Effects of Multi-Electrode Renal Denervation on Insulin Sensitivity and Glucose Metabolism in a Canine Model of Type 2 Diabetes Mellitus

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ABSTRACT

Purpose: To evaluate the effects of multi-electrode catheter-based renal denervation (RDN) on insulin sensitivity and glucose metabolism in a type 2 diabetes mellitus (T2DM) canine model.

Materials and Methods: Thirty-three dogs were divided equally into 3 groups: bilateral renal denervation (BRDN) group, left renal denervation (LRDN) group, and sham operation (SHAM) group. Body weight and blood biochemistry were measured at baseline, 20 weeks, and 32 weeks, and renal angiography and computerized tomographic (CT) angiography were determined before the procedure and 1 month, 2 months, and 3 months after the procedure. Western blot was used to identify the activities of gluconeogenic enzymes and insulin-signaling proteins.

Results: Fasting plasma glucose (9.64 ± 1.57 mmol/L vs 5.12 ± 1.08 mmol/L; $P < .0001$), fasting insulin (16.19 ± 1.43 mIU/mL vs 5.07 ± 1.13 mIU/mL; $P < .0001$), and homeostasis-model assessment of insulin resistance (HOMA-IR; 6.95 ± 1.33 vs 1.15 ± 0.33; $P < .0001$) in the BRDN group had significantly decreased at the 3-month follow-up compared with the SHAM group. Western blot analyses showed that RDN suppressed the gluconeogenetic genes, modulated insulin action, and activated insulin receptors–AKT signaling cascade in the liver. CT angiography and histopathologic analyses did not show any dissection, aneurysm, thrombus, or rupture in any of the renal arteries.

Conclusions: These findings identified that multi-electrode catheter-based RDN could effectively decrease gluconeogenesis and glycogenolysis, resulting in improvements in insulin sensitivity and glucose metabolism in a T2DM canine model.

ABBREVIATIONS

AKT = protein kinase B, Ang II = angiotensin II, BRDN = bilateral renal denervation, BUN = blood urine nitrogen, Cr = creatinine, G6Pase = glucose-6-phosphatase, HFD = high-fat diet, HOMA-IR = homeostasis-model assessment of insulin resistance, HPLC = high-pressure liquid chromatography, InsR = insulin receptor, LRDN = left renal denervation, NCD = normal-chow diet, PEPCK = phosphoenol-pyruvate carboxykinase, RDN = renal denervation, SHAM = sham operation, STZ = streptozotocin, T2DM = type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM), the pathophysiology of which includes insulin resistance, hyperglycemia, and a variable degree of insulin secretory deficiency (1), accounts for ~90% of all diabetic patients (2). Many studies have indicated that the sympathetic nervous system plays a pivotal part in the development of insulin resistance and T2DM, and that renal nerves participate in blood pressure control, renal function, and glucose metabolism (3,4). It has

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been shown that increased sympathetic nervous system activation plays a significant role in insulin resistance (5), and insulin resistance can induce an increase in sympathetic nervous system activation (6).

In the past decade, catheter-based renal denervation (RDN), an ablation technique targeting renal sympathetic nerves, has been used for resistant hypertension (7). However, the efficacy of RDN in the treatment of resistant hypertension is still controversial (8–10). Early studies have shown improvements in insulin sensitivity and glucose metabolism, as well as lower blood pressure and sympathetic nerve activity after RDN (11–13), which might be a combination of the beneficial effects of sympathoinhibition and the reduced release of noradrenaline on regional hemodynamics (14,15). In some animal studies in which RDN was performed either surgically or chemically (16, 17), reduced sympathetic nerve activity and elevated insulin sensitivity were observed. There was no significant reduction in fasting glucose and no effect on systemic sympathetic activity demonstrated in the DREAMS study (18), which used the Symplicity Flex device with monopolar electrodes for RDN.

In a recent clinical trial of multi-electrode RDN on patients with metabolic syndrome, the authors clarified that multi-electrode RDN could reduce elevated sympathetic nerve activity and restore the normal neural response to oral glucose loading (19). Nonetheless, the effects of multi-electrode RDN for the treatment of T2DM in an experimental animal and the pathophysiology of multi-electrode RDN on T2DM have not been systematically examined. Therefore, in the present study, it was hypothesized that multi-electrode catheter-based RND could improve insulin sensitivity and glucose metabolism in a canine model of T2DM.

MATERIALS AND METHODS

Animals

A total of 33 beagles (10–11 months old, of either sex) were provided by the Animal Center of Southeast University. They were housed in individual cages and subjected to controlled conditions (20–24°C temperature, 40%–70% humidity, and 12h:12h light-dark cycle), and with free access to water. The Guide for the Care and Use of Laboratory Animals (20) was followed, and the study completely conformed to the National Health and Medical Research Council of China on Animal Experimentation and was approved by the Animal Ethics Committee of Southeast University.

Study Timeline

Baseline (W0) assessments of body weight and fasting blood levels were performed on all of the animals while they were on a normal-chow diet (NCD; 3,600 kcal/d, 27% protein, 38% carbohydrate, and 35% fat). The dogs were then fed a high-fat diet (HFD; 5,110 kcal/d, 20% protein, 27% carbohydrate, and 53% fat) for 16 weeks (W16). Subsequently, animals received 18.5 mg/kg streptozotocin (STZ) solution via intravenous injection (21) and reduced food intake for the following week, were fed the HFD for an additional 3 weeks, and then subjected to an intravenous glucose tolerance test at 4 weeks after STZ (W20) to confirm that the T2DM model developed successfully. The dogs were then equally randomized into 3 groups: bilateral renal denervation (BRDN) group, left renal denervation (LRDN) group, and sham operation (SHAM) group. The procedure was performed on all of the animals, which were subsequently fed the HFD for another 12 weeks (W32) (Fig 1).

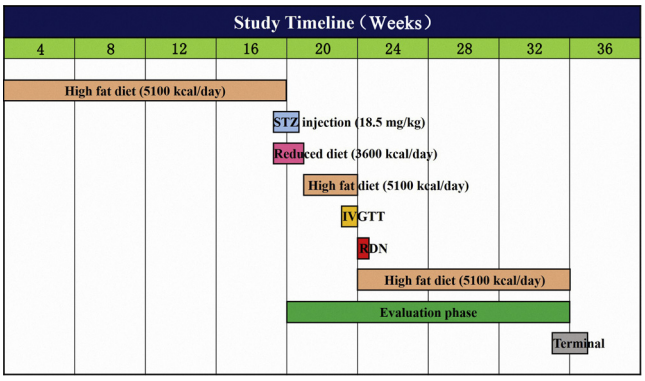

Figure 1. Study timeline. Baseline assessments of body weight and fasting blood were performed on all of the animals while they were on a normal-chow diet. Then the dogs were fed a HFD for 16 weeks. After that, they received 18.5 mg/kg STZ solution via intravenous injection and reduced food intake for the following week, and then were fed the HFD for an additional 3 weeks, followed by an IVGTT 4 weeks after STZ. At week 20, the procedure was performed on all of the dogs, and they were fed the HFD for another 12 weeks after the procedure. IVGTT = intravenous glucose tolerance test; STZ = streptozotocin.

Blood Biochemistry

Blood samples were collected from the lateral hind legs at W0, W20, and W32. Plasma triglyceride, total cholesterol, low-density lipoprotein, blood urine nitrogen (BUN), creatinine (Cr), and fasting plasma glucose were quantified with the use of commercially available kits (Rongsheng Biotech, Shanghai, China). Fasting insulin was measured with the use of a radioimmunoassay kit (Academy of Atomic Energy, Beijing, China). Homeostasis-model assessment of insulin resistance (HOMA-IR) was calculated with the use of the following equation: (fasting plasma glucose [in mIU/mL]) × (fasting insulin [in mmol/L])/22.5 (22). The serum level of noradrenaline was measured with the use of a commercial enzyme-linked immunosorbent assay kit (Titerzyme Kits, Michigan), and angiotensin II (Ang II) was measured with the use of a radioimmunoassay kit (Beijing Chemclin Biotech Co, Beijing, China), according to the manufacturers' specifications.

Renal Denervation

The canines were fasted overnight before the procedure. Then, 0.05 mg/kg atropine was administered intravenously and the animals were anesthetized with the use of 20–30