Glucagon-like peptide 1: new therapies for Type 2 diabetes

Andrea El-Ouaghlidi and Michael A Nauck

We usually assume that the ups and downs of blood glucose are solely responsible for changes in the release of insulin into the circulation, such as in response to a meal. However, the release of insulin from the pancreas is supported by signals from the alimentary canal (gut). When food is transported from the stomach into the small intestine, from which glucose, fat and proteins are absorbed into the blood, gut hormones are released into the circulation. Around 50% of the insulin secreted into the blood in response to a typical meal is released only through the effect of these gut hormones — gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Andrea El-Ouaghlidi and Michael A Nauck report on the potential use of these hormones as promising new therapies for the management of Type 2 diabetes.

If GIP and GLP-1 are missing or inactive, the release of insulin is reduced, and a higher rise in blood glucose levels will therefore be expected. In people with Type 2 diabetes, the hormone GIP no longer acts on insulin release and/or blood glucose. The exact reasons are not known.2

In contrast, GLP-1 is able to normalize the levels of blood glucose in Type 2 diabetes through several mechanisms:
• the release of insulin is stimulated
• the release of glucagon (a hormone that raises glucose concentration) is suppressed
• gastric emptying is decelerated, slowing the entry of nutrients into the circulation

GLP-1 could be the therapeutic answer to many of the medical problems experienced by people with Type 2 diabetes.

Normalization of blood glucose
During fasting, concentrations of GLP-1 are low. With food stimuli, such as mixed meals, these increase by 3-10-fold. Higher concentrations of GLP-1 can normalize blood glucose in previously hyperglycaemic people.
with Type 2 diabetes within 3-4 hours. It has been possible to improve blood glucose control for periods up to 1 week with intravenous GLP-1. In this way, blood glucose has been normalized to below 7.0 mmol/l or 125 mg/dl in the majority of people studied so far, regardless of the stage of their condition or previous diabetes treatment.3

No other drug in use or under development is as effective in reducing blood glucose without provoking the risk of low blood glucose (hypoglycaemia). This is because the GLP-1-induced secretion of insulin and glucagon are glucose-dependent. This ensures that while high concentrations of GLP-1 alone cannot stimulate insulin secretion, neither can they interfere with the body’s counter-regulatory response which protects against hypoglycaemia.

Limitations
GLP-1 is a protein (peptide hormone) that under normal circumstances is broken down in the gut when ingested with food. Furthermore, within a few minutes it is degraded into inactive components in the body’s circulation by the enzyme dipeptidyl peptidase IV (DPP-4). In the general circulation, only 15-25% of secreted or administered GLP-1 remains in the intact, biologically active form. Therefore, it is impossible to administer GLP-1 in tablet form or even as long-term subcutaneous injection therapy.3

GLP-1 derivatives
However, GLP-1 has been chemically modified to ensure more prolonged action after a single subcutaneous injection. This results in GLP-1-like molecules with similar pharmacological effects but with a longer period of action and resistance to degradation by DPP-4. Such GLP-1 derivatives are currently under clinical development.

Accidentally, a naturally occurring GLP-1-related protein was discovered in the saliva of an American lizard: the Gila monster (Heloderma suspectum). The synthetically produced agent exenatide (developed by Amylin Pharmaceuticals and Eli Lilly & Co) has successfully undergone phase 3 clinical trials. Exenatide significantly reduces postprandial and fasting blood glucose levels in people with Type 2 diabetes. After approval by health authorities, exenatide will be available in the USA after 2005.

Liraglutide (Novo Nordisk), a modified GLP-1, is another artificial

Insulin resistance (insulin insensitivity) is a decreased response to the effects of insulin at the cellular level. Compensation for this leads to high levels of insulin in the blood (hyperinsulinaemia), but diabetes develops when this compensation is exhausted.

A person who has excessively high levels of blood sugar (glucose) is described as hyperglycaemic.
Future Directions

Table: The effects of GLP-1 and its derivatives

- Increased insulin release
- Reduced glucagon secretion
- Delayed gastric emptying
- Satiety, reduced appetite, slow weight reduction
- Growth of insulin-producing beta cells in the pancreas

Almost complete normalization of blood glucose in people with Type 2 diabetes

GLP-1-related agent. Liraglutide allows once-daily dosing. The treatment of people with Type 2 diabetes with liraglutide for several weeks reduces HbA1c levels without increasing weight. Liraglutide will shortly enter the last phase of clinical trials prior to approval in the USA and in Europe.

Another derivative in current development is CJC-1131 (ConjuChem Inc). This may offer the possibility of a dosage interval of around 1 week. Longer-term clinical studies are planned.

Enhancing GLP-1 with enzyme inhibitors

Inhibiting the action of the enzyme DPP-4 can increase the percentage of biologically active GLP-1 by up to five-fold. Therefore, DPP-4 inhibitors can enhance the insulin-producing activity of the body’s own GLP-1 or GIP. Since these inhibitors are small molecules, they can be administered as tablets, which would be an advantage compared to GLP-1 derivatives that need to be injected. DPP-4 inhibitors do not exclusively inhibit the breakdown of GLP-1 and GIP, but also of other naturally occurring hormones or cytokines. Whether this might lead to side effects in humans needs to be carefully examined. So far, no serious complications have been noted.

The drug LAF237 (Novartis) is the most advanced DPP-4 inhibitor in clinical development. In people with Type 2 diabetes, treatment for 4 weeks reduced fasting and postprandial blood glucose levels, as well as glycated haemoglobin (HbA1c) levels.

GLP-1 has the potential to achieve full normalization of blood glucose control without a risk of hypoglycaemia.

Potential advantages

The most promising feature of GLP-1 is the potential to reach a full normalization of blood glucose control without a risk of hypoglycaemia (low blood glucose). Uniform effects can be achieved with standard dosage regimens. Furthermore, GLP-1 induces moderate weight loss. Side effects such as nausea and vomiting at very high concentrations (higher than 500 pmol/l) are unpleasant but not dangerous. The greatest hope, however, is the preservation or even the growth of insulin-producing beta cell mass, and thus the resulting potential to halt the progression of Type 2 diabetes.

References