Pre-clinical studies on potential new treatments for type 2 diabetes and metabolic disease

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Introduction

Type 2 diabetes is currently undertreated in most countries and the focus is on blood glucose control rather than the pathophysiology of the disease. Optimal treatment of type 2 diabetes requires drugs to:

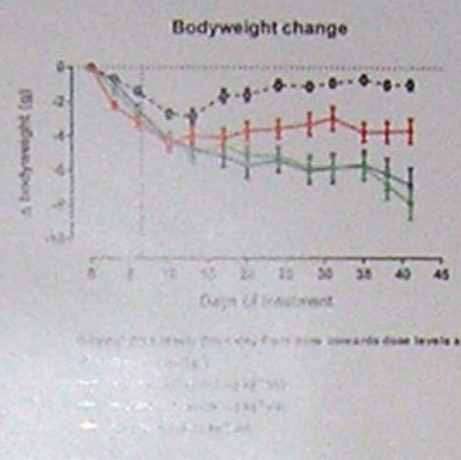
* Inhibit hepatic glucose output.
* Improve insulin sensitivity in skeletal muscle and adipose tissue leading to increased glucose uptake.
* Reduce the release of fatty acid from adipose tissue.
* Increase glucose dependent insulin secretion.

The ultimate aim of treatment should be preservation of pancreatic islet cell function.

To achieve these objectives with existing drugs would require a combination of metformin, a thizolidinedione insulin sensitiser and a GLP-1 agonist, i.e. 3 separate drugs, one of which is injectable.

The Buckingham Institute of Translational Medicine (BITM) undertakens primary work to identify new molecular targets and to collaborate with biotech and pharma companies (acting as a specialist contract research organisation) to evaluate pioneering compounds. In addition BITM is undertaking studies to identify plant-based extracts that are efficacious and which could be developed into a therapeutic product.

Fig 1 Effect of an edible plant extract on body weight change in high-fat diet induced obese mice



Both an aqueous and methanolic extract reduced body weight gain. The original dose of an amount equivalent to 250 mg/kg of the original plant was reduced to 125 mg/kg after 9 days as a result of rapid fall in weight

Fig 2 Dexascan analysis of body fat content and plasma leptin concentration at the end of the study

Fig 2a
Percentage of fat

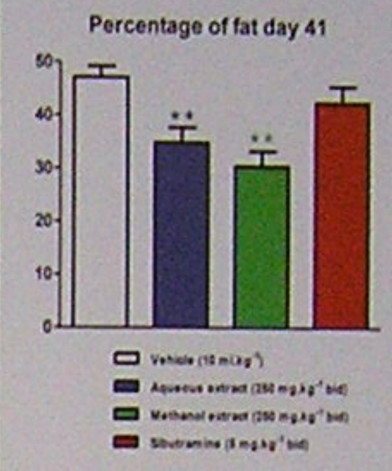
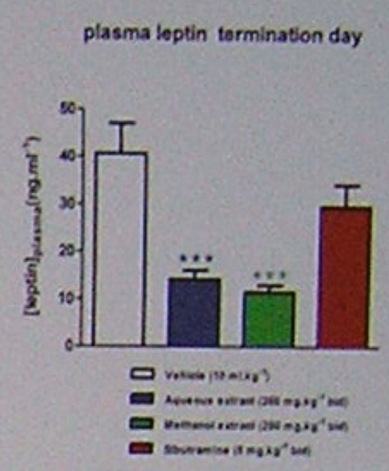


Fig 2b
Plasma leptin



Both the methanolic and aqueous extracts reduced the fat mass but there was no effect on lean mass. Also there was no effect on food intake over the 41 days of dosing. Plasma leptin decreased in parallel with body fat reduction.

Animal models available

Diet induced obese mice and rats
ob/ob mice
Zucker *fa/fa* rats
db/db mice
ZDF male and female rats
HFD/STZ mice

Techniques available

Glucose tolerance test
Insulin tolerance test
Pyruvate tolerance test
Food intake and food choice
Energy expenditure and thermogenic responses
Body composition
Euglycaemic hyperinsulinaemic clamp
Hepatic glucose output
Insulin secretion studies *in vivo* and isolated islets
Metabolic analytes
Hormones such as insulin, GLP-1, glucagon, ghrelin, leptin and adiponectin
Adipokines and cytokines
Immunohistochemistry

Fig 3 Oral glucose tolerance and plasma insulin concentration

Fig 3a

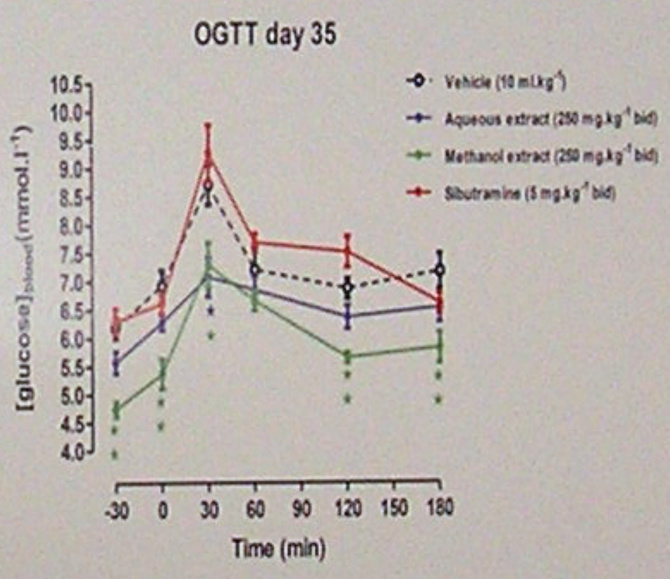
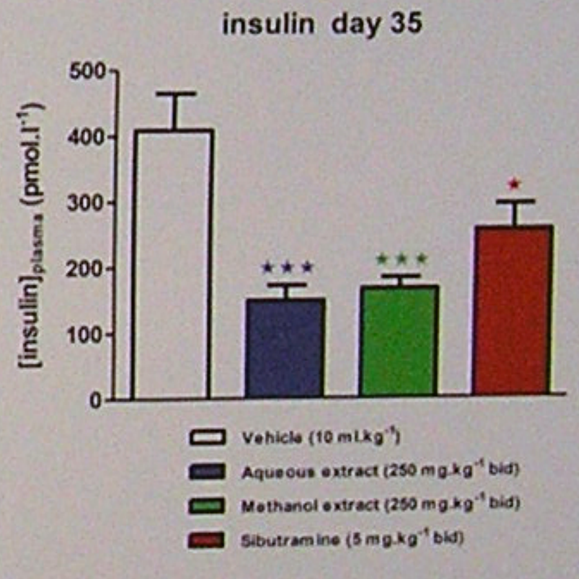


Fig 3b



The two extracts resulted in improved glucose tolerance ,whereas the anti-obesity drug sibutramine only had a minor effect. The 5h-fasted plasma insulin concentration was also reduced, indicating improved insulin sensitivity

Fig 4 Effects of FFA1, FFA4 and dual agonist on glucose tolerance and insulin concentrations

Fig 4a

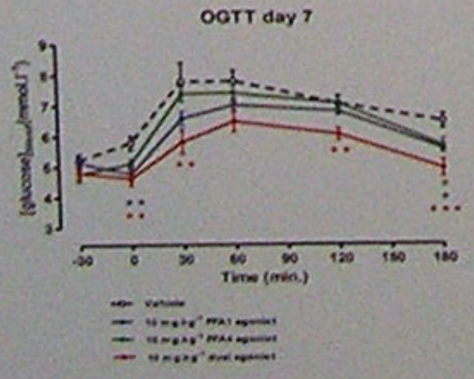
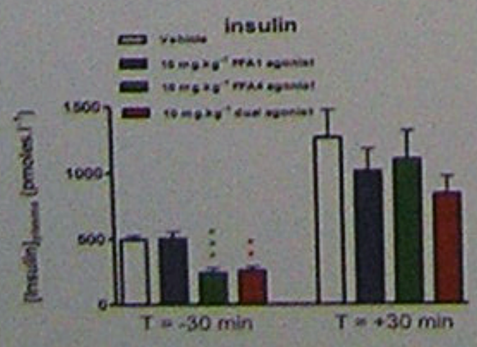


Fig 4b



After 7 days treatment daily to diet-induced obese mice, the dual agonist and the FFA1 agonist improved glucose tolerance, but the FFA4 agonist improved insulin sensitivity.

Fig 5 Effects of FFA1, FFA4 and dual agonist on energy expenditure

Fig 5a

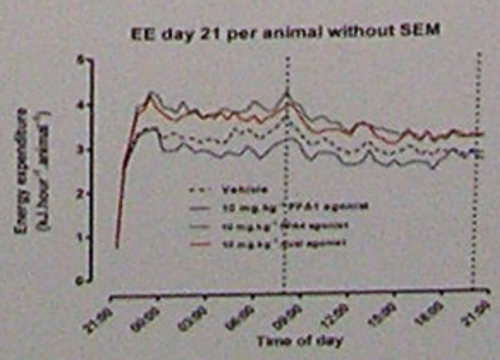
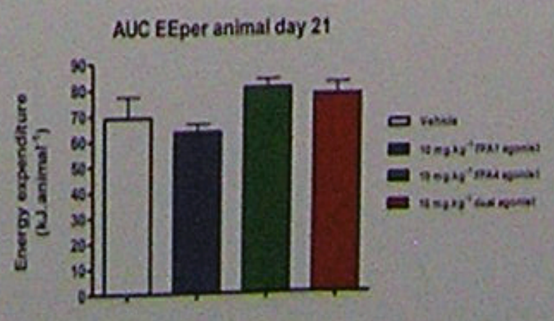


Fig 5b



Energy expenditure, measured by indirect calorimetry, was increased in mice treated with FFA4 and a dual agonist but not by a FFA1 agonist

Fig 6 Effect of FFA1, FFA4 and dual agonist on body fat content

Fig 6a

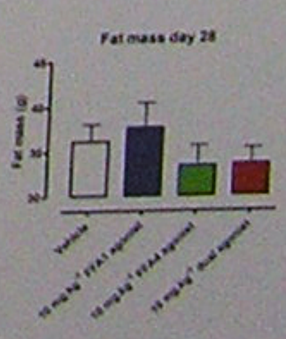
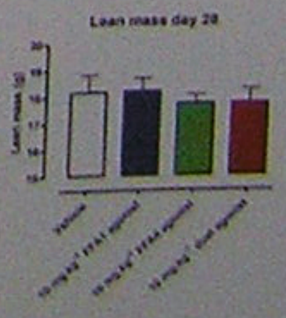


Fig 6b



In line with changes in energy expenditure the FFA4 agonist and dual agonist decreased fat mass of high fat diet mice with little effect on lean body mass