Beta-cell Defects in Type 2 Diabetes and the Possibility of Treatment Options with GLP-1-based Therapies

a report by
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Type 2 Diabetes as a Progressive Disease

In type 2 diabetes, beta-cell dysfunction plays a major part not only in the pathogenesis of the disease, but also in disease progression over time. Under normal conditions, blood glucose concentrations are regulated within a very tight range. After a meal, insulin secretion from the beta cell is stimulated, whereas glucagon secretion from the alpha cells is suppressed. Insulin facilitates glucose uptake into the cells, whereas glucagon stimulates glucose production in the liver.

In the development of type 2 diabetes, environmental influences (most importantly diet and sedentary lifestyle) and genetic factors lead to the development of insulin resistance (i.e. reduced insulin sensitivity of the peripheral tissues, mainly the muscles, liver and adipose tissue) that only in the early stages can be compensated by hypersecretion of insulin from the beta cells. Already in pre-diabetes (impaired glucose tolerance (IGT)), the pattern of insulin secretion is disturbed and the rapid and accentuated first phase of insulin secretion observed in non-diabetic subjects after a sudden rise in plasma glucose is lost. This results in elevated blood glucose concentrations after a meal. With the further deterioration of insulin sensitivity, beta-cell function further worsens, leading to fasting hyperglycaemia. Under chronic hyperglycaemic conditions and persisting insulin resistance, insulin secretion further deteriorates. The concomitant lack of suppression of glucagon secretion from the alpha cells additionally contributes to high blood glucose concentrations due to increased glucose output from the liver. Finally, morphologically, a decrease in beta-cell mass due to increased cell death of beta cells and deposition of amyloid in the remaining beta cells can be found.[1]

Classical Treatment Options Do Not Influence the Natural Course of Type 2 Diabetes

With the classical treatment options of type 2 diabetes, a steady decline of beta-cell function is observed, since none of the current treatments is aimed at the amelioration of beta-cell deterioration. Therefore, none of these therapeutic options for type 2 diabetes is able to influence the natural course of the disease.

Sulphonylureas, which have been in use for half a century now, and chemically related metiglinides stimulate insulin release from remaining functional beta cells due to interference with the adenosine triphosphate (ATP)-dependent potassium channel on the cell membrane. Metformin and thiazolidinediones (TZDs) predominantly act on the peripheral tissues as 'insulin sensitisers'. Alpha glucosidase inhibitors slow the resorption of monosaccharides from the intestinal tract. Exogenous insulin as well has no direct effect on beta-cell function and beta-cell mass.[2]

Gastrointestinal Hormones and Anti-diabetic Effects

Gastrointestinal hormones from the gut stimulate insulin secretion after a meal. They are responsible for orally administered glucose evoking a greater insulin response than an intravenously administered glucose dose calculated to lead to identical serum glucose excursions. The difference in the insulin response was labelled the 'incretin effect' and the gastrointestinal hormones stimulating insulin secretion after oral glucose ingestion were called 'incretins'. The term 'entero–insular axis' was coined for the sum of the metabolic, neural and hormonal effects of the small intestine on the endocrine pancreas. The incretin effect is reduced or even absent in patients with type 2 diabetes. The two hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), are the most important incretin hormones in humans. Whereas GIP does not stimulate insulin secretion in patients with type 2 diabetes, GLP-1 still does so (see *Figure 1*).

The reason for these diverging properties of GIP

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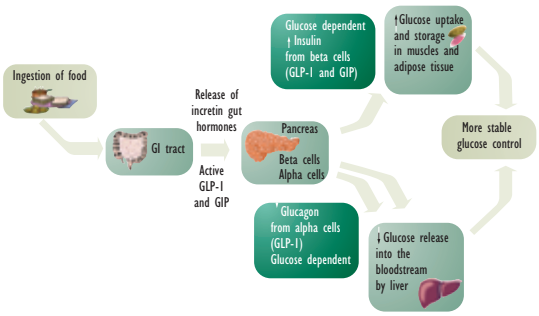
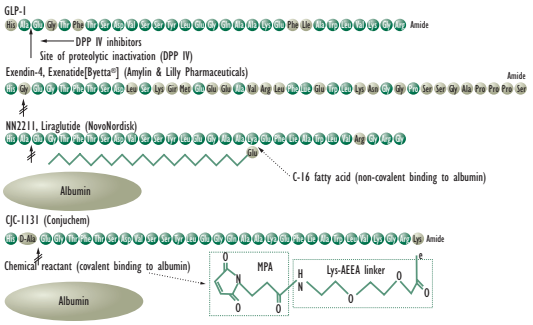
Figure 1: Incretins (GLP-1 and GIP) Regulate Glucose Homeostasis Through Effects on Islet-cell Function



The presence of nutrients in the gastrointestinal tract rapidly stimulates the release of incretins: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Collectively, GLP-1 and GIP exert several beneficial actions, including stimulating the insulin response in pancreatic beta cells (GLP-1 and GIP) and inhibiting glucagon secretion from pancreatic alpha cells when glucose levels are elevated. Increased insulin levels improve glucose uptake by peripheral tissues, while the combination of increased insulin and decreased glucagon reduces hepatic glucose output.

Figure 2: Native GLP-1 and Possible Molecular Changes to Create Long-acting Incretin Mimetics



The amino acid sequences of native glucagon-like peptide-1 (GLP-1) and the incretin mimetics exenatide, liraglutide and CJC-1131 are shown. In the GLP-1 molecule, amino acids in a position that is essential for receptor binding and biological activity are shown in pink and amino acids that can be modified within the molecule without drastic loss in biological activity are shown in green. In the incretin mimetics, amino acids that are different from the native GLP-1 sequence are depicted in blue. Also, the N-terminal cleavage site of dipeptidyl peptidase-4 (DPP-4) is depicted by a red arrow. The schematic molecular changes of the currently available incretin mimetics and possible albumin binding are shown.

and GLP-1 regarding the incretin effect in type 2 diabetes are not yet completely elucidated. The promising therapeutic potential of GLP-1 as a pharmacological tool for treating type 2 diabetes was proposed, along with the further characterisation of the incretin effect, in the 1990s. In contrast to other insulinotropic agents, such as the sulphonylureas, the insulinotropic effect of GLP-1 depends even more closely on the actual glucose concentration, providing the possibility of glucose normalisation without the risk of hypoglycaemia. In patients with type 2 diabetes, exogenous GLP-1 given intravenously as a continuous infusion increases insulin secretion and normalises both fasting and postprandial blood glucose, even in subjects with long-standing type 2 diabetes with secondary failure to oral anti-diabetic drugs, especially sulphonylureas. It further has the ability to restore the blunted first phase of insulin secretion in type 2 diabetes.

Besides the glucose-lowering effects, GLP-1 has a variety of additional 'non-insulinotropic' physiological actions that may be advantageous in type 2 diabetes therapy (see *Table 1*) – it suppresses glucagon secretion from the alpha cells and slows gastric emptying. It therefore contributes to satiety and to a slower passage and resorption of carbohydrates. Additionally, GLP-1 acts as a mediator of satiety in the hypothalamus, where it is also found as a neurotransmitter. Patients with type 2 diabetes having received GLP-1 as a continuous infusion have lost body weight due to these GLP-1 actions. A very important further effect of GLP-1 is its effect on beta-cell mass. GLP-1 stimulates beta-cell formation from precursor cells and also inhibits their apoptosis. Additional effects of GLP-1 include cardioprotection, neuroprotection and endothelial function, which seem to be the most relevant for diabetes therapy with this peptide.[3]

Using the Therapeutic Potential of GLP-1

GLP-1 is metabolised by the enzyme dipeptidyl peptidase-4 (DPP-4) within a few minutes; therefore, GLP-1 itself is not very practical for type 2 diabetes therapy. Generally, either DPP-4-resistant peptides that bind to the GLP-1 receptor and show GLP-1-like biological effects, or substances inhibiting DPP-4, could be applied to utilise the therapeutic potential of GLP-1. For this reason, GLP-1 receptor agonists (DPP-4-resistant peptides with a high sequence similarity to GLP-1 and GLP-1-like biological effects) are currently under evaluation for clinical use. These GLP-1 receptor agonists are often referred to as 'incretin mimetics'. On the other hand, various DPP-4 inhibitors are also being developed and are already in phase III clinical trials.[4-6]

Incretin Mimetics

A selection of incretin mimetics is shown in *Figure 2*. The first incretin mimetic available in the US for the therapy of type 2 diabetic patients not optimally controlled with oral agents is exenatide (Byetta®, Eli Lilly & Amylin Pharamaceuticals). Exenatide is the synthetic form of the naturally occurring peptide exendin-4, which was discovered in the salivary gland of the Gila monster (*Heloderma suspectum*). This peptide has a high amino acid sequence similarity to GLP-1 and is not degraded by DPP-4. A twice-daily subcutaneous

administration of exenatide in clinical studies resulted in a significant improvement of glycaemic control without weight gain and an improvement in beta-cell function without causing hypoglycaemia in monotherapy. Hypoglycaemia occurred only in patients receiving exenatide and unadjusted doses of sulphonlylureas. Patients in an open extension of the studies comparing the efficacy and safety of exenatide with placebo had a sustained reduction in their glycosylated haemoglobin (HbA1c) concentrations over a period of two years and also a reduction in their fasting glucose concentrations.

A synthetic GLP-1 analogue, liraglutide (NN2211) (Novo Nordisk Pharmaceuticals), is DPP-4 resistant and possesses a biologically longer half-life than native GLP-1 due to the addition of a fatty acid side chain to the peptide molecule. Liraglutide is in phase II studies and other incretin mimetics are under development. Since incretin mimetics have a peptide structure, they have to be administered subcutaneously.

Unlike insulin treatment, which requires substantial dose adjustment, there will be a standard therapeutic GLP-1 receptor agonist dose for most patients. Dosing of the incretin mimetics will probably be uncomplicated because the probability of hypoglycaemia is low. Nausea (not more than experienced with metformin therapy) may be observed during the beginning of treatment, but can be controlled with mild antiemetic drugs and usually ceases within a few days. Long-acting formulations that have to be injected less than once daily are being developed and in clinical studies.[3-6]

Table 1: Favourable Effects of GLP-1-based Therapies in Type 2 Diabetes

Potential for normalising glucose/glycosylated haemoglobin
Glucose-dependent effect, fewer hypoglycaemias
Various principles of action (e.g. glucagonostatic effect)
No dose titration – 'one size fits all'
Moderate weight loss possible or weight neutral
No severe side effects/broad therapeutic range
Positive effect on Islet-cell regeneration/neogenesis: retards the progression of type 2 diabetes

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DPP-4 Inhibitors

The therapeutic principle of GLP-1 can also be implemented by inhibiting GLP-1 degradation. Support for this approach to therapy also comes from the observations that glucose tolerance is improved in animals in which the enzyme has been genetically deleted and in animals treated with DPP-4 inhibitors. Various substances with DPP-4 inhibition properties are currently being tested in pre-clinical and clinical trials. Two compounds already advanced in phase III clinical trials are vildagliptin (LAF 237, Galvus®, Novartis Pharma) and sitagliptin (MK0431, Januvia®, Merck Pharmaceuticals). Saxagliptin (Brystol-MyersSquibb Pharmaceuticals) and further substances are also in clinical studies. In clinical studies, vildagliptin lowered HbA1c in type 2 diabetic patients not sufficiently treated with metformin. Sitagliptin® also effectively lowers HbA1c and reduces diurnal fluctuations in glucose concentration. So far, DPP-4 inhibitors (or 'incretin enhancers') also seem to be effective in improving glycaemic control in type 2 diabetic patients. DPP-4 inhibitors are orally active substances and do not have to be injected like the incretin mimetics. On the other hand, the observed weight loss seen in patients with type 2 diabetes treated with incretin mimetics is so far not observed in patients on DPP-4-inhibitor therapy. The DPP-4 inhibitors are weight neutral in clinical studies so far (see *Table 2*).

The application of DPP-4 inhibitors retards endogenous GLP-1 degradation, but there is still some uncertainty as to whether all effects of DPP-4 inhibitors are mediated by the prolongation of the biological half-life of the peptide. One puzzling finding might support this: in patients with type 2 diabetes, concentrations of active GLP-1 after meal ingestion are doubled

Table 2: Major Differences Between GLP-1 Receptor Agonists and DPP-4 Inhibitors

Important pharmacological action of drug class	GLP-1 receptor agonists	DPP-4 inhibitors
Mechanism of stimulation of insulin secretion exclusively by GLP-1	Yes	Probably not only GLP-1 (other peptides also?)
Restoration of lack of biphasic insulin secretion	Yes (Exanatide)	Not tested
Counter-regulation by glucagon preserved in hypoglycaemia	Yes	Not tested
Inhibition of gastric emptying	Yes	Marginal
Effect on body weight	Weight loss	Weight neutral
Predominant adverse effects	Nausea	None
Mode of administration	Subcutaneous	Oral

by DPP-4 inhibition (compared with placebo), and glucose control improves. In contrast, when similar increases in GLP-1 levels are produced by exogenous infusion, these have little or no effect on insulin secretion or glucose levels. This suggests that mediators other than GLP-1 may contribute to the therapeutic effect of DPP-4 inhibition. Because DPP-4 is involved in the degradation of many peptide hormones, the action of DPP-4 is less specific than GLP-1 receptor agonists.[4,5]

Outlook and Perspectives

The therapeutic principle of GLP-1 with the multiple mode of action besides its glucose-normalising effect adds a new and attractive perspective to diabetes therapy. Since incretin mimetics and GLP-1 analogues are peptides, they have to be injected. This fact and their potential costs will probably give them a place in clinical practice for patients who have failed on oral therapy and in whom insulin therapy is not an alternative due to weight problems or possible hypoglycaemia. Theoretically, GLP-1-like agents may be also useful in slowing the progression of type 2 diabetes or to be used as anti-obesity agents due to their effects on body weight and beta-cell mass and function, but here lifestyle intervention and metformin are also effective. Incretin mimetics have the advantage of exclusively activating the GLP-1 receptor and therefore exerting exclusively the desired GLP-1-like effects in comparison with DPP-4 inhibitors. DPP-4 inhibitors have the benefit of being oral (and maybe less costly) agents, but their multiple effects besides raising endogenous GLP-1 concentrations are currently not completely elucidated (see *Table 2*). So far, only data from clinical trials covering a timeframe of a little more than one year are available. Long-term effects of GLP-1 analogues, incretin mimetics and DPP-4 inhibitors, for example on beta-cell proliferation and on the brain, have to be followed in clinical practice. ■

The therapeutic principle of GLP-1 with the multiple mode of action besides its glucose-normalising effect adds a new and attractive perspective to diabetes therapy

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