**Effect of Empagliflozin on Body Weight, Glucose Control and Plasma Parameters in STZ-Induced Diabetic Rats Fed a High-Fat Diet: Comparison with Exenatide**

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**BACKGROUND AND AIMS**

Empagliflozin is a novel, potent and selective sodium glucose cotransporter-2 (SGLT-2) inhibitor in clinical development for the treatment of type 2 diabetes. Empagliflozin inhibits the reabsorption of glucose in the kidney and promotes disposal of excess glucose via the urine. In this study, the potential utility of empagliflozin to control glycaemia in an experimental model of type 1 diabetes was investigated. The effect of empagliflozin on body weight, glucose control and plasma parameters in rats fed a high-fat diet and administered a low dose of streptozotocin (STZ) to induce diabetes was determined and compared to the GLP-1 receptor agonist, exenatide.

**RESULTS**

**METHODS**

Male Sprague-Dawley rats (mean body weight approx 430g) were maintained on a high-fat diet. Animals underwent baseline oral dosing with vehicle one week prior to STZ treatment and for two weeks afterwards. Subsequently, animals were dosed with vehicle (po q.d.) (n=12), empagliflozin (10 mg/kg po q.d.) (n=12), or exenatide (30 µg/kg/day) (n=12) administered via a subcutaneous osmotic minipump for 29 days. The non-STZ group was dosed with vehicle (po q.d.). Animals that did not receive exenatide were implanted with a minipump filled with sterile saline (ALZET 2ML4).

Body weight and food intake were monitored daily for 29 days. Animals underwent an oral glucose tolerance test (OGTT) (2 g/kg) on Day 23 after an overnight fast. Blood samples (4-hour fasted) were taken at termination (Day 29) and assayed for plasma glucose, insulin, TAG, HbA1c and glycerol (0.10 mM vs 0.18 mM; p<0.05) (Figure 1A) and reduced average daily food intake (15.9 g vs 20.0 g, p<0.01) compared to STZ-treated controls. Exenatide did not significantly improve glucose control in an OGTT (p=NS) for the AUC or fasting plasma glucose (0.7 mg/dl vs 0.16 mg/dl) (p=NS) (Figure 1B).

**CONCLUSIONS**

1. Administration of a low dose of STZ in Sprague-Dawley rats fed a high-fat diet produced an insulinopenic model of type 1 diabetes characterised by reduced plasma insulin, raised plasma glucose and HbA1c, impaired glucose tolerance and reduced body weight compared to vehicle controls.

2. Empagliflozin significantly improved glycaemic control in STZ-induced diabetic rats, as evidenced by reductions in fasting plasma glucose, insulin, TAG and HbA1c, and improved glucose tolerance during an OGTT, without having significant effects on body weight or food intake.

3. In contrast, despite producing significant weight loss by reducing food intake, exenatide did not markedly improve glycaemic control in this insulinopenic model of type 1 diabetes.

4. This study demonstrates the antiadipogenic effect of empagliflozin in an animal model of type 1 diabetes in which insulin secretion is markedly impaired. In contrast to the majority of current treatments, the insulin independent mechanism of action of empagliflozin means that it could be investigated as a treatment for type 1 diabetes, used in addition to insulin.

**REFERENCES**


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