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CARDIAC CHARACTERISATION OF A NEW RAT MODEL OF TYPE 2 DIABETES

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Aims We aim to develop a type 2 diabetic rat model which represents closely the characteristics of the diseased state in type 2 diabetic humans such as hyperglycaemia, hyperinsulinaemia, dyslipidaemia and obesity. We based our model on the type 2 diabetes was proposed by Reed *et al*[1], which combines high fat diet and streptozotocin (STZ) instead of relying on a genetic manipulation for disease development like many other rat models. We proposed to determine the optimal dose of streptozotocin (STZ) injection and to investigate cardiac-specific abnormalities in this new model of type 2 diabetes, to determine its suitability for studying diabetic cardiomyopathy.

Methods Male Wistar rats were fed a high fat diet followed by an intraperitoneal injection of STZ at either 15, 20, 25 or 30 mg/kg body weight.

Results We observed a dose-dependent increase in plasma glucose and non-esterified fatty acids with increasing concentration of STZ. There were dose-independent increases in cardiac and hepatic triglycerides, and decreases in cardiac and hepatic glycogen content in all diabetic rats. With increasing concentrations of STZ there were dose-dependent increases in cardiac UCP3, PDK4 and MCAD protein levels, and decreases in GLUT4 and GLUT1 protein levels. Consequently, the dose of 25 mg/kg STZ was chosen for further metabolic studies. These diabetic rats showed a 39% increase in fasted insulin concentrations and 73% increase in glucose concentrations. Isolated heart perfusion using ^{3}H-glucose demonstrated that both insulin-independent and insulin-stimulated glycolytic rates were decreased by 56% and 43%, respectively, in diabetic hearts compared with controls, in the absence of any change in systolic function.

Conclusions This demonstrates that high fat feeding combined with 25 mg/kg STZ induces a cardiac metabolic phenotype that resembles that found in type 2 diabetic patients