**Report 7:** Studying Mechanisms and Treatment of Impaired Glucose Tolerance and Type 2 Diabetes

## Background to the Research

Type 2 diabetes is characterised by a deterioration of metabolic control, namely islet dysfunction and insulin resistance. In order for future treatments to be successful, they should aim to correct these defects. Often animal models are used to investigate molecular mechanisms in the disease state. However, as human diabetes is a complex multi-factorial disease, historically no one animal model has been suitable. This is a summary of some work being undertaken as part of the Ob-Age project (EU project number QLK6-2002-02288) which has investigated markers of type 2 diabetes and impaired glucose tolerance in a diet-induced obese mouse (DIOm) model.

The high-fat, diet-fed C57BL/6J mouse model was developed during the 1980s and has since been used by researchers to investigate the pathophysiology of insulin resistance and type 2 diabetes. It is also of use when testing out new drug treatments, as the metabolic changes observed are comparable to those seen in the human disease. In this study, the mouse model was used to demonstrate the effect of a potential new treatment – an orally active inhibitor of the enzyme dipeptidyl peptidase-IV (LAF237). Dipeptidyl peptidase-IV inactivates glucagon-like peptide-1 which is an insulin-releasing hormone and is required for the regulation of blood glucose levels.

## Research Undertaken

Female C57BL/6J mice were divided into 2 groups; one group was maintained on a high-fat diet (58% energy from fat), the other group was fed a ‘normal’ diet (11.4% energy from fat) for up to 12 months. Over the duration of the study, body weight, blood glucose and insulin concentrations were monitored. The extent of insulin resistance was determined using intravenous and oral glucose tolerance tests. An oral glucose tolerance test was also performed after 4 weeks of treatment with LAF237 in the drinking water to determine if the model was suitable for assessing the efficacy of treatments.

## Main Findings

Unsurprisingly, the mice fed the high-fat diet had an increased body weight compared to those maintained on a normal diet. The investigators observed stable hyperglycaemia and progressively increased hyperinsulinaemia in the mice

on the high-fat diet. This is indicative of progressively worsening insulin resistance. After only one week on the high-fat diet, blood glucose levels were raised and intravenous glucose tolerance tests showed reduced glucose elimination and impaired insulin secretion. This demonstrates two distinct mechanistic characteristics of impaired glucose tolerance and type 2 diabetes; namely insulin resistance and islet dysfunction. Metabolic efficiency (that is the energy intake per gram body weight gain) was raised in both the mice fed a high-fat diet and those on a normal diet. However, the increase was attenuated in the mice fed the high-fat diet. Thus the weight gain observed in the high-fat group cannot be fully explained by increased energy intake; there was also a concomitant reduction in metabolic rate.

The concentration of glucose in the blood was consistently 1mmol/l higher in the mice maintained on the high-fat diet than in those on the normal diet throughout the 1 year study period. However, insulin levels continued to rise in the mice maintained on the high-fat diet. This suggests that insulin resistance progressively increased but there were compensatory mechanisms which kept the hyperglycaemia stable at 1mmol/l. When challenged with an intravenous glucose tolerance test, there was no compensation for the insulin resistance and there was a marked deterioration of glucose elimination. This, along with similar patterns observed following an oral glucose tolerance test, highlights that insulin secretion is defective in this model. When the DPP-IV inhibitor was administered in the drinking water of both groups of mice, there was an augmentation in insulin secretion resulting in improved glucose tolerance.

**Conclusions and Future Directions**

This work has demonstrated that the high-fat, diet-fed C57BL/6J mouse is a robust model for studying impaired glucose tolerance and early stage type 2 diabetes, as it exhibits similar metabolic defects as are observed in the human disease. Improvements in glucose tolerance were observed when a DPP-IV inhibitor was administered indicating that this model is also suitable for studying the effects of new treatments. This mouse model is now being used to investigate the role of adiponectin, lipid accumulation and *Ob-Rb* function during the development of diet induced obesity and the early stages of type 2 diabetes.

Winzell MS & Ahren B (2004) The High-Fat Diet-Fed Mouse: A Model for Studying Mechanisms and Treatment of Impaired Glucose Tolerance and Type 2 Diabetes. *Diabetes* **53** (3) S215-9