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High-intensity interval versus moderate-intensity continuous training: Superior metabolic benefits in diet-induced obesity mice

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ABSTRACT

Aims: Exercise is beneficial in obesity, however, the debate about the value of high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) has been long lasting. Therefore, here we have compared the possible beneficial effects of two different exercise training regimes in a mouse model of diet-induced obesity (DIO).

Materials and methods: Following 7 wk. on high fat diet (HFD), ten-week-old male ICR mice (n = 30) were assigned to HIIT, distance-matched MICT or remained sedentary for the next 8 constitutive weeks while maintaining the dietary treatments. Age-matched sedentary mice with standard diet were used as a control (n = 10). Exercise was performed on a motorized treadmill for 5 days a week.

Key findings: Both modes of exercise ameliorated adiposity and related metabolic dysfunction induced by HFD and sedentary lifestyle, while mice following HIIT exhibited significantly lower body weight, percentage of fat mass and smaller adipocyte size. HIIT was more favorable in preventing liver lipid accumulation by restoring mRNA levels of genes involved in hepatic lipogenesis (*SREBP1*, *ACC1*, *FAS*) and β-oxidation (*PPARα*, *CPT1a*, *HAD*). In addition, HIIT was more efficient in mitigating adipose tissue inflammation and insulin insensitivity, partly dependent on abrogating phosphorylation of JNK/IRS1 (Ser307) pathway. Moreover, only HIIT led to pronounced beige adipocyte recruitment in inguinal subcutaneous adipose tissue.

Significance: We conclude that HIIT contribute a more favorable regulation of metabolic dysfunctions in DIO mice compared with MICT.

1. Introduction

Obesity, which is associated with cardiometabolic dysfunction, diabetes, respiratory disease, certain types of cancer, and osteoarthritis, has become one of the most serious threats to human health [1–3]. Lifestyle interventions against the obesogenic environment including unhealthy diet and sedentary behavior is deemed to be the most important strategy in tackling obesity [3].

Traditionally, the moderate-intensity continuous training (MICT) has been the most common type of exercise recommended to improve body composition, cardiorespiratory fitness, insulin resistance (IR), and lipid profile [4,5]. However, many people fail to accomplish the "traditional training programs", ascribing to "lack of time" or "lack of enjoyment". Accumulating studies have suggested high-intensity interval training (HIIT) yield more favorable results in weight loss, metabolic and cardiovascular status improvement than those with MICT [6–10]. Moreover, HIIT is perceived to be more enjoyable, serving as a stronger driver of exercise participation and adherence [11], as HIIT involves alternating short bursts of high intensity exercise with recovery periods or light exercise [12]. In contrast, some other evidences supported similar health benefits of HIIT and traditional endurance exercise [13,14], even argued that HIIT may not be safe and tolerable [15]. Therefore, elucidating which exercise regime improves the metabolic status of individuals with obesity is essential.

Exercise training improves whole-body energy metabolism largely attributed to adaptations in skeletal muscle [16–18]; however, training also affects many other tissues, including liver and adipose tissue. Exercise has yielded improvements in dyslipidemia of individuals affected by obesity, primarily through restoring the gene expression of molecules related to fat oxidation and lipogenesis [19,20]. Hitherto the effect of HIIT on hepatic lipid metabolism at transcriptional and protein level remains largely unexamined. In addition, adipose tissue is one of the most important organs linked to obesity-associated IR and chronic inflammation, since low-grade inflammation caused by an

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accumulation of adipose tissue and ectopic fat contributes to the pathogenesis of IR [21]. Although emerging evidences has proven that HIIT can improve insulin sensitivity [7,13,22], controversy lies in whether improvements are attributable to the exercise training per se or fat loss. Thus, it remains to be better understood the molecular responses to HIIT that incorporates inflammatory signaling and insulin sensitivity pathways in the adipose tissue.

Despite the competence of exercise on expending energy stored in white adipose tissue (WAT) is such a cliche, recent studies focusing on the role of exercise in the activation of brown adipose tissue (BAT) shed lights on new strategies combating obesity [23–25], since activating BAT relates to stimulation of resting energy expenditure, nonshivering thermogenesis [26], and improvements in glucolipid homeostasis [27,28]. Also, the possibility of increasing energy expenditure by inducing a brown-like metabolic phenotype in WAT (a process nowadays called 'browning') is of great therapeutic interest. However, the kind of exercise prescription potentially recruiting brown and beige adipocytes remains undetermined.

The present study aimed to clarify how HIIT would influence obesity-related physiological variables, and compare changes in these adaptations with traditional MICT in a mouse model of high fat diet (HFD) induced obesity. We proposed a mechanistic link between HIIT and advantageous metabolic homeostasis, providing theoretical basis for development of new and improved options to prevent and treat obesity and its related complications.

2. Material and methods

2.1. Ethics statement

This study was approved by the Animal Ethics Committee of the Institute of Genome Engineered Animal Models for Human Disease, Dalian Medical University (Permit Number: SYXK (liao) 2013–0006). All the experimental methods were carried out in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health.

2.2. Animals and diets

For diet-induced obesity (DIO) phenotype, 3-weeks old male ICR mice (purchased from Institute of Genome Engineered Animal Models for Human Disease of Dalian Medical University, China) were fed with HFD (45%kcal fat, MD12032, Medicience Ltd.) for 7 weeks. Then the DIO mice were randomly assigned to different interventions (n = 10 in each group): HIIT, MICT or sedentary lifestyle (SED), and continued to consume the HFD. Meanwhile, lean control mice (CON) (n = 10) fed a standard control diet (10%kcal fat, MD12031, Medicience Ltd.) over the entire period were also included. Five mice per cage with access to food and purified water ad libitum were maintained on a 12/12 h light/dark cycle with lights on at 08: 00 in a temperature (23 ± 2 °C) and humidity (60%) controlled room.

2.3. Exercise protocol

Exercise was performed on a motored mice treadmill (FT-200, Techman Soft) at 25° inclination 5 days/week (Monday to Friday) for 8 weeks, according to a protocol slightly modified from that described by Kemi et al. [29]. Both groups started with a warm-up at 5 m/min, where after HIIT consisted 10 bouts of 4 min high-intensity (85–90% VO_{2max}) treadmill running, interspersed by 2 min active rest (5 m/min); whereas MICT consisted of distance-matched continuous running, corresponding to 65–70% of VO_{2max}. The pace during HIIT and MICT was increased gradually from 16 to 26 m/min and 9 to 13 m/min over 8 weeks respectively (detailed in supplementary information, Table S1 and S2).

2.4. Glucose tolerance tests (GTTs) and insulin tolerance tests (ITTs)

After 15 weeks of feeding and training, mice were fasted overnight (20:00–8:00) with free access to drinking water. A baseline blood sample (fasting blood glucose, FBG) was collected from the tail of fully conscious mice followed by an oral gavage of glucose (2.0 g/kg bw), and blood was taken from the tail at 15, 30, 60, 90 and 120 min post-gavage. For ITTs, mice were fasted for 5 h (9:00–14:00) and insulin injection (0.75 unit/kg bw) (FosunPharm) was administered by intraperitoneal injection. Blood samples were collected as pre-described. The blood glucose concentration was determined with a glucometer (Onetouch Ultra, Johnson). GTTs and ITTs were manipulated 48 h after treadmill running to minimize the acute insulin sensitizing actions of exercise. To normalize for differences in basal glucose concentrations, these data were displayed as the area under the curves (AUCs) with subtraction of basal glucose concentrations.

2.5. Sample preparation

At the end of the experiment, mice were sacrificed after 12 h of fasting. Liver, retroperitoneal WAT (rWAT), epididymal WAT (eWAT), inguinal subcutaneous white adipose tissue (scWAT), interscapular brown adipose tissue (iBAT), and gastrocnemius muscle were removed and weighed. Blood samples were collected and serum was separated by centrifugation (3000 rpm, 15 min). All samples were quick-frozen in liquid nitrogen and stored at − 80 °C for further use.

2.6. Biochemistry assay

The serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), high-density-lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were measured by auto chemistry analyzer (Hitachi7600–210, Japan),and high-sensitivity C-reactive protein (hs-CRP) by automatic special protein analyzer (Siemens BN^{T}II, German) according to the manufacturer's instructions. IL-6, adiponectin were analyzed using commercial kits (Merck Millipore) according to the manufacturer's standards. Fasting insulin (FINS) levels were analyzed using a mouse insulin ELISA kit (Thermo). Homeostasis model assessment of insulin resistance (HOMA-IR, an indicator of systemic insulin resistance) = FBG (mmol/L) × FINS (mU/L)/22.5. TG levels in liver were analyzed using a commercial kit (A110-1, Nanjing Jiancheng Bioengineering Institute, China). Briefly, small portions of liver tissue (50 mg) were collected and homogenized in ice-cold 100% ethanol (450 mL). After centrifugation, the supernatant was collected for analysis based on the glycerol lipase oxidase (GPO-PAP) method. Samples were reacted with the mixture from the kit and were incubated at 37 °C for 10 min, and absorbance at 510 nm was read with a microplate reader (Spectra MR, Dynex Technologies, USA).

3. Histological analysis

3.1. Hematoxylin and eosin (H & E) staining

Parts of liver and eWAT were excised, washed with ice-cold PBS, and fixed in 10% formalin. After being dehydrated in a grade alcohol series and embedded in paraffin wax, sections of tissue (thickness of 4–5 μm) were prepared and stained with H & E for histopathology and visualized by an Olympus BX63 microscope and pictured by Image Pro Plus7.0 software. Adipocyte size was calculated from three randomly selected fields of view for each animal as Singh et al. described [30], using the National Institutes of Health Image J software.

3.2. Immunohistochemistry (IHC) analysis

Paraffin-embedded adipose tissues (iBAT, scWAT, and eWAT) were