Effects of two GLP-1 mimetics (liraglutide and exenatide) on aspects of glucose and lipidmetabolism and islet cell function in humans during daily life conditions and during hypoglycaemia

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ABSTRACT

This PhD-dissertation is based on two clinical studies carried out at the Medical Research Laboratories M and the Institute of Pharmacology, Aarhus University Hospital. The theme of the dissertation glucagon like peptide-1 (GLP-1) which is a hormone secreted from the human intestine. GLP-1 stimulates insulin secretion and suppresses glucagon. Furthermore, it reduces appetite, decelerates gastric emptying and has trophic effects on pancreatic β-cells. Thus, the hormone has very attractive effects for the treatment of type 2 diabetes. The native hormone has a very short half-life in plasma. Therefore, long acting analogues have been developed.

The aim of the first study was to explore the effects of the GLP-1 analogue liraglutide on 24 hours' glucose and hormone profiles during daily life conditions, on α- and β-cell function, and on endogenous glucose production in type 2 diabetic patients.

We found that a one week treatment with liraglutide led to significantly reduced plasma glucose levels (~20%), both post prandially and in the fasting state. Insulin secretory capacity was markedly increased. Liraglutide significantly reduced glucagon levels, both during 24h profiles and during arginine stimulation. Finally, we found a significantly decreased endogenous glucose production with liraglutide as compared to placebo.

The insulinotropic and glucagonostatic effects of GLP-1 and its analogues could hypothetically lead to an increased risk of hypoglycaemia. The aim of study 2 was therefore to explore the effects of the GLP-1 receptor agonist exenatide on insulin secretion and on counterregulatory hormones during stepwise hypoglycaemia in healthy individuals.

We found that exenatide infusion led to significantly elevated insulin levels during euglycaemia. Insulin secretion rates were increased 3.5 fold at this glucose level. At glucose levels of 4 mmol/l and below, there were no differences in insulin levels between exenatide and placebo treatment. Thus, exenatide's insulinotropic effects are glucose dependent and only present at glucose levels above 4mmol/l. At euglycaemia, we found significantly lower glucagon levels with exenatide as compared to placebo. During hypoglycaemia there were no differences in glucagon levels between treatment arms. Thus, the glucagonostatic effect of exenatide is also glucose dependent and absent during hypoglycaemia. The remaining counterregulatory response was not significantly changed by exenatide infusion.

In summary, the two studies have shown that GLP-1 mimetics are new, potential anti-diabetics that efficiently lower plasma glucose through insulinotropic and glucagonostatic effects. In addition, the risk of hypoglycaemic episodes is negligible during treatment with GLP-1 mimetics.