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Optimization of high-fat diet fed streptozotocin induced Wistar rat model for screening antidiabetic agents

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High-fat diet (HFD) fed streptozotocin (STZ) induced Wistar rats are frequently used as animal models of type 2 diabetes mellitus for screening novel antidiabetic agents. As the composition of HFD, age and strain of rats, dose of STZ and the intended degree of pathophysiological changes vary among studies, the development of a model that best fits to a particular research setting is pivotal. Furthermore, ensuring the long-term stability and establishment of an adequate biochemical profile of the model are necessities which have been addressed by limited studies to date. This study attempted the development of a model which mimics type 2 diabetes mellitus for screening of novel antidiabetic drugs. Wistar rats were fed with a HFD (60% calories from fat) for four weeks, followed by STZ intraperitoneal injection (30, 40 and 50 mg/kg). Rats with fasting serum glucose >11.1 mmol/L were enrolled for the study. There were five groups (n=10/group); healthy rats, HFD fed rats, HFD+STZ (30 mg/kg) rats, HFD+STZ (40 mg/kg) rats, HFD+STZ (50 mg/kg) rats. The glycemic status of the rats was monitored weekly by the routine conduct of oral glucose tolerance tests. Experimental rats were euthanized after 28 days and blood samples were collected for biochemical investigations. Glycemic status of the model was assessed by determining fasting serum glucose, insulin, glycated hemoglobin (HbA_{1c}) and homeostatic model assessment-insulin resistance (HOMA-IR). Lipid profiles were assessed by determining total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) levels. STZ induced rats (30, 40 and 50 mg/kg) showed a significant dose dependent increase in fasting serum glucose (by 67, 61 and 136%) and insulin (by 19, 15 and 13%) concentrations ($p<0.05$). HOMA-IR was above 2.5 and increased in a dose dependent manner by 98, 108 and 176% in STZ induced rats (30, 40 and 50 mg/kg). However, only the STZ (50 mg/kg) induced group of rats showed fasting serum glucose concentration of 13.71 ± 1.01 (>11.1 mmol/L) and a significant increase in HbA_{1c} by 66% compared to the healthy rats ($p<0.05$). Further, the STZ 50 mg/kg rats showed stable hyperglycemia throughout the study period. STZ induced rats (30, 40 and 50 mg/kg) also showed a significant dose dependent increase in TC (by 6, 7 and 9%), and TG (by 16, 15 and 23%) respectively ($p<0.05$). However, only the STZ induced (50 mg/kg) group of rats showed significant increase in serum concentrations of LDL-C (by 12%) and VLDL-C (by 16%) compared to the healthy rats ($p<0.05$). Only slight changes in HDL-C levels were observed in the STZ induced groups of rats however, the values were not significant ($p>0.05$). The results revealed that the Wistar rats fed with HFD rich in saturated fat for four weeks followed by a single intraperitoneal dose of STZ (50 mg/kg) would produce stable diabetic model which closely mimic pathophysiological features of type 2 DM characterized by insulin resistance and dyslipidemia.

Keywords: High-fat diet, Streptozotocin, Diabetes

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