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Research article

Comparison of lactate threshold, glucose, and insulin levels between OLETF and LETO rats after all-out exercise

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Abstract

Otsuka Long-Evans Tokushima Fatty (OLETF) rats are an animal model for obesity and Non Insulin Dependent Diabetes Mellitus by hyperphagia. The lactate threshold (LT) is used to determinate aerobic capacity and exercise intensity in individuals. The purpose of this study was to determine whether velocity at the LT (V_{LT}), glucose, and insulin levels of OLETF differs from Long-Evans Tokushima (LETO) rats after all-out exercise on treadmill running. In the results, we found that V_{LT} level of OLETF rats (17.8 ± 1.39 $m \cdot min^{-1}$) was significantly lower than that of the LETO rats (20.5 ± 1.33 $m \cdot min^{-1}$). The blood glucose levels immediately after all-out exercise increased in OLETF (from 7.23 ± 0.36 to 9.38 ± 1.77 $mmol \cdot L^{-1}$) and decreased in LETO rats (from 6.36 ± 0.27 to 4.42 ± 0.71 $mmol \cdot L^{-1}$), and the insulin level was decreased in both the OLETF (from 34.4 ± 7.7 to 20.13 ± 8.63 $\mu U \cdot ml^{-1}$) and LETO (from 15.29 ± 2.6 to 5.72 ± 1.49 $\mu U \cdot ml^{-1}$) rats immediately after the all-out exercise, but the difference was not significant. Our results suggest that the different V_{LT}, blood glucose and insulin levels should be considered to compensate for the differences between the OLETF and LETO rats. Moreover, the V_{LT} will be a useful reference for the future studies on exercise training of OLETF rats.

Key words: NIDDM; OLETF, treadmill running, all-out exercise, lactate, velocity of lactate threshold.

Introduction

It is well known that animals including humans with obesity and diabetic mellitus have decreased aerobic exercise capacity (Kjaer et al., 1990). Such individuals require exercise prescription with proper exercise intensity compared to healthy individuals (ACSM, 1997). The reason is that although the absolute intensity is the same, the relative intensity is different depending on the individual.

Physical training has been established as an important prevention strategy and treatment against pathology (Ivy et al., 1999). It improves glycemic control, decreases the atherogenic lipidic profile, and reduces weight, abdominal obesity and cardiovascular risk. It also improves the mood and self-esteem and relieves emotional stress (ACSM, 1997). Among the parameters to be considered in the exercise program for its own pathological conditions, the exercise intensity has received special attention. The lactate threshold (LT) is highly specific to exercise performance (Carvalho et al., 2005). Running increases metabolic demands more than at the resting state which is further enhanced when the running velocity exceeds above the LT. The LT is a point during exhaustive, all-out exercise at which lactic acid builds up in the blood stream faster than the body can remove it. The rate at which the body can remove the lactate is overwhelmed by the production and accumulation in the working skeletal muscles (Wasserman et al., 1973). At this stage, hormonal and sympathetic nervous system including various stress responses are activated to meet the increased physical demands (Farrell et al., 1983; Soya 2001). Such changes indicate that LT is an important factor for correct interpretation of exercise effects. The LT is a useful measure for deciding exercise intensity for training, and can be increased greatly with training. Training in LT is a popular method of improving high intensity endurance performance. The accumulation in the blood lactate observed during a graduated exercise test is usually interpreted as indicative of increased participation of the anaerobic metabolism as the energy source (Simoes et al., 1999). Lactate is a by-product of the anaerobic energy pathway, a process which provides energy to muscles by partially breaking down glucose without the need for oxygen.

However, although numerous studies have been performed to identify the effects of exercise training on diabetic models, most of the studies did not consider the different exercise capacity such as forced treadmill running velocity between diabetic and control rats. Almost all literatures on exercise with diabetic models performed running exercise at the same treadmill velocity between the models and controls. That is, there are only a few articles which applied or considered relative velocity between the groups. It is important that exercise capacities like LT differ according to the animal's strain. Therefore, when an exercise training study is performed using animals of different strains, the exercise intensity should be considered and the results should be interpreted accordingly.

Otsuka Long-Evans Tokushima Fatty (OLETF) rats are a commonly studied animal model for obesity and Non Insulin Dependent Diabetes Mellitus (NIDDM). The OLETF rats are hyperphagic consuming roughly 30-40% more than Long-Evans Tokushima (LETO) controls when they become 20 weeks old (Kawano et al., 1994). Both male and female OLETF rats become obese demonstrating different weight trajectories compared to LETO rats (Mori et al., 1996). However, the OLETF rats show a

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sexual difference in the incidence of diabetes mellitus; by 24 weeks of age, the disease has developed in more than 90% of the males, whereas the blood glucose level is still normal in most females (Shi et al., 1994). The plasma glucose levels following oral glucose loads are elevated as early as eight weeks and by 24 weeks the male OLETF rats are hyperglycaemic and hyperinsulinaemic (Kawano et al., 1992). Usually, the NIDDM rats have inappropriate metabolic potentials because of the insulin-stimulated and glucose uptake disorder.

The OLETF rats become spontaneously obese and NIDDM with the hyperphagia expressed as a significant increase in the size of meals due to the lack of cholecystokinin-1 (CCK-1) receptors followed by development of hyperlipidemia, fatty liver, and diabetes (Kawano et al., 1994). CCK-1 inhibits food intake by reducing the meal size (Moran et al., 1998). The OLETF rat model is similar to human with NIDDM due to obesity. Because exercise is known to be effective in preventing or improving insulin resistance and impaired glucose tolerance of NIDDM (Greenberg and McDaniel, 2002; Bassuk and Manson, 2005), the OLETF rats have been often used to investigate positive effects on physiological or biochemical factors on exercise, for example, improvement of lipid profile such as glucose, insulin, total cholesterol, triglyceride and leptin, changes of appetite regulating factors in brain hypothalamus and hepatic fatty acid oxidation (Miyasaka et al., 2003; Bi et al., 2005). However, as far as we know, no one has identified the LT level of the OLETF rats on the treadmill which is a criterion of running velocity for set exercise intensity. Until now, all the studies on exercise effects using OLETF rats adopted wheel running as spontaneous exercise method. There is no study performed using treadmill running as forced exercise method. Thus, in the present study the LT level of the OLETF rats was identified through the forced treadmill running.

The purpose of this study was to determine whether the gradual incremental increase in running velocity alters the pattern of lactate and LT levels in OLETF and LETO rats and how glucose and insulin levels change immediately after all-out running exercise.

Methods

Experimental animals

Thirty week old male OLETF (n = 8) and LETO (n = 6) rats were housed in group cages illuminated from 07:00 to 19:00 (12:12-h cycle) with room temperature varied from 21 to 23°C. During the entire experimental period, the animals received commercial chow for rodents and water *ad libitum*. All rats were housed at laboratory conditions for 3 weeks. All procedures were performed in accordance with the Institutional Guidelines for Animal Care at the National Institutes of Health *Guidelines for the Care and Use of Laboratory Animals.* The use of animals was received and approved by the animal care review committee at the Korea University.

Treadmill running habituation

The protocols of the habituation and the exercise test were the same as in a previous study (Soya et al., 2007). Briefly, rats were initially acclimated to run 5 days/wk for 2 wks with a graded increase in velocity (from 10 to 25 m/min) for 30 min on the treadmill for adaptation.

Surgery

Before treadmill running habituation, the rats were anesthetized with zoletil 50 (10 mg/kg, i.p.; Vibac Laboratories, Carros, France) for surgery. For the blood analysis of lactate and glucose, a silicone catheter was inserted into the jugular vein and fixed by a 35 mm silk thread. The exteriorized distal end of the catheter was fixed at the animal's nape as described in a previous study (Chang et al., 2007).

Experimental procedures and exercise protocol

Three days after surgery, the rats were kept individually in their cages until the start of the running tests for full recovery. Then, we sought to determine whether LT was significantly different between OLETF and LETO rats using treadmill running exercise. Two hours before the experiment, the rats were fasted by removing chow to minimize the glucose effect from consumption just prior to the measurement. In the experiment, both OLETF and LETO rats with the same increasing velocity (initial velocity was 5m/min and 2.5m/min increase every 3 min) at 0% grade until their all-out exercise.

Measurement of blood lactate, glucose, and insulin levels

Lactate levels (1500 STAT PLUS, YSI Inc.) were determined from whole blood samples with glucose (Accu-Chek, Germany) by blood obtained before, during and immediately after exercise (maximum blood lactate level) on the treadmill. At least 30 µL of blood sample was taken from the jugular vein catheter 30 seconds before increasing treadmill velocity to measure blood lactate and glucose levels. For plasma insulin measurement at rest and all-out exercise, at least 200 µL of blood sample was taken prior to start of exercise and immediately after all-out exercise on the treadmill. The samples were processed by centrifugation at 4□ at 10,000g for 10 min, and the plasma was extracted and stored at -80□ before analysis. Plasma insulin levels were determined by radioimmuno assay (Rat insulin kit, Linco Research Inc., USA).

Calculation of LT and HOMA-IR levels

The velocity at the LT (V_{LT}) was determined from the non-liner increase in blood lactate levels vs. running velocity using modified regression analysis (Green et al., 1983; Beaver et al., 1985). HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) in rest and immediately after all-out exercise was calculated using the following formula: HOMA-IR = insulin ($\mu U \cdot ml^{-1}$)×glucose ($mmol \cdot L^{-1}$)/ 22.5

Statistical analysis

All the data were represented as mean ± standard error of the mean (SEM). The body weight and V_{LT} were analyzed by student's t-test. The other factors (glucose, lactate, insulin, HOMA-IR) were analyzed by a 2 × 2 ANOVA with repeated measures and a student's t-test about difference between OLETF and LETO rats only in rest using SPSS 15.0 statistical package. The statistical significance was accepted at the level of $p < 0.05$.

Results

Body weight, blood glucose, insulin and HOMA-IR levels

The data of blood glucose, insulin and HOMA-IR levels while the rats were doing the incremental treadmill running are shown in Figure 1.

The body weight was significantly heavier in OLETF (498.1 ± 15.7 g) than in LETO rats (453.8 ± 9.7 g) ($p < 0.05$). The OLETF rats (7.23 ± 0.36 mmol·L^{-1}) developed hyperglycemia compared to LETO rats (6.36 ± 0.27 mmol·L^{-1}), but it was not significant. The blood glucose levels immediately after all-out exercise increased in OLETF (from 7.23 ± 0.36 to 9.38 ± 1.77 mmol·L^{-1}) and decreased in LETO rats (from 6.36 ± 0.27 to 4.42 ± 0.71 mmol·L^{-1}). The changes of the glucose levels from rest to all-out exercise showed significant difference between OLETF and LETO rats ($p = 0.013$). The resting insulin levels were significantly higher in the OLETF (34.4 ± 7.7 µU·ml^{-1}) than in LETO (15.29 ± 2.6 µU·ml^{-1}) rats ($p = 0.009$). The insulin level was decreased in both the OLETF (20.13 ± 8.63 µU·ml^{-1}) and LETO (5.72 ± 1.49 µU·ml^{-1}) rats immediately after the all-out exercise, but the difference was not significant. The resting HOMA-IR was significantly higher in the OLETF (10.38 ± 2.04) than LETO (4.31 ± 0.77) rats ($p = 0.031$). The HOMA-IR levels changed in both the OLETF (11.3 ± 5.65) and LETO (1.34 ± 0.56) rats immediately after all-out exercise, but the difference was not significant.

Blood lactate levels and V_{LT}

The blood lactate levels of the resting state were 1.58 ± 0.17 in OLETF and 0.95 ± 0.1 mmol·L^{-1} in LETO rats (Figure 2). The maximum blood lactate levels were significantly elevated in both OLETF (4.4 ± 0.43 mmol·L^{-1}) and LETO (5.87 ± 0.23 mmol·L^{-1}L) rats. The changes of the blood lactate levels from rest to all-out exercise showed significant difference between OLETF and LETO rats ($F=16.397$, $p=0.02$). The major finding of current study demonstrated that the V_{LT} of OLETF (17.8 ± 1.39 m·min^{-1}) was significantly lower than that of LETO (20.5 ± 1.33 m·min^{-1}) rats (Figure 3B).

Discussion

The OLETF rat is an animal model with mild obesity and NIDDM caused by an absence of food intake inhibition due to a lack of functional CCK-1 receptors (Miyasaka et al., 1994; Takiguchi et al., 1998), impaired insulin sensitivity, and increased resistance to insulin (DeFronzo et al., 1992). Accordingly, such rats overeat (Moran et al., 1998) and have decreased responsiveness to ingested fats (Schwartz et al., 1999). In addition, the rats with decreased physical activity favor their weight gain (Sei et al., 1999). The male OLETF rats usually begin showing diabetic symptoms and insulin resistance when they become 20 weeks old (Kawano et al., 1994), and spontaneously develop NIDDM after 25-30 weeks of age (Mori et al., 1996). The OLETF rats used in this study were 30 weeks old which had already passed the onset of diabetic mellitus and they were significantly heavier (8.9%) than the LETO rats.

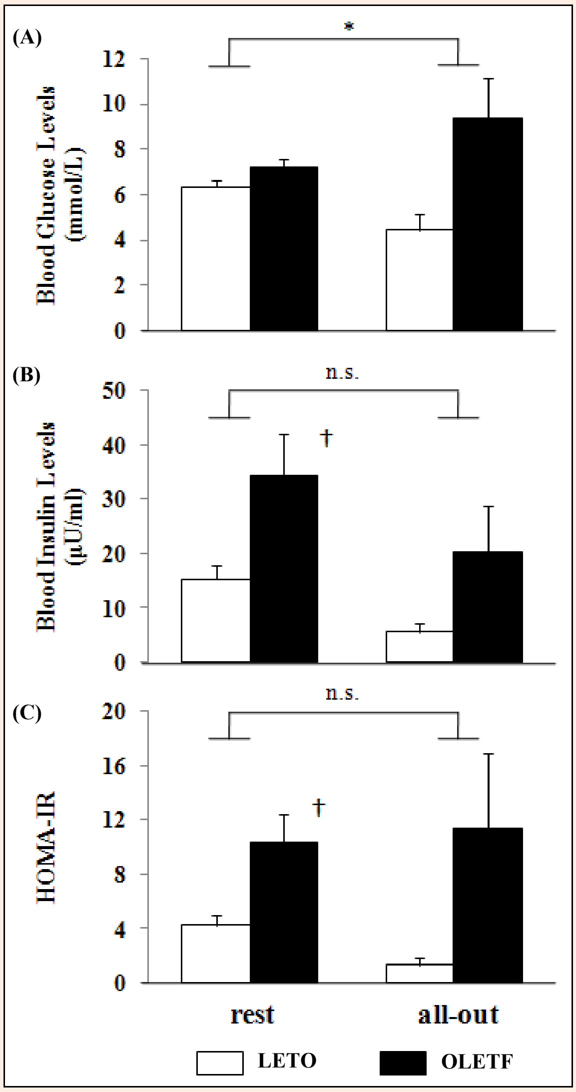

Figure 1. Change of (A) blood glucose, (B) blood insulin, (C) HOMA-IR levels from rest to immediately after all-out exercise in OLETF (n = 8) and LETO (n=6) rats. Each rat ran with incremental running velocity by every 3 minutes until all-out condition. Immediately after all-out condition, blood samples were collected from fixed catheter of nape and treadmill exercise was stopped. Values represent mean ± SEM. * significant difference between groups ($p < 0.05$). † significant difference between resting OLETF vs. resting LETO rats using *student's t-test* ($p < 0.05$).

In our investigation, the resting blood glucose level of OLETF was higher than that of LETO rats, although it was not significant. The reason for such result is assumed to be due to a mildly elevated rest glucose level in LETO rats. Although we could not confirm the glucose sensitivity of the two groups using the glucose tolerance test, the results immediately after all-out showed significantly increased and decreased glucose levels in diabetic and control models respectively, indicating that the rats used in the study were indeed diabetic and control models (Fig

1A). Such changes in glucose levels during exercise in normal subjects have been well established in both humans and animals (Kjaer et al., 1990). The glucose utilization as fuel increases in response to all-out running exercise (Holloszy et al., 1996). However, the OLETF skeletal muscle is not likely to be able to use blood glucose as a fuel effectively due to impaired insulin-mediated glucose disposal. According to the literature, in general prolonged exercise in animals including humans with or without diabetes show gradual decrease in blood glucose levels in general (Bussau et al., 2007; Marliss and Vranic, 2002). However, blood glucose after a short-term supramaximal exercise increase in NIDDM patients (Kjaer et al., 1990). It is because the glucose transport activity enhanced during exercise persists immediately after exercise (Minuk et al., 1981). Noticeably, intensive exercise may increase the risk for a transient metabolic decompensation, which could be life threatening (i.e., acute hypoglycemia) (Szewieczek et al., 2007).

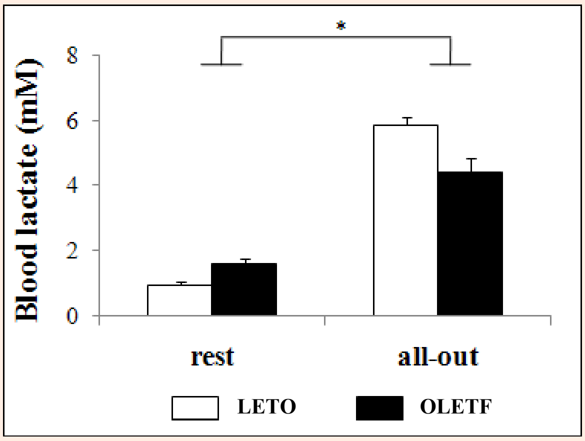

Figure 2. Comparison of blood lactate levels from rest to immediately after all-out exercise (maximum blood lactate levels) in OLETF (n = 8) and LETO (n = 6) rats. Each rat ran with incremental running velocity by every 3 minutes until all-out condition. Immediately after all-out condition, blood samples were collected from fixed catheter of nape and treadmill exercise stopped. Values are expressed as mean ± SEM. * significant difference between groups ($p < 0.05$).

The OLETF rats were severely hyperinsulinemic with resting plasma insulin concentration 2.2-fold higher than that of the LETO rats in our study (Figure 1B). Serum insulin level tends to decline during exercise (Galbo, 1977; Kjaer et al., 1990). Similar to many reports, insulin levels in this study also decreased in both OLETF and LETO rat immediately after all-out exercise. Interestingly, the insulin level in OLETF rats after all-out exercise was still 31.4% higher than that of the resting level in LETO rats indicating that OLETF rats maintained hyperinsulinemic condition even after all-out exercise.

HOMA-IR is an empirically developed mathematical formula based on the plasma glucose level and the plasma insulin levels that were developed as a surrogate measurement of *in vivo* insulin sensitivity (Matthews et al., 1985). Although statistically not significant, the HOMA-IR of LETO showed tendency to decrease (63.1 %) after all-out exercise which is contrary to the result of OLETF showing 8.0 % increase in HOMA-IR indicating no improvement in insulin sensitivity (Fig 1C). The reason for such large individual variability in the OLETF rats is assumed to be due to large individual variability of glucose and insulin levels immediately after all-out. Intense physical activity of all-out mode of exercise may have lead to large variations in blood glucose and insulin levels between the individual OLETF rats.

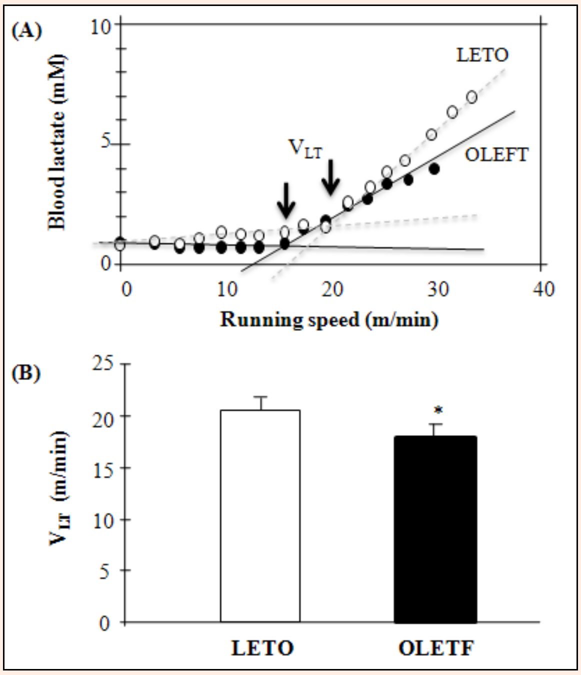

Figure 3. (A) A representative V_{LT} profile for OLETF and LETO rat is shown during an incremental running velocity protocol. The V_{LT} was determined from the non-linear increase in blood lactate levels vs. running speed using modified regression analysis. Each solid and dotted lines represent the LT velocities of OLETF (No. 2) and LETO rat (No. 11), respectively. (B) Comparison of V_{LT} between OLETF (n = 8) and LETO (n = 6) rats. Values are expressed as mean ± SEM. * $p < 0.05$.

As shown in Figure 2 and Figure 3A, the resting levels of blood lactate in OLETF were higher than that of LETO rats in accordance with other studies in which NIDDM patients were participated (Metz et al., 2005; Digirolamo et al., 1992). In contrast to the resting levels of blood lactate, the blood lactate levels immediately after all-out exercise (maximum blood lactate level) were lower in OLETF compared to LETO rats. In addition, the changes of the blood lactate levels from rest to immediately after all-out exercise showed significant difference between the OLETF and LETO rats ($F = 16.397$, $p = 0.002$). Lactate production accelerates as exercise becomes more intense and muscle cells can neither oxidize lactate at its rate of production nor meet any additional energy demands aerobically (McArdle et al., 1996). Generally, the higher the maximum blood lactate levels in humans and rats, the higher the aerobic capacity they have (McArdle et al., 1996). Therefore, our results suggest that the OLETF rats are likely to have lower aerobic capacity compared to the LETO rats.

This is the first study to determine V_{LT} from the treadmill running exercise in OLETF and LETO rats (Figure 3A and B). As represented by the solid and dotted LT velocity lines, the LT of level LETO rats consistently shows increased lactate levels from about 19 min compared to OLETF of about 16 min (Figure 3A). The point of acute lactate increase is delayed for those with better exercise capacity. Therefore, the difference in the point of acute lactate increase could be used to indicate the exercise capacity between the OLETF and LETO rats. Our results show that V_{LT} was lower in OLETF compared to LETO rats in similar to the results of maximum blood lactate levels. According to the study by Peterson et al (2008), different running velocities were applied to the rat models. In this study, the Zucker diabetic rats were allowed to run at lower running velocity (20 $m \cdot min^{-1}$) compared to the Zucker control rats (24 $m \cdot min^{-1}$) to compensate the differences in total workout due to the different body masses between the Zucker diabetic and control rats. However, criteria of aerobic capacity such as LT have not been considered appropriately when exercise intensity was applied. In general, not only intensity of exercise but also mode, frequency, and duration of exercise needs to be considered for the design of exercise studies. Additionally, when it comes to set exercise intensity, it is important to measure aerobic capacity such as LT, VO_2max or heart rate. Since the V_{LT} acquired through our study is a criterion for aerobic capacity of OLETF and LETO rats, the result of low V_{LT} in the OLETF compared to LETO rats implies that the application of relatively low exercise intensity is suitable for OLETF rats.

Conclusion

Our results suggest that different treadmill velocity should be used to apply relatively the same exercise intensity, and the different V_{LT} should be recognized to compensate for the differences between the OLETF and LETO rats. We believe that the V_{LT} obtained through this study will be a useful reference for the future studies on exercise training of OLETF rats, thus researchers will be able to apply the relative exercise intensity to OLETF and LETO rats.

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Key points

- The V_{LT} of OLETF was significantly lower than that of LETO rats.
- The changes of the blood lactate levels from rest to all-out exercise showed significant difference between OLETF and LETO rats.
- The result of low V_{LT} in the OLETF compared to LETO rats implies that the application of relatively low exercise intensity is suitable for OLETF rats.
- The different V_{LT} should be recognized to compensate for the differences between the OLETF and LETO rats.

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