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Fibroblast growth factor 19 improves cardiac function and mitochondrial energy homoeostasis in the diabetic heart

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In diabetic cardiomyopathy, mitochondrial fatty acid oxidation dominates over mitochondrial glucose oxidation, leading to metabolic disturbances. Fibroblast growth factor 19 (FGF19) acts as a metabolic regulator and may have a cardioprotective role on diabetic cardiomyopathy. In this study, we investigated the effects of FGF19 on energy metabolism. FGF19 treatment of diabetic hearts exhibited higher glucose uptake and lower lipid profiles, suggesting changes in energy metabolism. The protective effects of FGF19 prevented ventricular dysfunction in diabetic hearts and improved mitochondrial function by the upregulation of PGC-1α expression. On the other side, knockdown of PGC-1α by siRNA attenuated the effects of FGF19 on the enhancement of mitochondrial function and energy efficiency. Taken together, these results show that FGF19 exhibited improved mitochondrial efficiency, which might be associated with higher cardiac contractility in diabetic hearts. It is also of note that modulation of PGC-1α, which is responsible for the activation by FGF19, may be a therapeutic target for diabetic cardiomyopathy.

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1. Introduction

Diabetic cardiomyopathy (DCM) is a major cause of mortality in diabetic patients. It has been defined as a ventricular dysfunction that occurs without coronary artery disease and hypertension [1]. Altered myocardial substrate and energy metabolism has contributed to the theory of a viral aetiology underlying the pathogenesis of DCM [2]. The accumulation of cardiac free fatty acids and decreased insulin-mediated glucose uptake in diabetic patients enhance cardiac oxygen consumption and mitochondrial dysfunction, thereby resulting in cardiomyocyte death and ventricular dysfunction [3]. The beneficial effects of attenuating abnormal substrate metabolism in the heart may potentially prevent diabetes-induced cardiac injury and prolong long-term survival of patients with diabetes.

Human fibroblast growth factor 19 (FGF19) and its mouse ortholog, FGF15, have been identified as metabolic hormones [4]. Circulating FGF15/19 represses bile acid synthesis in the liver and promotes gallbladder filling [5,6]. In addition, FGF15/19 has broader effects on energy homeostasis. Transgenic mice expressing FGF19 in muscle have a higher basal metabolic rate and are resistant to high-fat-diet-induced weight gain [7]. Likewise, treatment of hepatocytes with FGF15/19 represses hepatic gluconeogenesis, TCA cycle flux, and fatty acid oxidation [8], suggesting that FGF15/19 works as a postprandial regulator of hepatic carbohydrate homeostasis.

The peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), whose decreased expression is consistently implicated in

Abbreviations: Fibroblast growth factor 19, (FGF19); peroxisome proliferator-activated receptor-γ coactivator, (PGC-1α); Diabetic cardiomyopathy, (DCM); streptozotocin, (STZ); thiobarbituric acid, (TBA); pressure-volume, (P-V); volume-pressure recording, (VPR); systolic blood pressure, (SBP); mean arterial pressure, (MAP); diastolic blood pressure, (DBP); heart rate, (HR); end-systolic pressure, (ESP); end-diastolic pressure, (EDP); stroke volume, (SV); ejection fraction, (EF); 2,3-butanedione monoxime, (BDM); mitochondrial isolation buffer, (MIB); peroxisome proliferator-activated receptor alpha, (PPARα); pyruvate dehydrogenase E1-alpha, (PDH E1α); glucose transporter 4, (GLUT4); palmitoyltransferase 1α, (CPT-1α).

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human or animal diabetic muscles, has recently emerged as a powerful regulator of cellular energy metabolism [9,10]. Notably, PGC-1a controls mitochondrial biogenesis and function, which in the muscle can contribute to fibre-type switching [11]. However, the underlying mechanisms by which FGF19 counteracts diabetes-induced myocardial mitochondrial dysfunction remains unclear.

In this report, we investigated the effects of FGF19 on mitochondrial energy metabolism. We hypothesized that FGF19 prevents ventricular dysfunction in diabetic hearts and prevents mitochondrial dysfunction by the upregulation of PGC-1α expression.

2. Materials and methods

2.1. Mice and mouse model

Male Sprague Dawley rats were obtained from the Model Animal Research Center of Harbin Medical University. The investigation conformed to the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (NIH Publication No. 85e23, revised 1996). All animals were treated in accordance with guidelines established by the Institutional Animal Care and Use Committee at Harbin Medical University.

For the diabetic animal model, rats (6 weeks old, male) were injected intraperitoneally with a single dose of streptozotocin (STZ) at 150 mg/kg. One week after the induction of diabetes, recombinant FGF19 (1 mg/kg, Prospec CYT-700) was given via intraperitoneal injection every other day from the fourth week to the twelfth week.

2.2. Metabolic parameter assessments

Plasma glucose, TC, TG, HDL-C, and LDL-C levels were determined using a commercial colorimetric assay kit (BioVision, Milpitas, CA, USA). Serum was used to determine MDA concentration levels using an HPLC-based assay (Thermo Scientific, CA, USA). Plasma MDA was mixed with H_3PO_4 and thiobarbituric acid (TBA) to produce TBA-reactive substances (TBARS). Plasma BARS concentrations were determined directly from a standard curve and reported as equivalent to the MDA concentration. Serum adiponectin levels were determined using an ELISA kit (Invitrogen, Life Technologies).

2.3. Serum plasma FGF19 assessments

Plasma FGF19 levels were determined using the quantitative sandwich enzyme immunoassay technique for FGF19 Quantikine ELISA Kit (R&D Systems, Minneapolis).

2.4. Tail-cuff BP measurement

Non-invasive BP measurements were conducted using the volume-pressure recording (VPR) tail-cuff method CODA (Kent Scientific Corporation). The BP was recorded at week 12 and at the end of the study. An average of the BP was taken from 10 cycles of measurements.

2.5. P- V loop assessment

The rats were anaesthetized with ketamine (60 mg/kg) and xylazine (0.15 mg/kg) via intraperitoneal injection before starting the P-V loop protocol. The right common carotid artery was identified, and a P-V loop catheter was inserted into it. After that, the systolic BP (SBP) and diastolic BP were determined with the catheter placed in the ascending aorta. LV function, including heart rate (HR), end-systolic pressure (ESP), end-diastolic pressure (EDP), dP/dtmax, dP/dtmin and stroke volume (SV), were determined when the catheter was advanced into the LV chamber. P-V loop data analysis was carried out using an analytical software program (LABSCRIBE2; iWorx System).

2.6. Isolation and culture of adult rat cardiomyocytes

The rats were anaesthetized and heparinized, and the hearts were rapidly excised and mounted on a Langendorff perfusion apparatus. The hearts were immediately perfused with Ca^{2+}-free buffer (120.4 mM NaCl, 14.7 mM KCl, 0.6 mM KH_2PO_4, 0.6 mM Na_2HPO_4, 1.2 mMMgSO$_4$-7H2O, 10 mM Na-HEPES, 4.6 mM $NaHCO_3$, 30 mM Taurine, 10 mM 2,3-butanedione monoxime (BDM), 5.5 mM glucose, pH 7.1). Collagenase II (1.5 mg/mL, Invitrogen) and $CaCl_2$ (50 mM) were added to the perfusion solution to initiate enzymatic digestion. After 20 min of digestion, the ventricle was quickly removed into the perfusion solution containing 10% calf serum and 12.5 mM CaCl2 and gently torn into small pieces. The cell suspension was then filtered through a 70 mm nylon cell strainer (Fisher Scientific, Waltham, MA). The cardiomyocytes in the suspension were pelleted down by gravity for 10 min and re-suspended in a M199 medium supplemented with selenium/insulin/transferrin (Sigma-Aldrich, St. Louis, MO) and plated into Matrigel-precoated 6-well plates for the subsequent experiments.

2.7. Transfection with siRNA

Gene silencing by small interfering RNA (siRNA) involves a small double-stranded RNA that degrades the target mRNA. The PGC-1α-siRNA duplex was synthesized by Shanghai GenePharma Co., Ltd. (Shanghai, China) (siRNA-PGC-1α:5′-GACGAAGCAGA-CAAGACCGGU-3’); In the control group, the cells were treated with either the transfection reagents (vehicle) or a non-targeting siRNA (siRNA-NC:5′-UUCUCCGAACGUGUCACG-3′). The cells were transfected with 200 nM siRNA by using the X-treme siRNA Transfection Reagent (Roche Applied Science, Penzberg, Germany), according to the manufacturer's instructions.

2.8. Mitochondrial isolation

Using a medium-fitting glass Teflon Potter-Elvehjem homogenizer, the cardiac tissues were manually homogenized in the mitochondrial isolation buffer (MIB buffer; 250 mM sucrose, 0.5 mM Na_2EDTA, 10 mM Tris, and 0.1% BSA at pH 7.4), and the homogenate was clarified by centrifugation two times at $1000\times g$ for 5 min. The supernatant was centrifuged twice at $11000\times g$ for 10 min, and the mitochondrial pellets were collected and diluted with three volumes of MIB buffer.

2.9. Western blot

Protein samples were loaded onto an SDS page (4–15%) for separation. The separated proteins were then transferred to polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). The membranes were then blocked with 5% non-fat milk at room temperature for 1 h in Tris-buffered saline containing Tween-20. Primary antibody incubation (FGF19, pyruvate dehydrogenase E1-alpha (PDH E1α), glucose transporter 4 (GLUT4), peroxisome proliferator-activated receptor alpha (PPARα), carnitine palmitoyltransferase 1α (CPT-1α), peroxisome proliferator-activated receptor gamma coactivator (PGC-1α), beta-tubulin and α-porin, all from Cell Signaling Technology) was carried out overnight at 4 °C. Secondary antibody incubation with peroxidase-conjugated Affinipure goat anti-rabbit IgG or anti-mouse IgG-labelled secondary

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