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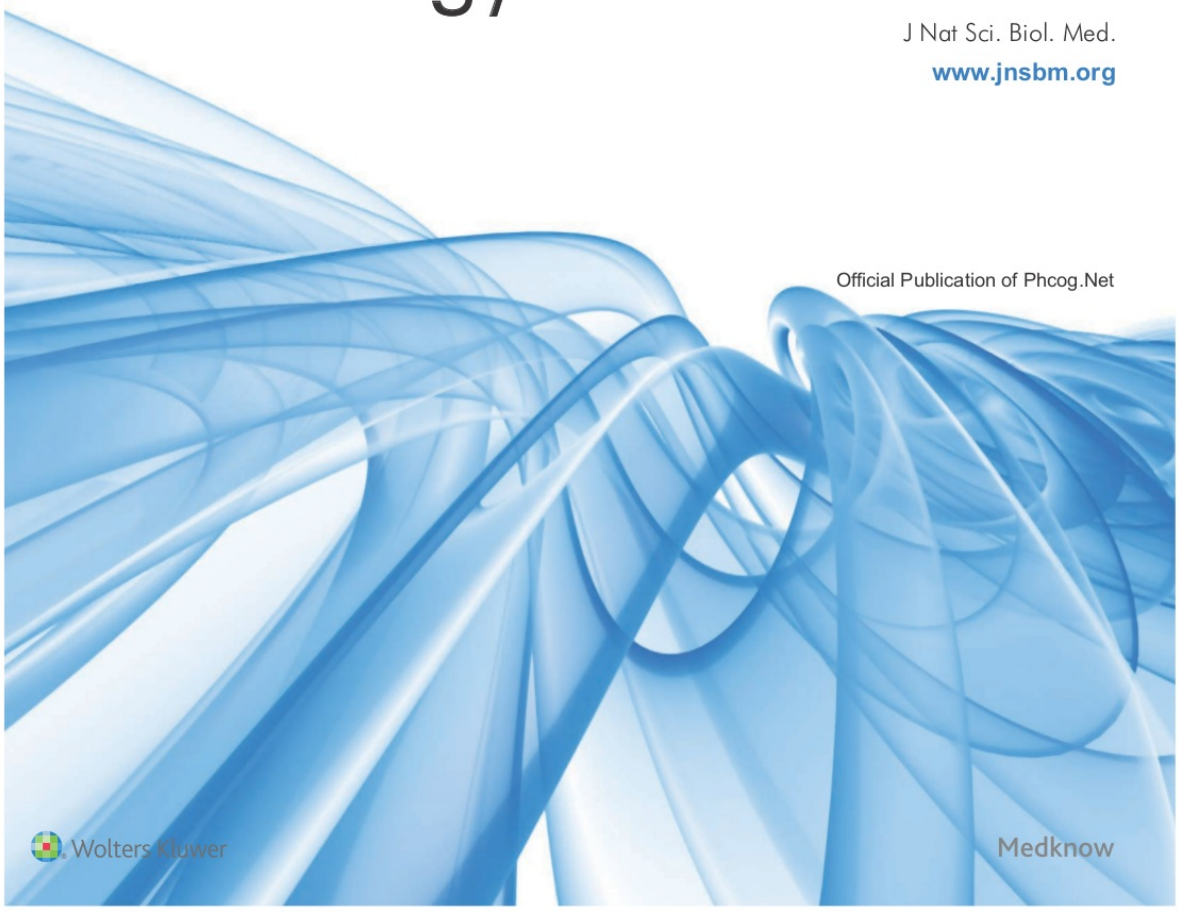

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Original Article

Effect of Interval and Continuous Training on Proliferator-Activated Receptor Gamma Coactivator-1α and Lactate Dehydrogenase B Levels in Adult Rat Heart

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Abstract

Introduction: Mitochondrial biogenesis is affected by peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and can be induced through physical exercise. Lactate from the skeletal muscle produced in the heart during exercise can be used as an energy source through conversion by lactate dehydrogenase B (LDH B). This study compared the effects of continuous training (CT) and interval training (IT) on PGC-1α and LDH B levels in the adult rat hearts. **Materials and Methods:** Fifteen male adult Wistar rats (12 months old) were randomly divided into three groups as follows: A control Group (c), a CT group and an IT group. Training was conducted using a rodent treadmill, 5 days/week for 8 weeks. The duration was 50 min for the CT group. In the IT group, training consisted of 4 bouts of 4 min of exercise, followed by rest intervals of 1 min. Speed was increased each week. After 8 weeks of training, the rats were sacrificed, and the levels of PGC-1α and LDH B in heart tissue were measured using enzyme-linked immunosorbent assay. **Results:** Differences in PGC-1α levels between groups were statistically significant ($P = 0.008$), while differences in LDH B levels were not statistically significant ($P = 0.063$). Levels of PGC-1α and LDH B were higher in the CT group than in the IT group. **Conclusion:** We concluded that CT has a greater effect on energy metabolism in the heart than IT.

Keywords: Continuous training, heart, interval training, lactate dehydrogenase B, proliferator-activated receptor gamma coactivator-1α

Introduction

Heart function requires considerable energy production through oxidative phosphorylation in mitochondria. Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is a transcriptional coactivator that functions as the main regulator for mitochondrial biogenesis and cardiac metabolism. The expression of PGC-1α can be induced through physical exercise.[1,2] Frequency, intensity, time or duration, and type of physical exercise can have variable effects.[3] Interval training (IT) consists of high intensity, short to longer bouts of exercise (equal to or greater than maximum steady-state lactate levels), interspersed with recovery periods (light exercise or rest).[4] Continuous training (CT) is performed over a long exercise period. Both of these exercises are believed to improve mitochondrial biogenesis through its main regulator PGC-1α.[5] The lactate from the skeletal muscle produced during physical exercise can be used as an energy source in the heart and will be converted by lactate dehydrogenase (LDH).[6,7] LDH is a tetrameric enzyme that catalyzes the lactate-pyruvate reaction and consists of two subunits types: M (muscle) or LDH A and H (heart) or LDH B. These two subunits can form five possible tetramers (isoenzymes): H4, M4, and three mixed tetramers (MH, M2H2, and M3H). LDH A converts pyruvate to lactate and is expressed in the skeletal muscle, while LDH B converts lactate to pyruvate and is expressed more in the heart muscle.[7-9] PGC-1α is induced through exercise and can increase LDH activity in the skeletal muscle and heart.[8,9] Several studies showed that LDH B activity was increased after exercise, but others showed decreased or unchanged LDH B activity. Factors that can influence this activity include the

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intensity and duration of exercise, subject or animal fitness, and the type of exercise.[10] Therefore, the aim of this study was to compare the effect of interval versus continuous training on proliferator activated receptor gamma coactivator-1α (PGC-1α) and lactate dehydrogenase B (LDH B) levels in adult rat heart.

Materials and Methods

Animals

This *in vivo* experimental study was approved by the University of Indonesia Ethics Committee. Fifteen male Wistar rats (12 month old), weighing 300–400 g, were evenly and randomly divided into a control group without treatment (C), a CT group and an IT group. With access to water and food *ad libitum*, the rats were placed in a clean room with the temperature maintained at 23°C, using a 12 h day/night cycle. Acclimatization to the cage environment was performed for 5 days.

Exercise treatment

Before the start of treatment, the animals were acclimatized for 5 days to the treadmill speed of 15 m/min, 10 min/day. From the following week until the 8th week, the CT group was given 50 min of exercise that consisted of warming up for 5 min at 6 m/min, followed by 40 min of continuous running on the treadmill, speed was gradually increased from 9 m/min in the 1st week to 15 m/min in the last week, and ended with a cooling down period at 6 m/min for 5 min. The IT group was given 30 min of exercise that consisted of warming up for 5 min at 6 m/min, followed by 20 min of exercise (4 bouts of 4 min at higher intensity, gradually increased from 16 m/min in the 1st week to 25 m/min in the last week, with rest intervals of 1 min), and cooling down for 2 min at 6 m/min. Both training protocols were performed for 5 days per week for 8 weeks. This physical exercise protocol was used in a previous preliminary study measuring plasma lactate levels.[5,6,11]

Sample collection and measurement of proliferator-activated receptor gamma coactivator-1α and lactate dehydrogenase B levels

At the end of the 8th week, the animals were sacrificed, and the hearts were isolated and stored at −80°°C. Homogenates were made according to the working protocol of each enzyme-linked immunosorbent assay kit using left ventricular myocardium. A Bradford test was performed to measure total protein levels. An ELISA kit (Cusabio; CSB-EL018425RA) was used to measure PGC-1α levels, with another ELISA kit (MyBioSource; MBS764976) used to measure LDH B levels.

Statistical analysis

Data analysis was performed with SPSS, Statistics Package for the Social Sciences program (SPSS,Inc., Chicago, USA) for windows; preliminary analysis was performed with the Shapiro–Wilk test to confirm the normality of data distribution, followed by the determination of homogeneity of variation. One-way analysis of variance (ANOVA) was used, with a $P < 0.05$ as the criterion for statistical significance. A *post hoc* Games-Howell test was used to show significant differences between groups.

Results

Measurement of proliferator-activated receptor gamma coactivator-1α levels

After 8 weeks of exercise, the heart tissue level of PGC-1α in the CT group (36.78 ± 2.26 pg/mg total protein) was higher than that in the IT group (24.10 ± 1.19 pg/mg total protein) and C group (22.79 ± 7.22 pg/mg total protein). Differences in PGC-1α levels between groups were statistically significant ($P = 0.008$; ANOVA) [Figure 1]. A *post hoc* Games-Howell test showed significant differences between CT and IT groups ($P = 0.006$).

Measurement of lactate dehydrogenase B levels

After 8 weeks of exercise, the heart tissue level of LDH B in the C group (2.32 ± 0.27 ng/mg total protein) was higher than that in the CT group (2.18 ± 0.11 ng/mg total protein); and IT group (1.72 ± 0.12 ng/mg total protein), but the difference were not statistically significant ($P = 0.063$; ANOVA) [Figure 2].

Discussion

In our study, the level of PGC-1α was higher in the CT group than in the IT and C groups. PGC-1α activity and expression are very sensitive to extracellular and physiological cues.[2,12] During physical exercise, skeletal muscle contraction will increase, and Ca^{2+} influx will activate calcium/calmodulin-dependent protein kinase, phosphorylate cAMP response element-binding protein, and activate PGC-1α. In addition, an increase in ATP energy requirements will activate 5' AMP-activated protein kinase (AMPK) signals that can phosphorylate PGC-1α directly. In the heart, PGC-1α will bind to transcription factors, including estrogen-related receptor, peroxisome proliferator-activated receptors and nuclear respiratory factor; this will activate genes that express key enzymes involved in fatty acid oxidation, fatty acid transport, and lactate metabolism.[1,2,12] A long duration of CT at low speed allows

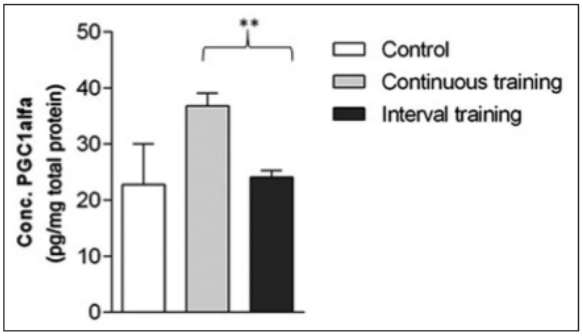

Figure 1: Proliferator-activated receptor gamma coactivator-1α level after 8 weeks of treatment. Data mean standard error, $P < 0.01$ between groups. A *post hoc* Games-Howell test showed $P < 0.01$ between continuous training versus interval training

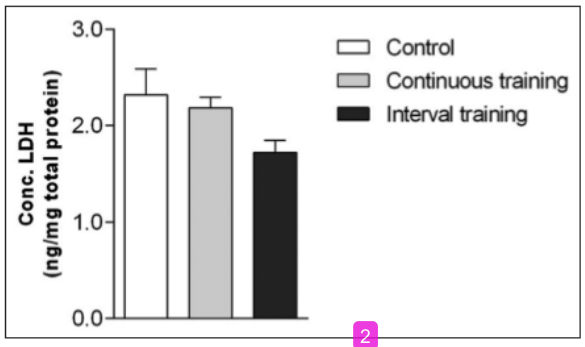

Figure 2: Lactate dehydrogenase B levels after 8 weeks of treatment. Data mean standard error, $P > 0.05$ (not significant)

the heart to use energy through aerobic fatty acid oxidation. An increase in AMPK during muscle contraction will reduce malonyl-CoA formation and accelerate fatty acid oxidation because resistance to carnitine palmitoyltransferase 1 does not occur.[13,14] Oxidation and uptake of fatty acid were higher with 60 min of exercise than with 30 min of exercise,[15] and more fatty acid oxidation occurred during moderate exercise at 65% of $VO_{2,\ peak}$ than during exercise at 25% or 85% of $VO_{2,\ peak}$.[16] This is because cardiomyocytes have a high capacity for fatty acid oxidation and oxygen consumption. Overexpression of PGC-1α *in vivo* is associated with an increase in O_2 capacity and fatty acid oxidation.[2] Fatty acid oxidation will produce 60%–90% of energy needs in the heart.[14]

IT, consisting of short duration, high-intensity exercise, uses anaerobic metabolism to produce energy through glycolysis.[4] An increase in heart rate also gradually changes the supply of energy, with a shift to carbohydrate or blood glucose metabolism.[17] Therefore, IT with higher intensity and shorter duration can increase glucose oxidation.[5] In addition, PGC-1α mRNA expression during IT is only temporary, with a relatively short half-life (20 min) before undergoing ubiquitination and proteasome degradation.[5,12] PGC-1α will increase >10-fold within 4 h after the last training session and return to the baseline level within 24 h of recovery.[18] In this study, we measured PGC-1α levels more than 24 h after the last training session; this may account for the low level obtained with IT.

During exercise, energy requirements in skeletal muscle will increase rapidly through glycolysis and glycogenolysis, leading to lactate production. Lactate will be released into the circulation and accumulate if not taken up by tissue.[4,6] Lactate is a potential energy source in the heart.[14,19] Lactate derived from the skeletal muscle will be taken up by the heart by monocarboxylate transporter 1 into the mitochondria. Once inside the mitochondria, lactate will be converted to pyruvate by LDH B. Pyruvate will be oxidized by pyruvate dehydrogenase to acetyl CoA, which will enter the tricarboxylic acid cycle to produce energy.[7,8] LDH B is widely expressed in oxidative fibers, especially in the heart.[7-9] Normally, LDH is stored at low-levels in the tissue, but stimulation in the form of exercise can cause an increase in lactate catalyzed by LDH B.[6,20] Several studies have suggested that LDH B is a downstream target of PGC-1α induced by exercise in the skeletal muscle,[9] and heart muscle.[8] However, the mechanism is still unclear. Many factors influence enzyme activity, including the intensity and duration of exercise, subject fitness, and type of exercise.[10] Other studies found that extreme exercise can increase the risk of damage in heart myocytes, with high LDH levels detectable in plasma and heart tissue.[20]

In this study, LDH B levels in both CT and IT groups were lower than those in controls. Levels of LDH B were higher in the CT group than in the IT group. It was thought that the supply of energy from fatty acids predominated during CT, with the use of lactate as an energy source less than that in IT, due to low lactate production. Continuous prolonged exercise can suppress oxidation of glucose and reduce lactate oxidation.[21] However, in IT, higher intensity exercise will cause anaerobic glycolysis in the skeletal muscles, which increases blood lactate accumulation. However, in the rest period between exercise bouts, this lactate can be taken up by tissue to be oxidized, contributing to increased lactate clearance (minimal with a 30 s rest). Furthermore, IT can increase the activity of LDH,[6] which may cause increased use of LDH B, leading to a decrease of LDH B in tissue. In CT, the levels of PGC-1α and LDH B are higher than those in IT during energy metabolism in the heart tissue. However, the mechanism is still unclear, and further research is needed.

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Conflicts of interest

There are no conflicts of interest.

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