



Resistance High-Intensity Interval Training (HIIT) Improves Acute Gluconeogenesis from Lactate in Mice

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Abstract: High-intensity interval training (HIIT) markedly activates muscle anaerobic glycolysis and increases blood lactate. As the liver is a major organ for lactate clearance from the bloodstream, it might improve gluconeogenesis from lactate (NEO-lac) after a period of resistance HIIT. NEO-lac was evaluated by *in situ* liver perfusion in mice subjected to a resistance HIIT for 4 (T4) or 8 (T8) weeks, or not trained (T0). Perfusion was carried out immediately after an incremental exercise session to test the acute NEO-lac. Muscle strength (expressed as relative maximum load) and blood lactate were higher in T4 than in T0, but NEO-lac did not differ, possibly because of energy discharge of the liver and substrate overload. After 8 weeks of HIIT (T8), both muscle strength and liver NEO-lac increased, but blood lactate did not. The resistance HIIT for 8 weeks modulated liver gluconeogenic efficiency and capacity, which are important mechanisms for the improved clearance of blood lactate.

Keywords: Lactate, Resistance HIIT, Mouse, Liver, Performance

1. Introduction

When there is an intense use of glucose as energy source, such as in high-intensity exercise, muscle pyruvate tends to build up because of saturation of the cyclic acid cycle. Under these circumstances, it is reduced to lactate, a reaction catalyzed by cytosolic enzyme lactate dehydrogenase (LDH). Although the energy yield of this pathway, known as anaerobic glycolysis, is low, it represents a fast mean of replenishing ATP that does not depend on the complete oxidation of energy substrates (carbohydrates or fatty acids);

that is, it is an oxygen-independent pathway [1, 2]. In addition, the LDH reaction restores the NAD^+ needed for glycolysis to continue.

Blood lactate concentration depends on its turnover, its rates of addition to and removal from the bloodstream. These can vary according to the physiological circumstances, among which exercise [3]. Blood lactate is altered as a function of exercise type, duration and intensity; the level of training of the individual is influential as well [4]. Blood lactate is used for the assessment of aerobic capacity because it is a residual product of glycolysis that is easily measured and has a high correlation with exercise performance [5-8].

In general, the blood lactate of a subject increases exponentially from a certain exercise intensity, known as lactate threshold or anaerobic threshold [7]. In practical terms, this means that well-trained individuals have the anaerobic threshold at higher exercise intensities than less trained or sedentary subjects.

Constantly, but especially after an intense exercise session, lactate is again converted to glucose through gluconeogenesis (NEO-lac), which takes place primarily in the liver. Glucose can then be stored by the liver as glycogen or released to the bloodstream, from where it is taken up by skeletal muscles for immediate use or to replenish muscle glycogen [9]. Therefore, the liver is important for blood lactate removal and its conversion to glucose, so that NEO-lac can have a direct impact on the anaerobic threshold: the higher the rate of NEO-lac, the more intense an exercise must be to reach the anaerobic threshold.

High-Intensity Interval Training (HIIT) is characterized by repeated high-intensity, short-duration exercises intercalated with active recovery (low-intensity exercise) or rest. In aerobic protocols – which are more common – HIIT exercises reach heart rates above 80% the maximum, or oxygen consumption above 85% the VO_{2peak} [10-12]. HIIT is effective in improving performance and physical conditioning, cardiovascular health and in modifying the muscle energy metabolism. Because it is a high-intensity training, HIIT is reported to provide these improvements after shorter training periods compared with conventional training protocols [10, 11, 13-15].

HIIT demands that muscle energy production is complemented by the anaerobic glycolytic system, resulting in increased lactate production by the muscle [16, 17]. As training progresses, blood lactate after each training session raises less and less, which was attributed to several adaptations of muscle oxidative metabolism that would diminish lactate release during the exercise sessions [10, 17].

In parallel with this, an enhancement of liver NEO-lac may take place, with more efficient removal of blood lactate. Trainings such as HIIT, by repeatedly exposing the liver to a surge of blood lactate, could induce this organ to improve NEO-lac. Therefore, both tissues (muscle and liver) must contribute to the reduced blood lactate after a period of HIIT and bring the anaerobic threshold to higher exercise intensities. Based on these assumptions, this work investigated acute alterations of the liver NEO-lac after a period of strength HIIT in Swiss mice. The hypothesis was tested that the training protocol devised for this investigation would enhance the liver efficiency and capacity of converting lactate to glucose, and that this can be demonstrated even immediately after an exercise session (that is, in an acute condition of increased blood lactate).

2. Methods

2.1. Animals and Experimental Groups

The procedures were approved by the Ethics Commission

on the Use of Animals (CEUA) of the State University of Maringá, Brazil (CEUA protocol 6388181017). Adult male Swiss mice weighting on average 30 g at the beginning of the experiments were supplied by the Central Animal House of the University and kept in individual plastic boxes with continuous and free supply of water and rodent chow in an environment of controlled temperature ($23\pm2^{\circ}\text{C}$) and photoperiod (12 h light/12 h dark).

Three days after their arrival, the mice were randomly assigned to 3 groups. Group T0 (n=10) was not trained (sedentary group); groups T4 (n=10) and T8 (n=10) were subjected to a resistance HIIT protocol for 4 and 8 weeks, respectively.

2.2. Familiarization and Training

Training was carried out employing a vertical stair for mice measuring 105 cm length, 8 cm wide and inclined 80%. At the top of the stair there was a 12 cm³ dark chamber for the animal to rest. The base of the stair was 10 cm distant from the floor to avoid contact of the animal's tail or the workload system with the ground [18]. The workload system was attached to the base of the tail with adhesive tape. Fishing sinkers were used as external loads.

During 3 alternate days, all the animals (groups T0, T4 and T8) were familiarized with the stair. Initially, the mouse was placed at the chamber at the top of the stair and, on the following trials, at sites progressively closer to the base of the stair, from where the animal could climb to the chamber [18, 19].

The maximum load (ML) incremental tests were carried out following a previously established protocol [18]. Each climbing corresponded to a series, separated by a 1-min rest. In the first test (week 1), the initial workload was of 90% body weight (bw). In the following weeks (weeks 2 through 8), the initial workload was 100% the ML of the previous week. The external workload was increased by 8 g at each series and the ML tests were ended when exhaustion was detected. This was defined as the moment when the mouse could no longer complete the climbing after 3 non-painful stimuli to the tail. These tests were repeated each week to adjust the training load (pre-training ML test, in the morning, with the mice at fed state; groups T4 and T8) and immediately before liver perfusion (pre-perfusion ML test, in the afternoon, with the mice fasted for 6 hours; groups T0, T4 and T8). The pre-perfusion ML test started with 90% bw (group T0), 100% ML of week 4 (group T4) and 100% ML of week 8 (group T8).

Training lasted for 4 or 8 weeks (groups T4 and T8, respectively). Two weekly sessions of resistance HIIT were made, in alternate days, in the early morning (soon after the lights of the animal house turned on), with the mice at fed state. Each session was divided in 3 rounds, each composed of uninterrupted series (climbings) until exhaustion. There was a 1-min rest between rounds. All the sessions were carried out with 90% of ML of the week, established during the pre-training ML test. This training protocol was devised by the authors.

2.3. In Situ Liver Perfusion

Liver perfusion was made immediately after the pre-perfusion ML test, after 6 h of fasting. The purpose of the pre-perfusion ML test was to cause a blood lactate surge in a metabolic state (fasting) that favors liver gluconeogenesis.

The mice were anesthetized (thionembutal 40 mg/kg bw after lidocaine 5 mg/kg bw, i.p.) and the abdominal viscera were exposed; the portal vein and the inferior cava vein were cannulated. A blood sample was quickly collected from the heart to determine lactate concentration (test-strips and portable Accutrend Plus® device, Roche Diagnostics, Mannheim, Germany).

The liver was perfused with Krebs-Henseleit buffer (KH, pH 7.4, 37°C, O₂/CO₂ 95/5%) in a non-recirculating system entering through the portal vein and exiting through the inferior cava vein. Immediately after the beginning of the perfusion, the diaphragm was sectioned for euthanasia. Samples of the effluent fluid were collected from the cava vein every 5 min soon after exsanguination of the liver. During the collection, the liver was sequentially perfused as follows: 10 min with KH buffer (basal perfusion), 120 min with KH+lactate (stimulated perfusion) in increasing concentrations (2 mM; 4 mM; 8 mM; 10 mM; 15 mM; 20 mM; 20 min each), 20 min with KH+adrenaline 1 µM (stimulated perfusion). The duration of each period of the perfusion was sufficient to stabilize glucose output [18] (PEREIRA *et al.*, 2019). With this sequential perfusion it was possible to assess gluconeogenesis from lactate (NEO-lac) and adrenaline-stimulated glycogenolysis on the same organ.

Glucose content on the effluent samples was determined through enzymatic-colorimetric method (commercial kit

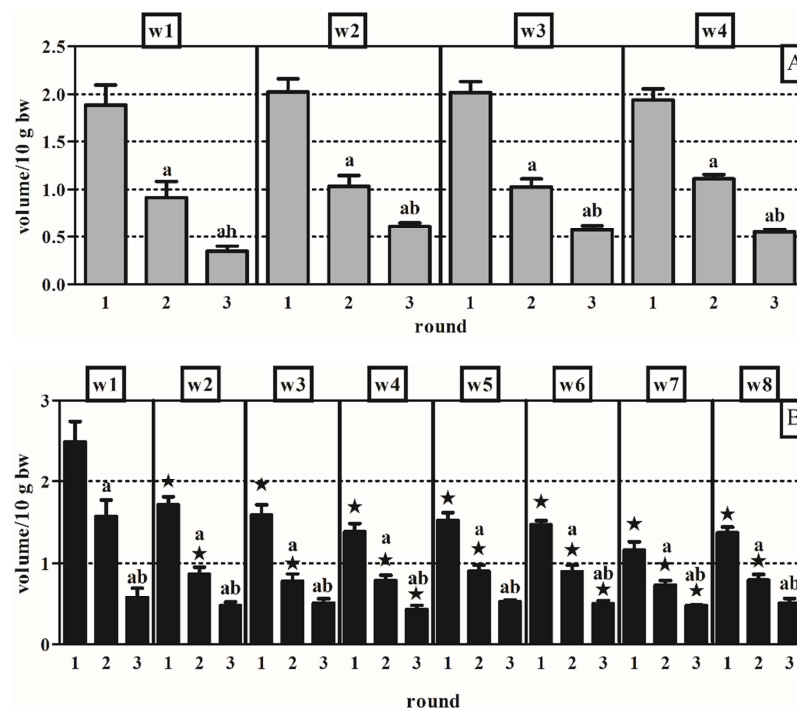
GoldAnalisa, Belo Horizonte, Brazil) and expressed as µmol/min per g liver. Glucose output at each period of the perfusion was expressed as area under curve (AUC, in µmol/g liver).

2.4. Statistical Analysis

Data sets were shown as mean±SEM of at least 8 repetitions and were subjected to the normality tests of Kolmogorov-Smirnov and Shapiro-Wilk. The experimental groups were compared through one-way ANOVA and Tukey *post-hoc* test. Data from the same group were compared with repeated measures ANOVA. The level of significance for all statistical comparisons was set at 5% ($p < 0.05$). Statistical analysis and graphs were made with the aid of Prism® 5.0 (GraphPad, San Diego, USA).

3. Results

In Figure 1 are shown the series of resistance HIIT that the animals of groups T4 (Figure 1A) and T8 (Figure 1B) completed on the vertical stair at each week of training. The series of each round of the 2 weekly sessions were summed and expressed relative to body weight. In both trained groups, the number of series (i.e., the training volume) decreased progressively from round 1 to round 3 ($p < 0.05$). There was no difference in training volume between corresponding rounds during the 4 weeks of training (T4, $p > 0.05$, Figure 1A). In group T8 (Figure 1B), the training volumes of the 3 rounds of week 1 were greater than those of the following weeks but did not change from week 2 through week 8 ($p > 0.05$).

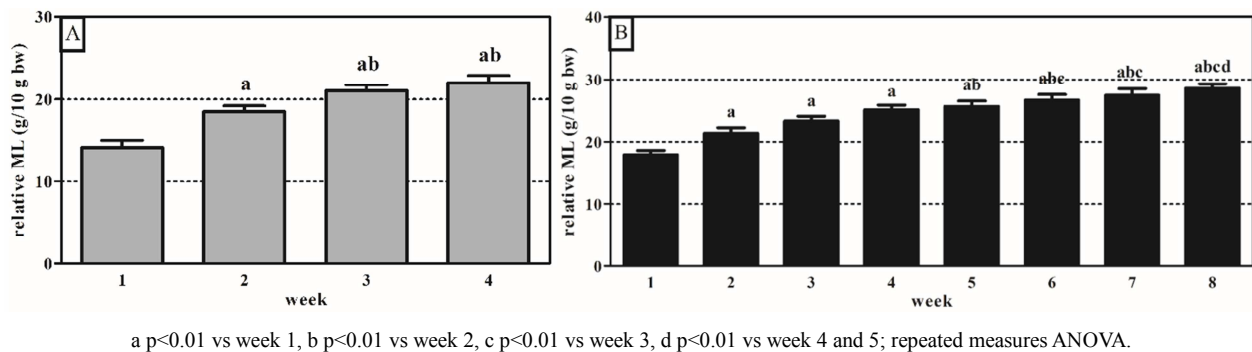


a $p < 0.01$ vs round 1, b $p < 0.01$ vs round 2, ★ $p < 0.01$ vs same round of week 1; repeated measures ANOVA.

Figure 1. Mean and SEM of the training volume of mice subjected to resistance HIIT for 4 weeks (group T4, $n=10$, A) or 8 weeks (groups T8, $n=10$, B). Each bar corresponds to the sum of the two training sessions of the week.

Figure 2 shows the relative ML of training of groups T4 (Figure 2A) and T8 (Figure 2B). In group T4, relative ML increased at weeks 2 and 3 ($p<0.05$ compared with the previous week). The relative ML of group T8 increased from week 1 to

week 2 ($p<0.05$), then stabilized until week 4 ($p>0.05$), and then increased progressively, so that ML was higher at weeks 5-8 compared with week 2, higher at weeks 6-8 than week 3, and finally higher at week 8 than weeks 4-5 ($p<0.05$).

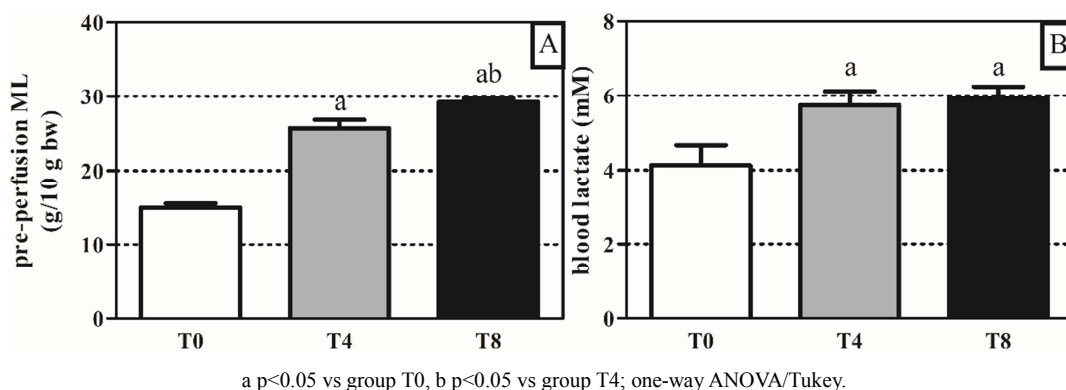


a $p<0.01$ vs week 1, b $p<0.01$ vs week 2, c $p<0.01$ vs week 3, d $p<0.01$ vs week 4 and 5; repeated measures ANOVA.

Figure 2. Mean and SEM of the relative ML of training of mice subjected to resistance HIIT for 4 weeks (group T4, $n=10$, A) or 8 weeks (group T8, $n=10$, B).

Figure 3A shows the performance of the animals of groups T0, T4 and T8 in the pre-perfusion ML test in terms of relative ML. In Figure 3B are the values of blood lactate immediately after the test, at the moment of liver perfusion. Group T0 had the lowest values of ML and lactate. In group

T4, pre-perfusion CM and lactate were significantly higher ($p<0.05$) than in group T0. The relative pre-perfusion ML of group T8 was even higher than in the other groups ($p<0.05$), while blood lactate did not differ from that of group T4 ($p>0.05$).



a $p<0.05$ vs group T0, b $p<0.05$ vs group T4; one-way ANOVA/Tukey.

Figure 3. Mean and SEM of the relative maximum load (ML) at the pre-perfusion ML test (A) and pre-perfusion blood lactate (B) of non-trained mice (T0, $n=10$) and mice subjected to resistance HIIT for 4 weeks (T4, $n=10$) or 8 weeks (T8, $n=10$).

Figure 4A illustrates the mean glucose output during *in situ* liver perfusion in the basal period (without the addition of compounds to the perfusion fluid) and the stimulated perfusion (with increasing concentrations of lactate and adrenaline). Figure 4B shows the corresponding AUCs of glucose output. In group T0, the mean glucose output was greater with 8 and 10 mM of lactate (6.6 and 7.3 $\mu\text{mol/g liver}$) ($p<0.05$) than with 2 mM (4.4 $\mu\text{mol/g liver}$) and was smaller with 20 mM (2.1 $\mu\text{mol/g liver}$) than with lower concentrations of the gluconeogenic precursor ($p<0.05$). In group T4, mean glucose output was smaller with 15 and 20 mM (3.4 and 0.9 $\mu\text{mol/g liver}$, respectively) ($p<0.05$), but did not differ for lactate concentrations of 2 to 10 mM (5.1 to 5.7 $\mu\text{mol/g liver}$) ($p>0.05$). In group T8, glucose output was greater with 4, 8 and 10 mM of lactate (12.1, 10.6 and 10.3 $\mu\text{mol/g liver}$) ($p<0.05$) and smaller with 20 mM (4.6 $\mu\text{mol/g liver}$) than with 2 mM (7.6 $\mu\text{mol/g liver}$) ($p<0.05$).

The comparison across the groups showed that during

basal perfusion glucose output was small and similar (1.8-2.2 $\mu\text{mol/g liver}$, $p>0.05$). Groups T0 and T4 did not differ ($p>0.05$) in AUC of glucose output at lactate concentrations between 2 and 10 mM. Glucose output of group T4 was smaller than T0 at lactate concentrations of 15 and 20 mM. At the end of the perfusion, when the liver was exposed to adrenaline, glucose output of groups T0 (0.3 $\mu\text{mol/g liver}$) and T4 (0.1 $\mu\text{mol/g liver}$) was similar ($p>0.05$).

At all lactate concentrations (2 to 20 mM, Figure 4B), glucose output was markedly greater in group T8 than in the other groups ($p<0.05$). Accordingly, the maximum glucose output was also larger ($p<0.05$) in this group (T0=7.1; T4=7.3; T8=12.1 $\mu\text{mol/g liver}$) and took place at a lactate concentration (4 mM in group T8) lower than in groups T0 (10 mM) and T4 (8 mM). At the end of the perfusion, adrenaline caused a glucose output significantly higher in group T8 (2.4 $\mu\text{mol/g liver}$) than in the other groups (0.1-0.3 $\mu\text{mol/g liver}$) ($p<0.05$).

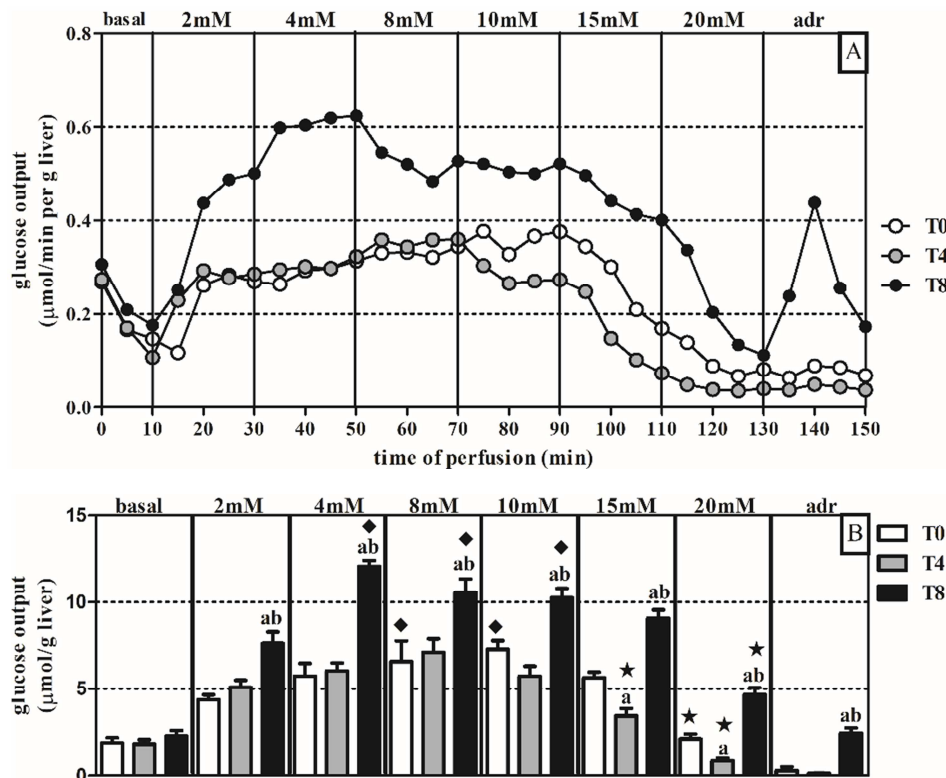


Figure 4. Mean glucose output (A) and mean and SEM of the AUCs of glucose output (B) during in situ liver perfusion of non-trained mice (T0, $n=8-10$) and mice subjected to resistance HIIT for 4 weeks (T4, $n=8-10$) or 8 weeks (T8, $n=8-10$).

a $p<0.01$ vs T0, b $p<0.01$ vs T4; one-way ANOVA/Tukey. ★ $p<0.01$ vs lower lactate concentrations within the same group, ◆ $p<0.01$ vs 2 mM within the same group; repeated measures ANOVA.

4. Discussion

The protocol of resistance HIIT devised for this investigation allowed the training of the mice based on individualized performances, as ML was recorded and applied to each animal. In addition, this resistance HIIT, similarly to other HIIT protocols employing aerobic exercises in humans and rodents [10, 11, 13-15], was effective in improving the performance of the trained mice: there was a progressive increase of the relative ML during the weeks of training in both groups: 55.5% in group T4 and 59.8% in group T8 relative to week 1, which was about 15 g/10 g bw.

These data on performance assure that the resistance HIIT was suitable to assess the major goal of this study: to evaluate if liver gluconeogenesis from lactate (NEO-lac) responds positively to a resistance high-intensity interval training or, in other words, whether this metabolic pathway can be modulated by this model of HIIT.

Glucose output during basal perfusion of the liver represents the release of glucose previously formed and/or stored in the hepatocytes. As the perfusion fluid is devoid of glucose, chemical gradient favors glucose exportation from the liver cells to the fluid [20, 21]. After 6 hours at post-prandial state, the endogenous stores of glycogen of the mice were, at least, decreased [21], so that a gluconeogenic

contribution for glucose output should be considerable. Certainly, taking into account the metabolic moment of the organism (intense anaerobic glycolysis in the muscles at the end of the pre-perfusion ML test), muscle lactate must have been an important substrate for this pathway.

When lactate perfusion began, the additional glucose output resulted of gluconeogenesis from the infused lactate (NEO-lac). Glucose output at almost all lactate concentrations was similar in groups T0 and T4; on the other hand, in group T8 glucose output at all lactate concentrations tested increased considerably.

Liver gluconeogenic efficiency is determined by glucose output at the physiological concentration of a given substrate; gluconeogenic capacity is defined as the glucose output at higher (saturating) concentrations of the substrate [22]. In resting rodents, blood lactate is around 2-3 mM [17, 22, 23], while that recorded immediately after the pre-perfusion ML test was at the range of 4-6 mM. Although 6 mM was not tested, the glucose output at 2, 4 and 8 mM of groups T0 and T4 indicates that the resistance HIIT for 4 weeks did not change the acute liver efficiency of NEO-lac, once glucose output was similar in the two groups at these lactate concentrations. The reduced liver capacity of NEO-lac in group T4 compared with T0 at lactate concentrations of 15 and 20 mM can be attributed to a lactate overload because of the higher relative ML of group T4 at the pre-perfusion test;

that is, it is likely that the liver of the T4 mice was energetically unloaded due to the intensity of the test few minutes before the perfusion [9]; together with the high exogenous infusion of lactate, this could have limiting consequences for the NEO-lac of the liver and, hence, for glucose output.

Lactate turnover by the liver was much better in group T8, as seen by the larger glucose output at all lactate concentrations in comparison with groups T0 and T4. This suggests that the resistance HIIT protocol employed in this investigation improved the liver efficiency and capacity of NEO-lac, as assessed by the larger glucose output both at physiological and saturating lactate concentrations.

As a bonus, the 8-week resistance HIIT also promoted a larger storage of glucose by the liver, as demonstrated by the increased glucose output in group T8 during the infusion of adrenaline. Being a glycogenolytic agent, adrenaline stimulates glycogen degradation and glucose release to the bloodstream [24]. The glycogen in the liver of the mice of group T8, even after 130 minutes of perfusion, was possibly synthesized indirectly from several precursors, but especially lactate [25], as this substrate was released at each training session, thus leading to the storage of the surplus glucose in the liver.

Adaptations of liver energy metabolism to training, mostly aerobic exercise, have been described, and include increased oxidative capacity, mitochondrial biogenesis, lipid oxidation and improved gluconeogenesis [9]. The present study adds the resistance HIIT as a promoter of liver adaptations important for the metabolization of lactate, the major byproduct of this type of exercise [16].

What is the relationship of the results obtained here with anaerobic threshold and performance? Although the relative ML of group T4 was higher than that of T0, it was matched by a higher blood lactate. It is as if these two groups were on the same curve of exercise intensity vs blood lactate, group T4 at a point ahead of group T0. Given that NEO-lac of group T4 did not differ from that of group T0, this would explain the higher blood lactate of group T4. This analysis contrasts with that of group T8, where the higher ML during the pre-perfusion test in comparison with group T4 was not matched by any additional increase of blood lactate. In parallel, the NEO-lac of this group (T8) was the largest at all lactate concentrations, and the improvement of this metabolic pathway very likely contributed to prevent the elevation of blood lactate despite the higher ML of group T8. In other words, by intensifying the conversion of lactate to glucose, the liver of group T8 kept blood lactate steady while muscle strength increased. This is precisely the expected relationship in an assessment of performance [7].

These results indicate that resistance HIIT for 8 weeks, in addition to its effects on physical performance, also conditions the energy metabolism of the liver, making it a more efficient gluconeogenic organ. Trained individuals need larger stores of muscle glucose, especially for high-intensity activities [7]. To accomplish this, the liver needs to be more prepared to metabolize the blood lactate (produced by

skeletal muscle during high-intensity exercise). The results of the present study show that this liver adaptation can be demonstrated even in an acute setting, in which the lactate surge in the bloodstream due to an incremental resistance test until exhaustion is followed by an intense NEO-lac. Therefore, liver energy metabolism is modulated by resistance HIIT as much as it is by other exercise modalities, and such modulation has a relevant role in the performance of this type of training.

5. Conclusion

The mice of the groups subjected to resistance HIIT had a significant gain of strength during the weeks of training. Liver gluconeogenesis from lactate immediately after an incremental resistance exercise session was enhanced after 8 weeks of resistance HIIT. Thus, it is possible to state that resistance HIIT improved the acute efficiency and capacity of the liver gluconeogenesis from lactate in Swiss mice.

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