Netherlands
The Journal of Medicine

REVIEW

Incretins: a new treatment option for type 2 diabetes?

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ABSTRACT

This article describes how the discovery of a protein almost 100 years ago led to a clinical treatment for type 2 diabetes. Food intake, but also stimulation of the sympathetic nervous system (for example physical exercise), stimulates the secretion of glucagon-like-peptide-1 (GLP-1), derived from the glucagon precursor proglucagon in the small intestine. GLP-1 stimulates the production and secretion of insulin, the release of somatostatin, glucose utilisation by increasing insulin sensitivity and in animal studies also β-cell function and expansion (proliferation). It inhibits glucagon release, gastric emptying, appetite and food intake via the central nervous system and in animal experiments also apoptosis of β-cells.

Since GLP-1 has to be administered parenterally and its half-life is short, a long-acting GLP-1 receptor agonist (exenatide) and a long-acting GLP-1 analogue (liraglutide) have been developed as well as an inhibitor of DPP-IV (the enzyme that breaks down endogenous GLP-1). Clinical studies with exenatide and liraglutide as monotherapy show a significant increase in the postprandial insulin concentration as well as a smaller increase in the postprandial glucose values. Adding these drugs to standard oral glucose-lowering medication shows improvement in glucose and insulin concentrations and HbA_{1c} compared with adding placebo. The effect of exenatide on HbA_{1c} is the same as adding a long-acting insulin analogue (glargine), but the increase in weight after adding insulin is not seen after exenatide, where even a small decrease in weight is found. This is an important advantage, because most type 2 patients are already obese. Whether less β-cell apoptosis and maintenance of β-cell function occurs, as has been shown in animal studies, has to be awaited.

Clinical studies with the oral DPPIV inhibitors sitagliptin and vildagliptin show promising results, but are only published as abstracts at scientific meetings.

KEYWORDS

Incretins, GLP-1 analogues, GLP-receptor agonist, DPP-4 inhibitors

INTRODUCTION

The treatment of type 2 diabetes mellitus includes correction of both insulin resistance and impaired insulin secretion. Therefore, besides lifestyle intervention, treatment consists of medical therapy with drugs that lower insulin resistance such as metformin and thiazolidinediones (TZDs) but also insulin secretaguoges (or insulin). Although hyperinsulinaemia is a hallmark of the first years after diagnosis, the first-phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by a peptide from the small intestine secreted after an oral glucose load. As early as in 1906, Moore discovered a chemical stimulant for the pancreas produced by the duodenum. In 1930, Labarre introduced the term 'incretin'. McIntyre *et al.* were the first to demonstrate an incretin effect in 1964. In 1969 Brown *et al.* isolated the protein and called it gastric inhibitory peptide. In 1982 Lund *et al.* identified the cDNA for preproglucagon. In 1983 Bell *et al.* cloned human cDNA for preproglucagon from which glucagon-like-peptide-1 and GLP-2 are a part. In 1987 Kreymann *et al.* demonstrated that GLP-1 indeed stimulates insulin-secretion in humans.[1]

THE ENTEROINSULINAR AXIS: INCRETINS

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-I are the two most important incretins produced by the duodenum. The hypothalamus also produces an incretin, pituitary adenylate cyclase-activating peptide

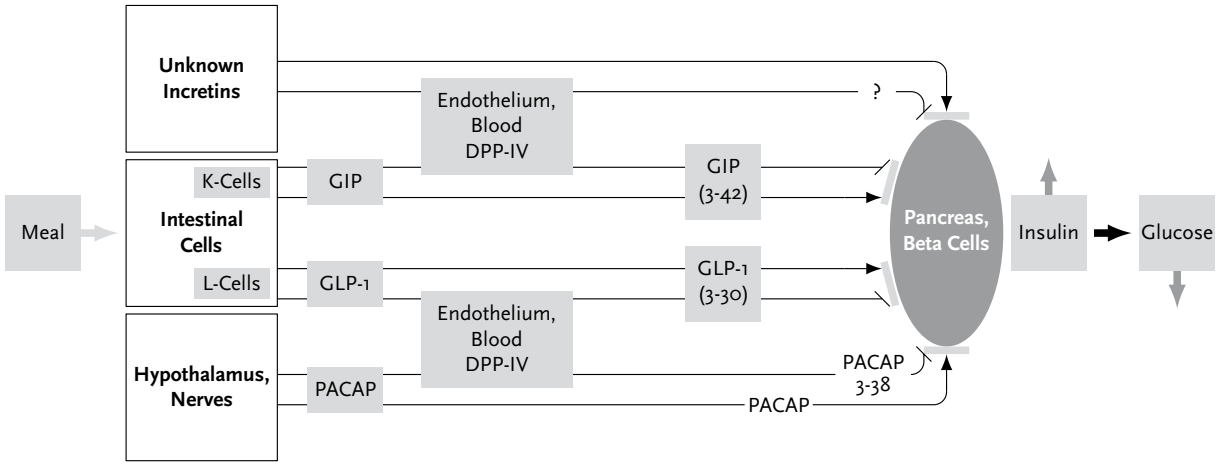
(PACAP); the exact contribution of this peptide to insulin secretion is not clear yet. GIP induces ±60% of the incretin effect. *Figure 1* shows the enteroinsulinar axis: the uptake of carbohydrates and amino acids in the gut results in an endocrine response in the islets of Langerhans. It also causes neurotransmission to both the islets, the liver and via the nuclei of the medulla oblongata to the hypothalamus. Efferent neurons from the hypothalamus and medulla oblongata activate the vagus nerve and the pancreas and inhibit the gastrointestinal tract.[2,3] The endogenous secretion of GIP in type 2 diabetes is normal and exogenous administration of GIP does not increase the insulin response. The endogenous secretion of GLP-1 in type 2 diabetes, however, is decreased. Exogenous administration does induce insulin secretion.[4]

GLP-1 is predominantly produced in the small intestine. After intake of carbohydrates a sixfold increase in the plasma concentration is observed. The time of action is only a few minutes. It is cleared from the plasma by the liver and the kidney.[5] The effect of GLP-1 on different tissues is shown in *table 1*. GLP-1 stimulates insulin production and insulin release after food intake, somatostatin release, glucose uptake by increasing insulin sensitivity and in animal models also β-cell function and expansion (proliferation). It inhibits glucagon release, gastric emptying, appetite and food intake via the central nervous system and also apoptosis of the β-cells. It also influences body temperature, energy expenditure, fluid and salt retention and release of pituitary hormones.[6-8] Administration of GLP-1 to people with type 2 diabetes lowers both fasting and postprandial glucose and decreases appetite and food intake.[9,10] Probably indirectly, as a result of reduced intake of free fatty acids and glucose, insulin sensitivity and β-cell function increase (less glucose toxicity). GLP-1 has to be administered parenterally and has a short half-life, which makes it unsuitable for daily use. Therefore, GLP-1 analogues have been developed with a longer half-life by making natural GLP-1 resistant to the degrading enzyme dipeptidyl peptidase IV (DPP IV), which made twice daily subcutaneous dosing possible. Also a GLP-1 receptor agonist has been developed (exenatide) with a GLP-1-like action. Finally, drugs that increase endogenous GLP-1 by inhibiting DPP-IV, the enzyme responsible for degradation of GLP-1, are becoming available.

Table 1. *Effects van GLP-I on several tissues*

Tissue	Effect
Stomach	Delays gastric emptying
Small intestine	Slows gut motility
Liver	Stimulates glycogen synthesis
Fat	Stimulates glycogen synthesis Inhibits lipogenesis
Skeletal muscle	Stimulates glycogen synthesis
Exocrine pancreas	Inhibits enzym release
Endocrine pancreas	Stimulates insulin release Stimulates somatostatin release Stimulates Beta-cel neogenesis Stimulates synthesis of proinsulin Inhibits glucagon synthesis Inhibits apoptosis of Beta-cells
Central nervus system	Inhibits food intake Stimulates satiety Increases body temperature Stimulates TSH, LH and vasopressin secretion
Kidney	Stimulates sodium excretion Inhibits H+ excretion Inhibits glomerular hyperfiltration
Heart	Increases blood pressure Increases heart rate

Figure 1. *Schematic overview of the production and action of the incretines: GIP, GLP-I and PACAP on the Beta-cel. DPP-IV inhibitors inhibit the degradation of these incretines.*



GIP = Gastric Inhibitory Peptide; GLP-I = Glucagon-Like Peptide-I; PACAP = Pituitary Adenyl-Cyclase-Activating Peptide.

CLINICAL STUDIES

Exenatide

As is often seen in medicine, exenatide was discovered more or less by chance. The peptide from the saliva of the Gila monster happened to be homologous with GLP-1 for 53%, showed more affinity for the GLP-1 receptor than GLP-1 itself and was DDP IV resistant. It enhances insulin secretion, delays gastric emptying and lessens food intake. The plasma half-life is three to four hours.[9] Clinical studies show both effects on glucose regulation, body weight and lipid parameters.

Studies with exenatide as add-on therapy with oral hypoglycaemic drugs

Exenatide has been added to either sulphonylurea,[12-14] metformin, or a combination of both in people with type 2 diabetes and HbA_{1c} >7% on this medication only. The glycaemic result after 30 weeks was similar in all studies and showed a significant decrease in both fasting and postprandial glucose and a change in HbA_{1c} of -0.8% compared with +0.1% with placebo. In the first study, HbA_{1c} decreased significantly in comparison with placebo (slight increase) and even more with exenatide 10 μg subcutaneously twice daily. Starting with a mean HbA_{1c} of 8.6%, 41% of patients reached an HbA_{1c} of <7% after 30 weeks. There was a significant decrease in body weight of 1.6 kg after 30 weeks. Extension studies of two years show that the favourable effects on fasting glucose and HbA_{1c} are sustained.[15-17] Among patients who completed the 82 weeks of treatment, mean body weight further decreased from −2.1 kg at 30 weeks to −4.4 kg at 82 weeks, respectively.
Exenatide BID has recently been reported to have favourable effects as add-on therapy with TZDs and with combination therapy of TZD+metformin.[18]

Studies comparing exenatide with insulin/as add-on therapy with insulin

In two studies[19,20] exenatide was compared with insulin glargine once daily added to the same oral glucose-lowering drugs over a period of 26 weeks. The dose of glargine was titrated to reach a fasting glucose of 5 mmol/l. A similar reduction in HbA_{1c} of -1.1% was achieved. The fasting glucose was significantly lower in the glargine-treated patients, whereas exenatide provided significantly lower postprandial blood glucose values. The fluctuation in blood glucose values was significantly less with exenatide than with insulin glargine. Given the epidemiological data that lower postprandial glucose values are more important than fasting glucose in reducing the risks of cardiovascular disease this may contribute more to reduction of CVD risks than is indicated by the reduction in HbA_{1c}. The group treated with glargine showed an increase in body weight of 1.8 kg, whereas in the group treated with exenatide a weight loss of 2.3 kg was seen. Hypoglycaemia at night was significantly more often seen in the group treated with glargine. Hood evaluated the use of exenatide in patients with type 2 diabetes using insulin and/or oral hypoglycaemic drugs with an HbA_{1c} ≤7.0%.[21] The patients using an insulin secretagogue were able to discontinue its use, and the patients using insulin could reduce the mean daily dose by -37% and the number of injections by -39%. The average weight loss in the 3.6 months was -5 kg compared with a weight gain of +4.8 kg in the preceding 2 years.
Post-hoc interim analyses of the 82-week completer cohort[20] showed a significant 12% increase in HDL cholesterol, a 16% lowering of triglycerides and 3% lowering of diastolic blood pressure. Total cholesterol, LDL-C, apolipoprotein B and systolic blood pressure did not improve significantly.

Exenatide was approved by the FDA as an adjunctive treatment for type 2 diabetes in patients unable to achieve adequate control using metformin and/or sulphonylurea therapy. In Europe the EMEA gave similar approval.
A slow-release preparation (LAR) for once-weekly subcutaneous administration has been tested in rats. A phase II exenatide LAR clinical trial in 45 patients with type 2 diabetes treated with metformin or diet and exercise showed promising results.[22]
Effects on increase in β-cell mass, as demonstrated in animal models, can only be shown with surrogate markers like durability of glycaemic control in humans. Long-term controlled clinical trials addressing this issue are currently being performed.

LIRAGLUTIDE

Liraglutide is a long-acting GLP-1 analogue that is 97% homologous to GLP-1, which makes it suitable for once-daily subcutaneous injection. Acylating the peptide with a free fatty acid chain improves binding to albumin, makes it less accessible to DPP-IV and inhibits renal filtration. Also the binding to albumin induces a slower resorption from the place of injection. Animal studies have shown that liraglutide decreases plasma glucose levels, increases insulin secretion, reduces glucagon secretion, inhibits gastric emptying and appetite, resulting in a reduced body weight and increased β-cell volume.[10]
Phase I studies in humans have been performed, while phase II studies have been completed[23-28] or are ongoing. Hypoglycaemia is seldom reported with liraglutide as monotherapy. Dose-titration studies investigated doses of up to 2 mg/day. In the five-week study by Nauck *et al.*[27] liraglutide added to metformin monotherapy reduced fasting glucose by -3.9 mmol/l and HbA_{1c} by 1.2%. Liraglutide in combination with metformin was significantly more effective than metformin combined

with glimeperide. Body weight was significantly lower in the metformin and liraglutide group *vs* metformin with glimeperide. Frequently reported side effects were nausea, vomiting and diarrhoea as with all GLP-1-like drugs, but adverse events were mild, transient and rarely caused discontinuation of liraglutide treatment.

DPP-IV INHIBITORS

Although studies in healthy volunteers show that administration of DPP-IV inhibitors alone decreases endogenous GLP-1 production, the administration of DPP-IV inhibitors induces a doubling of endogenous GLP-1 production and increases the ratio of active/total GLP-1 making a physiological insulin secretion possible in people with type 2 diabetes.[14] The DPP-IV inhibitors also increase the physiological effects of other incretins such as gastric inhibitory peptide and PACAP. The exact consequences of these additional effects are still not known. The possible advantage of DPP-IV inhibitors in comparison with GLP-1 analogues is that they cause little delay in gastric emptying, which might diminish gastrointestinal side effects. However, the effect is less powerful than that of LP-1, GLP-1-receptor agonists or GLP analogues and starts later (after a few weeks).

Twelve-week monotherapy with vildagliptin improves HbA_{1c} in patients with type 2 diabetes. The higher the baseline HbA_{1c}, the more the effect.[29] Vildagliptin at a dose of 100 mg for 4 weeks reduced fasting and postprandial glucose concentrations, as well as plasma glucagon levels, while the ratio of insulin to glucose increased.[30] Adding vildagliptin to metformin in patients with type 2 diabetes resulted in a decrease in HbA_{1c} of 0.8% after 12 weeks compared with placebo. This difference was maintained in a 52-week extension study.[31] Insulin secretion, measured by a postmeal area under the 0-30 min C-peptide curve, was increased in the vildagliptin group compared with metformin alone. Insulin sensitivity during meal ingestion also increased in the vildagliptin-treated patients.[32]

Clinical studies with sitagliptin and presentations at the American Diabetes Association and International Diabetes Federation meetings in June and December 2006, respectively, indicated that sitagliptin is well tolerated and effective in both monotherapy and in combination with metformin or pioglitazone without significant hypoglycaemia or weight gain.[33-35]

CONCLUSION

The development of GLP-1 analogues, GLP-receptor agonists and DPP-IV inhibitors offers new possibilities for the treatment of hyperglycaemia in people with type 2 diabetes. Although the pathophysiological processes in time and the natural history of type 2 diabetes are not quite clear, it is evident that both insulin secretion and insulin action are impaired at the start of the disease. Especially the first-phase insulin response is absent. In theory this would imply that treatment with GLP-1 analogues or receptor agonists with or without DPP-IV inhibitors in the early phase of the disease in combination with a drug that reduces insulin resistance, such as metformin and thiazolidinediones, is the most physiological treatment option. There is evidence, however, that these drugs are still effective further in the course of the disease when standard treatment is no longer effective. One of the most promising results of this new class of drugs is the absence of increase in weight and even weight reduction instead of the increase in weight often seen with the use of insulin secretagogues as sulphonylurea and insulin. Of course, results of long-term studies have to be awaited concerning both long-term efficacy and safety. However, if positive, the use of sulphonylurea derivatives, especially because of their possible adverse events in case of myocardial ischaemia, could become obsolete and insulin therapy only reserved for patients with absolute insulin deficiency.

This article was published in Dutch in the March 2006 issue of *Insulineresistentie*.

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