Experimental Gerontology 113 (2018) 150–162

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Beneficial alterations in body composition, physical performance, oxidative stress, inflammatory markers, and adipocytokines induced by long-term high-intensity interval training in an aged rat model

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ARTICLE INFO

Section Editor: Emanuele Marzetti

Keywords:
Aging
Inflammation
Adipocytokine
Oxidative stress
High-intensity interval training

ABSTRACT

Sarcopenia is associated with loss of muscle mass and function as well as oxidative stress, chronic low-grade inflammatory status, and adipocytokine dysfunction. It has been reported that sarcopenia can be attenuated by exercise training. The purpose of this study was to evaluate whether long-term high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) protocols could differentially modulate changes in body composition, physical performance, inflammatory parameters, and adipocytokines in fat tissues and serum, as well as oxidative parameters and insulin-like growth factor 1 (IGF-1) levels in skeletal muscle tissue of aged rats. Middle-aged (18-month-old) female Sprague Dawley rats (n = 36) were subjected to 8 months of MICT (26–m MICT) or HIIT (26–m HIIT) treadmill training (45 min, 5 times per week), and the results were compared with those of age-matched sedentary controls (26–m SED); 8-month-old (8–m SED) and 18-month-old (18–m SED) rats served as aging sedentary controls. Body composition parameters; physical performance; serum and skeletal muscle oxidative stress parameters; levels of IGF-1, a serum and fat tissue inflammatory marker; adipocytokine (leptin, adiponectin) levels; and plasma glucose and lipid metabolism-related parameters were analyzed among the five groups. The percent fat and body fat to lean mass ratio increased as a main effect with age, whereas 26–m HIIT but not 26–m MICT attenuated these alterations. The 26–m HIIT group showed a larger improvement in grip strength compared to that of 26–m MICT, with a similar increase in inclined plane performance, maximum running speed, and exhaustion over time as compared with the 26–m SED group. Notably, the 26–m HIIT group showed lower high-sensitivity C-reactive protein levels and higher IL-10 in serum compared with those of the 26–m SED and 26–m MICT groups. Both exercise protocols promoted increased skeletal muscle IGF-1 and decreased serum IGF-1 and adiponectin relative to those in the 26–m SED group, whereas only 26–m HIIT dampened the age-related decrease in plasma free fatty acids and increased serum leptin, along with providing lower fat tissue leptin as compared with that in the 26–m SED group. Moreover, the 26–m HIIT group showed lower serum and skeletal muscle malonylaldehyde and skeletal muscle 8-hydroxydeoxyguanosine (8-OHdG) levels than those in the 26–m MICT group, albeit similar decreases in serum and skeletal muscle 4-hydroxynonenal and serum 8-OHdG and increases in skeletal muscle superoxide dismutase 2 activity. In conclusion, HIIT initiated late in life exhibited greater beneficial effects in ameliorating aged-related elevations in oxidative stress and inflammation, as well as dysfunction of circulating adipocytokine levels, than a volume-matched MICT program. HIIT may therefore contribute to improvements in body composition and physical performance changes associated with aging.

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https://doi.org/10.1016/j.exger.2018.10.006
Received 5 September 2018; Received in revised form 5 October 2018; Accepted 5 October 2018
Available online 09 October 2018
0531-5565/

1. Introduction

Age-related changes in body composition, including increased adiposity and decreased muscle mass, are associated with declining physical endurance, power, and slower gait in older adults (sarcopenia), resulting in increased mortality and disability (Marzetti et al., 2018). These body composition changes increase systemic inflammation levels, potentially leading to increased incidence of chronic diseases, cardiovascular diseases, and sarcopenia (Campbell et al., 2009). In particular, elevated circulating levels of non-specific markers of chronic low-grade inflammation, including acute-phase high-sensitivity C-reactive protein (hsCRP) as well as cytokines such as interleukin-6 (IL-6), which are mainly derived from adipose tissue, have been found in elderly individuals (Pedersen et al., 2000). As these correlate with adiposity, sedentary lifestyle, and poor physical functioning and disability among the elderly and middle-aged women (Penninx et al., 2004), their elevation suggests that age-related chronic low-grade inflammatory status constitutes an important causative factor for sarcopenia (Brinkley et al., 2009).

Non-specific chronic inflammatory processes associated with excessive production of pro-inflammatory cytokines may in turn increase the production of reactive oxygen species (ROS) to play a paramount role in the pathogenesis of sarcopenia (Derbré et al., 2014), as these can promote declines in muscle mass and function/power (Sakellariou et al., 2014). Furthermore, aging-associated mitochondrial oxidative stress can result in mitochondrial DNA deletion mutations, which disrupt respiration in individual mitochondria and are linked to the activation of apoptosis as well as intra-fiber atrophy, breakage, and necrosis, contributing to fiber loss (Herbst et al., 2016). For example, mitochondrial superoxide dismutase 2 (SOD2) deficiency in aging mice is involved in age-associated oxidative damage to macromolecules, which may cause dysregulation of ROS-mediated cell signaling, resulting in myocyte apoptosis and thereby leading to muscle atrophy and loss of physical function (Lustgarten et al., 2011). Thus, targeting chronic low-grade inflammation and oxidative stress might provide an effective therapeutic tool for preserving muscle integrity and improving physical performance in late life (Vilela et al., 2018).

Exercise programs that use resistance and endurance training have been shown to improve skeletal muscle mass and power, aerobic power, and functional capacity in the elderly, attenuating age-related physiological declines (Marzetti et al., 2008; Robinson et al., 2017; Vilela et al., 2018). Recently, high-intensity interval training (HIIT) has received much attention owing to its physiological and psychological benefits. Moreover, HIIT, which is considered to be more enjoyable than traditional, moderate-intensity continuous training (MICT) (Thum et al., 2017), results in higher compliance in older populations than MICT (Shiraev and Barclay, 2012) and leads to improved indices of performance (Jabbour et al., 2017; Robinson et al., 2017; Sculthorpe et al., 2017; Seldeen et al., 2018), as well as improved clinical outcomes in a number of aging-related cardiovascular or metabolic disorders, including visceral fat, insulin sensitivity (Søgaard et al., 2018), and cardiopulmonary function (Heiskanen et al., 2016; Hwang et al., 2016; Kim et al., 2008; Klonizakis et al., 2014). However, although numerous studies have demonstrated beneficial impacts of short-term HIIT on skeletal muscle structure and function (Bell et al., 2015; Robinson et al., 2017; Seldeen et al., 2018; Wyckelsma et al., 2017), it is currently unknown whether long-term HIIT initiated late in life can fully combat aging-induced health problems, such as poor physical functioning, chronic low-grade inflammatory status, oxidative stress, and dysfunction of adipocytokine secretion.

To address these issues, in the present study, we determined the impact of a consistently applied HIIT training regimen on aging-related motor decline post-onset in an aged (18-month-old) rat model. The purpose of this study was to investigate: 1) age-related changes in body composition, physical functioning, inflammatory markers, oxidative stress, and adipocytokine secretion in the middle-aged rat, and 2) the effects of chronic HIIT on these parameters, especially as compared to those of a volume-matched MICT protocol in aged rats.

2. Methods

2.1. Animals and experimental design

A total of 60 Sprague-Dawley (SD) rats were purchased from Guangdong Medical Laboratory Animal Center (Foshan, Guangdong, China) at approximately 8 months of age. The rats were kept under an artificial 12-h light-dark cycle (6:00 AM–6:00 PM) at constant room temperature (23 ± 1 °C) in the Laboratory Animal Center, School of Sports Science and Physical Education, South China Normal University (SCNU). Water and food were available ad libitum. The animals were housed in their respective groups in a collective cage and received water and standard laboratory chow. Standard animal laboratory chow (56.8% carbohydrate, 22.5% protein, 3.5% lipids, and 17.2% other nutrients) and water were provided ad libitum. All experiments were approved by the Ethics Committee on Animal Experimentation of the Guangdong Medical Laboratory Animal Center and followed the Guidelines for the Care and Use of Laboratory Animals.

After 1 week of preconditioning feeding, all rats underwent body weight (BW), body composition, and physical performance measures including endurance and progressive running tests, inclined plane, grip power, and echocardiography within one week. Subsequently, 12 rats were randomly selected and euthanized with an intraperitoneal injection of ketamine (100 $mg \cdot kg^{-1}$) for use as 8-month sedentary (8 m–SED, $n = 12$) controls. The remaining rats were raised at the animal center of the School of Sports Science and Physical Education in SCNU until 18 months of age (pre-sarcopenic), and 12 rats were randomly selected for use as 18-month sedentary (18 m–SED, $n = 12$) controls. The remaining 36 rats were divided into three groups: 26-month sedentary (26 m–SED, $n = 12$); 26-month MICT (26 m–MICT, $n = 12$); and 26-month HIIT (26 m–HIIT, $n = 12$). The 26 m–SED group rats were handled in an identical manner to the exercised groups but did not participate in any exercise treatment for the 8-month duration of the experiment. After the end of the treatment protocol (26 months of age, category sarcopenic) (Siddharth et al., 2017), all animals were killed via anesthetic 48 h after physical performance measures (Fig. 1).

During the 8-month duration of the experiment, a total of 12 rats were excluded from the study: two rats from the 26 m–SED group (owing to severe eye infections), four rats from the 26 m–MICT group (two rats died from exercise-unrelated causes and two rats were excluded owing to severe claw infections), and six 26 m–HIIT rats (two rats owing to nonadherence to the training protocol and four rats because of severe claw and tail infections).

2.2. Maximal oxygen uptake measurement and exercise training

The maximal oxygen uptake (VO_{2max}) was determined using a treadmill for rodents with an indirect calorimetry analyzer (Harvard Apparatus®-Le405 gas analyzer, Panlab Technology for Bioresearch, Nagoya, Japan). O_2/CO_2 gas concentrations were used to calculate the intensity of the training for both training protocols based on the maximal velocity (100% maximal effort) of the VO_{2max} test on Friday of the 39th week. The test began with a warm-up (5 min, 10 $cm \cdot s^{-1}$, 0° inclination) after which the velocity was increased by 5 $cm \cdot s^{-1}$ every 3 min until the exhaustion of the animal. Based on the level of VO_{2max}, a treadmill speed corresponding to 70% VO_{2max} was determined and used for daily training.

After 10 months, at 18 months of age, rats were trained over the course of 2-week acclimatization to run on an adapted motor-driven treadmill designed for rats (model FD000043; Flyde Apparatus, Guangzhou, China). During the 1st week of training acclimatization, rats were individually placed into a treadmill lane at a 0° incline for a total of 10 min. At the start of the 2nd week of acclimatization, rats ran