of the disease.

In addition, GLP-1 inhibits glucagon secretion, and thereby reduces hepatic glucose production, an effect that is likely to contribute importantly to its glucose lowering effects in diabetic patients. Thus, in patients with type 1 diabetes and no residual beta cell secretory capacity, GLP-1 lowers glucagon secretion and also lowers blood glucose. Furthermore, GLP-1 inhibits gastric motility and emptying, and thereby strongly reduces postprandial glucose excursions. It also significantly inhibits appetite and food intake, and probably acts as one of the endocrine signals from the gut that terminates meal ingestion and signals interdigestive satiation. Most recently GLP-1 has also been suggested to exert protective effects on the heart and the blood vessels. All of these actions render GLP-1 of unusual interest in the context of diabetes treatment.

However, single subcutaneous injections of GLP-1 have little effect on blood glucose. The explanation is that the peptide is broken down extremely rapidly in the body. The culprit is the ubiquitous enzyme, dipeptidylpeptidase IV, which cleaves of the two N-terminal amino acids and renders the metabolite inactive. This process is so rapid and extensive that just a few per cent of what is injected subcutaneously survives in the intact, active form, and leaves the peptide with a half-life in the circulation of 1–2 min and a plasma clearance of two to three times the cardiac output. Clinically relevant agents GLP-1 analogues must therefore be resistant against DPP-IV and also exhibit less renal clearance which is the second mechanism whereby GLP-1 is eliminated.

Proof of concept for the efficacy of GLP-1 treatment was provided by Zander et al. who administered GLP-1 by continuous subcutaneous infusion for six weeks to subjects with severe long-standing diabetes. The treatment resulted in a lowering of fasting and average plasma glucose levels by 4–6 mmol/l, reduction of hemoglobin A1c by 1.3%, a weight loss of 2 kg, a reduction of free fatty acid levels, almost a doubling of insulin sensitivity and a dramatic restoration of beta cell function.

A mere substitution of amino acid no. 2 (Ala) in the GLP-1 sequence provides resistance towards DPP-IV, but such analogues are still eliminated extremely rapidly by the kidneys with half lives of 3–4 min. Substances with less renal clearance are therefore required.

One such substance is exendin-4, a 39 amino acid peptide with 53% sequence homology to GLP-1, isolated from the saliva of the lizard, Heloderma suspectum (the Gila monster). Exendin 4 is resistant towards DPP-IV and is cleared in the kidneys exclusively by glomerular filtration, as opposed to GLP-1 who also is extracted by peritubular uptake mechanisms. Thereby, exendin acquires an IV plasma half-life of 30 minutes, but otherwise seems to share all the actions of GLP-1.

There is apparently no mammalian counterpart of exendin-4, which is not the GLP-1 of the Gila Monster. A subcutaneous injection of the maximally tolerated dose of exendin-4 provides an exposure in the circulation for about five hours, and this has turned out to be sufficient for effective diabetes therapy in a twice-daily administration regimen. Exendin-4 has been developed for clinical use by the Amylin Corporation (www.Amylin.com) and is designated exenatide in its synthetic form.

The compound has been tested in several clinical trials, most recently in three controlled pivotal phase 3 studies comprising 1,494 patients. Exenatide was given for 30 weeks as an add-on therapy to type 2 diabetic patients inadequately treated with sulfonylureas, metformin or a combination of metformin and sulfonylureas. After 30 weeks treatment, fasting blood glucose concentrations were significantly reduced, HbA1c levels were reduced by approximately 0.8% in all groups and to or below 7% (a recommended value) in 41%, 46% and 34% of the patients in the three groups. Adverse effects were mild and generally gastrointestinal. Mild hypoglycaemia was noted in 28–36% of patients also receiving sulfonylurea. An important result was a significant, dose-dependent and progressive weight loss of 1.6 kg (SU and SU + metformin) and 2.8 kg (metformin) from baseline. In open-label extensions of these studies, exenatide has been given for a total of two years with continued effects on HbA1c and body weight. However, some patients (about 38% of patients after 30 weeks) appear to develop low titre antibodies against exenatide, and 6% developed antibodies with higher titre. In about half of these, the glucose lowering effect of exenatide appeared attenuated. Exenatide was approved by the FDA in April 2005. Information about the new drug, which is named Byetta, is available on the website of the company (www.BYETTA.com).