

# Enhancing insulin secretion:

## novel approaches to

# glucose control

✉ Jens Juul Holst

*When we eat, the concentration of glucose in our blood rises due to the uptake of glucose from the digestion of starch and other carbohydrates in the gut. In healthy people, the increase is modest; eating activates other processes that counteract any increase. One of the most important of these is the release of insulin from the beta cells in the islets of the pancreas.*

*If the increases in blood glucose that are normally observed after a meal are mimicked by direct infusion of glucose into the blood, the amount of insulin that is secreted is much smaller than that secreted in response to the meal. This difference is due to the release of 'incretin' hormones from the gut which further enhance glucose-induced insulin secretion. Jens Juul Holst reports on potential diabetes therapies based on pharmacologically enhancing or recreating the 'incretin effect'.*

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The incretin effect is responsible for up to 70% of the insulin that is released after the intake of carbohydrates. Two separate hormones produced by the gut are involved in the incretin effect.<sup>1</sup> One is called glucose-dependent insulintropic polypeptide (GIP); the other is called glucagon-like peptide-1 (GLP-1). Both are released in response to the intake of meals of mixed foods, and both directly and powerfully enhance glucose-induced insulin release from the beta cells.

The pancreatic islets also secrete another hormone, glucagon. In many ways, glucagon does the opposite of insulin. It is secreted from the pancreas when levels of blood glucose are low and causes the liver to produce glucose. GLP-1 (but not GIP) also strongly inhibits the secretion of glucagon, and thereby GLP-1 helps to switch off the glucose production of the liver once ingestion of carbohydrates begins.

What happens in the case of people with Type 2 diabetes? The incretin effect in such people is severely impaired.<sup>2</sup> It is likely that this defect contributes to one of the key problems in this condition: the inability of the beta cells to respond adequately to glucose. Research has demonstrated that the most likely cause for this incretin defect in people with diabetes is an impaired secretion of GLP-1 and an almost complete loss of insulin-stimulating activity by GIP.<sup>1</sup>

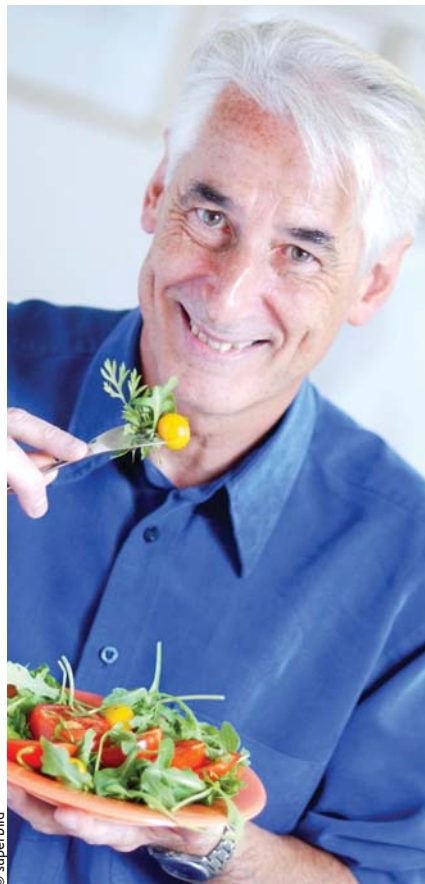
### Potential therapies

As a consequence of these observations, it was proposed that insulin secretion might be restored if people with diabetes were given GLP-1, partly in order to substitute the deficiency of this hormone and partly to substitute for the missing action of GIP. This has turned out to be true. With GLP-1, it may be possible to restore completely the ability of the beta cells of a person with diabetes to respond to glucose with adequate insulin secretion. Naturally, this has inspired many attempts to develop GLP-1 as a new treatment for Type 2 diabetes.

With GLP-1, it may be possible to completely restore insulin secretion in a person with diabetes.

In addition to its actions on insulin and glucagon secretion, GLP-1 was found to have other interesting

effects, such as inhibiting the emptying of the stomach. As a result of this, glucose enters the small intestine at a much lower rate. Thus less glucose is taken up from the gut and blood glucose increases are dampened. Because of these actions, GLP-1 may nearly normalize blood glucose levels in people with Type 2 diabetes. Furthermore, GLP-1 inhibits appetite and thus food intake (it is probably one of the normal physiological regulators of appetite and food intake), so weight gain is lessened. Finally, it has been shown to enhance beta-cell survival, though so far only in animal models of diabetes. This is of great interest since



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Type 2 diabetes involves the progressive destruction of beta cells over years.

### Overcoming the drawbacks

However, there is a major problem. GLP-1 is a small peptide (protein) hormone of 30 amino acids (the normal building blocks of proteins). If taken by mouth, it is destroyed immediately in the stomach, just like insulin. This means that it must be injected. Furthermore, it is destroyed extremely rapidly in the blood; after injection, it is de-activated within a few minutes by an enzyme called dipeptidyl-peptidase IV (DPP-IV).

In one study to find out whether a treatment of Type 2 diabetes based on GLP-1 is at all feasible, people with diabetes were given a continuous subcutaneous infusion of GLP-1 for 6 weeks (using portable pumps originally designed for insulin infusion).<sup>3</sup> In these people, levels of blood glucose were lowered by about 5 mmol/l (90 mg/dl), and the concentration of glycated haemoglobin (HbA<sub>1c</sub>, a measure of long-term glucose control) was greatly reduced; appetite and food intake were reduced, and the people lost weight (2 kg on average); their insulin sensitivity and their ability to secrete insulin were greatly enhanced, and the effect was fully maintained for the 6 weeks. There were no side effects. It was concluded that a GLP-1-based treatment for diabetes was feasible and likely to be effective. However, the problem of how to develop a clinically useful drug remained.

To tackle this problem, two approaches have been taken:

- ♦ the development of analogues of GLP-I that are resistant to the actions of DPP-IV and have longer duration of action than native GLP-I
- ♦ the development of DPP-IV inhibitors.

Both approaches have given encouraging results.

A GLP-1-based treatment for diabetes is feasible and likely to be effective.

### Resistant analogues

There are two principal groups of 'resistant analogues'. One group is based on a peptide isolated from a lizard. This peptide (exenatide) is quite similar in its structure and actions to native GLP-I. Exenatide is injected twice per day and has so far been demonstrated to be highly effective in a 30-week study.<sup>4</sup> Most of the people involved in this study have experienced a lasting improvement in glucose control, with HbA<sub>1c</sub> levels at or below 7.0% (a recommended target). The treatment resulted in a linear weight loss of approximately 1.8 kg. It is hoped that if approved by the US Food and Drug Administration, exenatide will be on the market in the US by 2005.

The analogues belonging to the other group all depend on a process of binding to a large molecule, such as albumin, in

which the analogue acquires the metabolic stability of the larger molecule. While these analogues have demonstrated their clinical efficacy and have been tolerated well, none of them have yet entered phase 3 clinical development, which means that their appearance on the market cannot be expected for at least another 2 years.

Exenatide has so far been demonstrated to be highly effective.

### Enzyme inhibitors

It has been demonstrated that inhibitors of DPP-IV are able to protect the body's own GLP-I. Thus, increases are produced in the concentrations of the intact active hormone. Importantly, these inhibitors are small stable molecules which can be taken orally as tablets. Because of the increased concentrations of GLP-I during DPP-IV inhibition, insulin secretion is enhanced, glucagon secretion is inhibited, and consequently blood glucose falls. This has been seen in people with Type 2 diabetes: most recently, results of 52 weeks of treatment were presented.<sup>5</sup> People with the condition were inadequately controlled by metformin alone, but addition of the inhibitor LAF 237 (Novartis) caused a significant and sustained improvement of glucose control (with HbA<sub>1c</sub> levels around 7.0%). In the control group by contrast there was a

significant worsening. This study could represent the first sign of a protective effect on the beta cells of humans of a GLP-I-based therapy. A number of companies are currently trying to develop clinically useful inhibitors, the first of which are expected to be on the market within a few years.

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### References

- 1 Vilsbøll T, Holst JJ. Incretins, insulin secretion and Type 2 diabetes mellitus. *Diabetologia* 2004; 47: 357-66.
- 2 Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986; 29: 46-52.
- 3 Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002; 359(9309): 824-30.
- 4 Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of Exenatide (Exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; 27: 2628-2635.
- 5 Ahren B, Gomis R, Standl E, Mills D, Schweizer A. Prolonged efficacy of LAF237 in patients with type 2 diabetes (T2DM) inadequately treated with metformin. *Diabetes* 53, 7-LB. 2004. Ref Type: Abstract