SAÚDE E PESQUISA
e-ISSN 2176-9206

ORIGINAL ARTICLE

https://doi.org/10.17765/2176-9206.2025v18e13000

COMBINATION OF CALORIC RESTRICTION AND RESISTANCE TRAINING IN MALE SWISS MICE

COMBINAÇÃO DE RESTRIÇÃO CALÓRICA E TREINAMENTO RESISTIDO EM CAMUNDONGOS SWISS MACHOS

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Received: 29 July 2024
Accepted: 06 Mar. 2025

ABSTRACT: This study analyzed the biometric and biochemical effects of the combination of caloric restriction (CR) and high-intensity interval resistance training on vertical ladder in adult Swiss mice. The feeding regimen (free feeding, group ND; or 30% CR, group RD) lasted 12 weeks. Training took place in weeks from 5 to 12. Group RD had relative food ingestion, body weight, lipid profile and liver glucose metabolism lower than group ND. Adiposity, systemic glucose metabolism and training performance of group RD were not altered by CR combined with training.

KEYWORDS: Adiposity. Blood glucose. Carbohydrate metabolism. Liver.

RESUMO: Este estudo analisou os efeitos biométricos e bioquímicos da combinação entre restrição calórica (RC) e treinamento resistido intervalado de alta intensidade em escada vertical em camundongos Swiss adultos. A intervenção alimentar (alimento livre, grupo ND; ou RC de 30%, grupo RD) durou 12 semanas. O treinamento dos grupos ocorreu nas semanas 5 a 12. O grupo RD teve ingestão relativa de alimento, massa corporal, perfil lipídico e metabolismo hepático de glicose menores do que o grupo ND. A adiposidade, o metabolismo sistêmico de glicose e o desempenho do grupo RD no treinamento não foram alterados pela RC combinada ao treinamento.

PALAVRAS-CHAVE: Adiposidade. Fígado. Glicemia. Metabolismo dos carboidratos.

INTRODUCTION

Nutrients obtained from food are made available to tissues after intestinal absorption. Nerves, hormones and other signals direct the flux of macronutrients (carbohydrates, amino acids and lipids) in the organism: immediate use or storage. The extensive and adaptable control of these destinations has the primary purpose of maintaining physiologically adequate blood glucose concentrations. Glucose is a vital metabolite and major energy substrate for many cells, such as neurons and erythrocytes, while other tissues are more flexible, being able to use either glucose or fatty acids[1].

Two periods are distinguished in nutrient flux, together with their predominant hormonal control. The absorptive period comprises the prandial (ingestion) and post-prandial (digestion and absorption) phases. At this period, the nutrients added to the blood are immediately used as energy substrates or stored. Insulin is the major hormone responsible for the destination of macronutrients in diverse cell types. During the post-absorptive period, or fasting, the digestive system is empty, and the energy for cell and tissue functioning is supplied by the own reserves of the body. The so-called counterregulatory hormones, of which glucagon is the most important, redirect the metabolic routes of the post-absorptive period[2,3].

Superimposed on the regular metabolic shifts of the absorptive/post-absorptive cycle are special metabolic demands, either acute or chronic, that may be regarded as types of physiological stress. In this report, caloric restriction (CR) and physical exercise are highlighted[3-5]. They are characterized by redirected substrate fluxes through the metabolic pathways to assure an appropriate energy supply to the tissues and, particularly, to maintain blood glucose levels.

CR and exercise are encouraged – and their benefits constantly reported – in both eutrophic individuals and patients with overweight/obese-associated clinical conditions, such as glucose intolerance, insulin resistance, type 2 diabetes mellitus and hypertension[1,5,6]. These are some of the most common and debilitating in many human populations, demanding large investments by the public health services and the pharmaceutical industry.

In contrast, in the long run, CR and regular physical exercise evoke convergent and adaptive physiological responses that make up the basis of the health-promoting effects of these physiological stresses[3]. Just to illustrate the argument: a 2012 review[5] compiles the positive results of several investigations about CR and exercise, either alone or combined, in health and disease. Another article[4] explores the benefits of these interventions in the treatment of cardiometabolic diseases.

Programs of CR in humans and experimental animals typically decrease the ingested calories by 10-40% of what could be eaten freely, as long as disease and malnutrition are avoided[5,7,8]. Since the 1950s it has been demonstrated that, in different organisms, this level of chronic CR prolongs life expectancy and prevents against a wide spectrum of age-related physiological and pathological alterations[5,7]. CR is also a viable alternative against overweight and obesity; decreases abdominal adiposity; improves glucose metabolism by decreasing fasting blood glucose and increasing insulin sensitivity; improves the plasma lipid profile; and changes the body metabolic biochemistry[4,5,7,8].

As physiological stress, physical exercise triggers acute and chronic changes on the functioning of many tissues and organs, not only on the active skeletal muscles[15]. As a regular and structured activity (training), it has the purpose of improving health or performance in a given sport modality[4]. Although format, type, frequency, intensity and other features of physical exercise affect the magnitude of the responses, in general it protects against several metabolic disorders, improves cardiorespiratory conditioning, increases skeletal muscle mass and force, reduces visceral adiposity and the risk of its comorbidities[5,6].

For several years, the research group of the authors collected consistent observations of decreased growth and less visceral fat deposition in male and female Wistar rats subjected to CR, irrespective of CR duration (30-90 days), age of intervention (since lactation or after major body growth), CR degree (30-50%) or litter size (three, eight or 12 puppies)[9-14].

A protocol of high-intensity interval resistance training using vertical ladder was designed by this research group. In Swiss mice, it improved glucose metabolism by the liver, with larger glycogen stores and higher gluconeogenic capacity[16,17].

Despite these observations on CR in rats and high-intensity resistance training in mice, there was a gap that needed to be filled in concerning the combination of both interventions, as in humans[3,4]. This would set a framework from which modified formats of these interventions – for instance, different degrees of CR or other training protocols – could be tested. To that purpose, the research group has chosen male Swiss mice, which normally attain good training performance, but whose response to CR had not been assessed. Therefore, this investigation tested the combination of CR and resistance training on biometric and biochemical variables of young adult male Swiss mice, and it is part of the dissertation of the first author.

METHODOLOGY

ANIMALS

The procedures were approved by the Ethics Commission in the Use of Animals (CEUA, certificate 7332010321) and followed the guidelines of the National Council of Animal Experimentation (CONCEA-Brazil).

Male adult Swiss mice aging seven weeks and averaging 25 g body weight were placed in individual plastic boxes with wood shavings bedding and continuous supply of water. The room had controlled temperature (23±2 ºC) and light/dark cycles of 12 h/12 h. Seven days of acclimation were allowed before any intervention.

The following experimental groups were settled (n=20-23 per group): ND (normal diet), mice fed freely with standard rodent chow, and RD (restricted diet), mice given 30% less food than their ND pairs of the same age. The chow ingested by group ND was recorded daily by subtracting the remaining amount from that supplied 24 hours earlier. The feeding regimen of groups ND and RD was maintained for four weeks (weeks 1 to 4 of the experimental period) before training and during the eight weeks of training (weeks 5 to 12 of the experimental period).

Body weight was recorded once a week. Before each experiment, the mice were deprived of food for 14 hours (18:00-08:00, overnight), and the experiments were carried out the next morning. Half the mice of each group were destined for *in vivo* tests and tissue removal; the other half was used for *in situ* liver perfusion.

TRAINING

The habituation, maximal load tests and training of the ND and RD mice were conducted on a vertical ladder designed for mice. The fishing sinkers used as load were placed in a plastic tube fixed at the base of the animal's tail. The protocols followed those of Muller et al[16,17].

Habituation to the ladder consisted of three climbing trials, without load, during the week preceding the training period (week 4). Before each trial the animals were left free to explore the ladder and climb to the resting chamber on the top.

The ND and RD mice were 12 weeks old when training began. During the training weeks, on Mondays, the mice were subjected to the maximal load incremental test to determine the load for the training sessions (Figure 1A). In the first test (week 5 of the experimental period, week 1 of training), the animals climbed the ladder with 90% body weight as initial load (first trial). After each successful trial, the animals had a one-minute rest, the load was increased (eight grams each trial), and a new climbing trial was made. This was repeated until exhaustion, when the animal was incapable of climbing the ladder after innocuous stimulation. The maximal load was the highest load (in g) carried for the whole length of the ladder. From the second training week onwards, the initial load of the test was 100% maximal load of the previous week.

Two sessions per week of high-intensity resistance training were carried out, on Wednesdays and Fridays. Each session had three rounds, each one composed of complete climbing trials until exhaustion; there was a one-minute interval between rounds, and all were carried out with 90% maximal load of the week (Figure 1B).

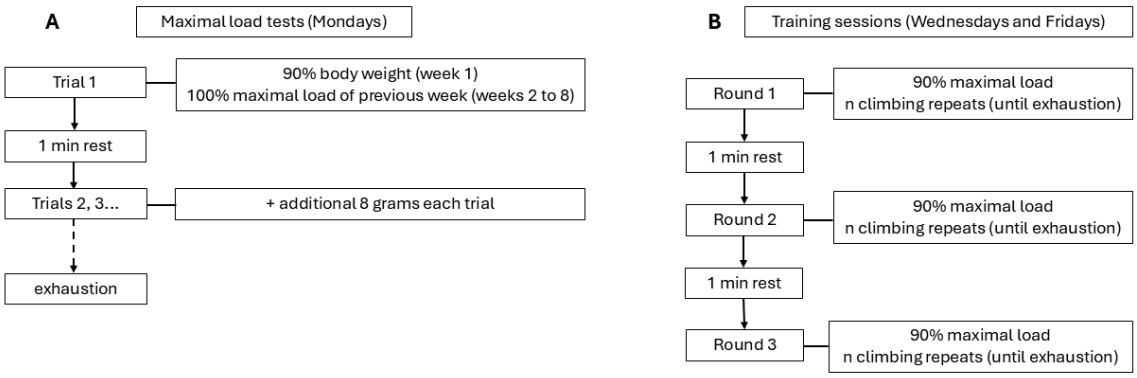

Figure 1. Schematic diagram of the interval resistance training protocol of male Swiss mice from groups ND and RD. (A) Maximal load test. (B) Training sessions.

IN VIVO TESTS

The mice were given oral glucose (1.5 g/kg diluted in water) for the glucose tolerance test (GTT). Blood samples were collected from a puncture at the tip of the tail at 0, 5, 10, 15, 20, 25, 30, 45 and 60 minutes after the gavage, time zero (0) being immediately before glucose administration. Blood glucose was determined with test strips and glucometer Optium Exceed® (Abbott, Brazil). After the test, the animals were returned to their boxes and refed. The total variation of blood glucose during the 60 minutes of the test was calculated as area under curve (AUC) using as baseline the blood glucose of each animal at time zero.

The insulin tolerance test (ITT) was performed 48 hours after the GTT. The mice were intraperitoneally injected with Novolin® (Novo Nordisk, Brazil) regular insulin (1 IU/kg) diluted in saline. Blood samples were collected at times 0, 5, 10, 15, 20, 25 and 30 minutes, time zero being the moment immediately before insulin injection; glucose was determined as before. After the test, the animals were returned to their boxes and refed. As blood glucose falls after insulin injection, the total variation of

blood glucose during the 30 minutes of the test was calculated as AUC using as baseline the blood glucose of each animal at 30 minutes.

TISSUE REMOVAL AND PLASMA BIOCHEMISTRY

Euthanasia was carried out 48 hours after the ITT through intraperitoneal injection of a lethal dose of anesthetic (lidocaine 5 mg/kg + thiopental 120 mg/kg). Visceral adipose tissue (retroperitoneal, mesenteric, periepididymal) and subcutaneous fat (inguinal) were entirely removed and weighed.

Blood was collected for biochemical determinations. Triglycerides, total cholesterol and HDL were determined (GoldAnalisa commercial kits, Brazil). The VLDL content was calculated as triglycerides/5 and the LDL content was given by total cholesterol – (HDL+VLDL)[18]. The atherogenic index was given as total cholesterol/HDL[19].

IN SITU LIVER PERFUSION

The mice were weighed and anesthetized with lidocaine 5 mg/kg + thiopental 40 mg/kg (intraperitoneal) and had their portal vein and cava vein below the liver canulated after laparotomy. Euthanasia occurred by hypovolemic chock and diaphragm sectioning.

The liver was perfused with Krebs-Henseleit (KH) buffer, pH 7.4, saturated with O_2/CO_2 (95%/5%) and warmed to 37 ºC before entering the liver through the portal vein.

After 20 minutes of stabilization for total removal of blood, samples of the effluent fluid were collected through the inferior cava vein each 5 minutes, the first being set as time zero. During the collection the liver was perfused for 10 minutes with KH buffer (basal perfusion) and then with KH buffer containing sequentially lactate 4 mM, alanine 4 mM and adrenaline 1 µM for 20 minutes each (stimulated perfusion).

The output of glucose was determined by enzymatic-colorimetric method (GoldAnalisa). Glucose concentration, given as mg/dL, was converted to µmol/min per g liver.

STATISTICS

Data sets were subjected to Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Parametric data were compared by t test, and non-parametric by Mann-Whitney. The level of significance was set at 5% for all the comparisons.

Graphical data are shown as box and whiskers, where the box limits are the 25% and 75% percentiles, whiskers are the minimum and maximum values, and the horizontal line in the box is the mean. Statistical analyses and graph construction used Prism® version 5.0 (GraphPad, USA).

RESULTS

The amount of food ingested by the ND and RD mice is shown in Figure 2A in relative terms, that is, per 10 g body weight. As the 30% CR was calculated from the ingestion of age-matched ND animals, irrespective of body weight, the percent relative ingestion of the RD mice ranged from 13% to 45% less than the ND group during the eight weeks of training. Even so, the relative values were significantly lower in group RD than in group ND.

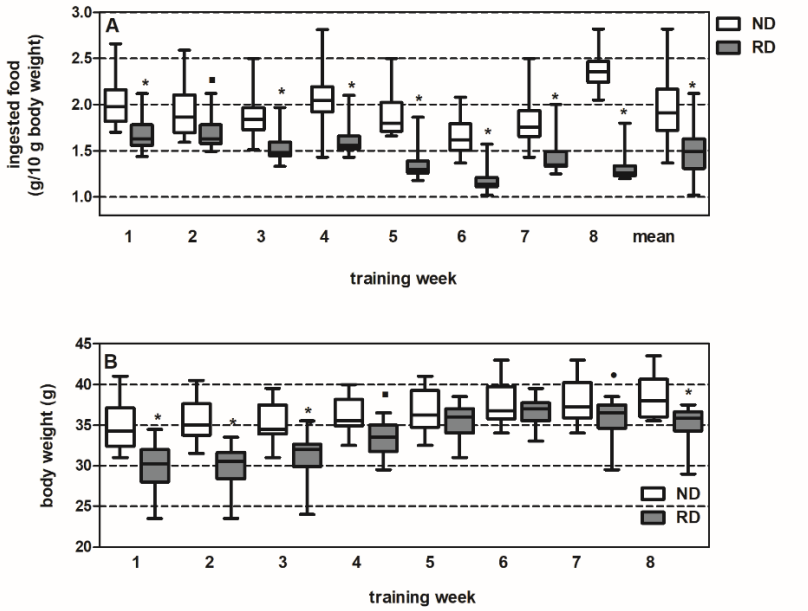

Figure 2. Relative food ingestion (A) and body weight (B) of male Swiss mice from groups ND and RD during eight weeks of interval resistance training. (A) *p<0.0001, ▪p<0.01, Mann-Whitney test. (B) *p<0.0001, ▪p<0.001, ●p<0.05, t test. Data shown as box and whiskers, n=18-22/group each week.

At the beginning of the feeding schedule (week 1 of the experimental period), the average weight of both groups was 30 g (data not shown). Body weight during the training period is shown in Figure 2B. From week 1 to week 12 of the experimental period, group ND gained 8.22±0.41 g and group RD gained significantly less weight – 2.05±0.37 g (mean±standard error, p<0.0001, t test). Except for weeks 5 and 6 of the training period, the RD mice weighed less than the ND group.

Figure 3A shows that the relative maximal load of group ND was higher than that of group RD at training weeks 1, 2, 5 and 6. Both groups had similar relative maximal loads at weeks 3, 4, 7 and 8. The maximal load of group ND increased on average 11.42 g/10 g body weight from week 1 to 8, while that of group RD increased on average 15.08 g/10 g body weight (p<0.0001 for both, paired t test).

RD mice made more climbing trials per week than the ND animals during the eight weeks of training (Figure 3B). The mean values of group ND ranged from 21.61 to 26.94, while those of group RD ranged from 29.45 to 48.70.

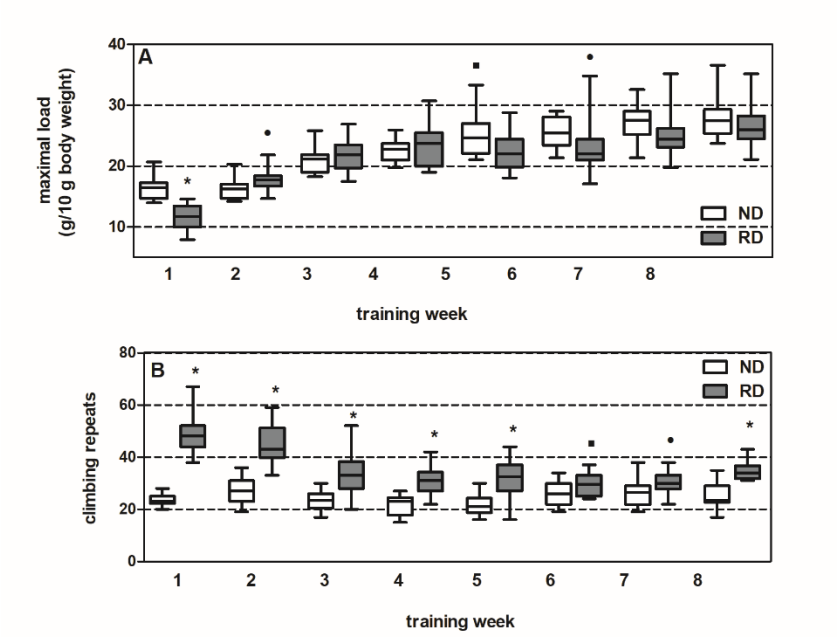

Figure 3. Relative maximal load (A) and climbing repeats (B) of male Swiss mice from groups ND and RD during eight weeks of interval resistance training. (A) and (B) *p<0.0001, ▪p<0.01, ●p<0.05, t test. Data shown as box and whiskers, n=18-22/group each week.

Figure 4A shows the relative weights of each fat pad (periepididymal, retroperitoneal, mesenteric and inguinal) and of the visceral fats together (periepididymal, retroperitoneal and mesenteric). Fat weights were not affected by the interventions, the per-weight values being similar in groups ND and RD. As for the plasma lipid profile (Figure 4B), cholesterol, triglycerides, VLDL and LDL were lower in group RD at the end of the 12-week experimental period.

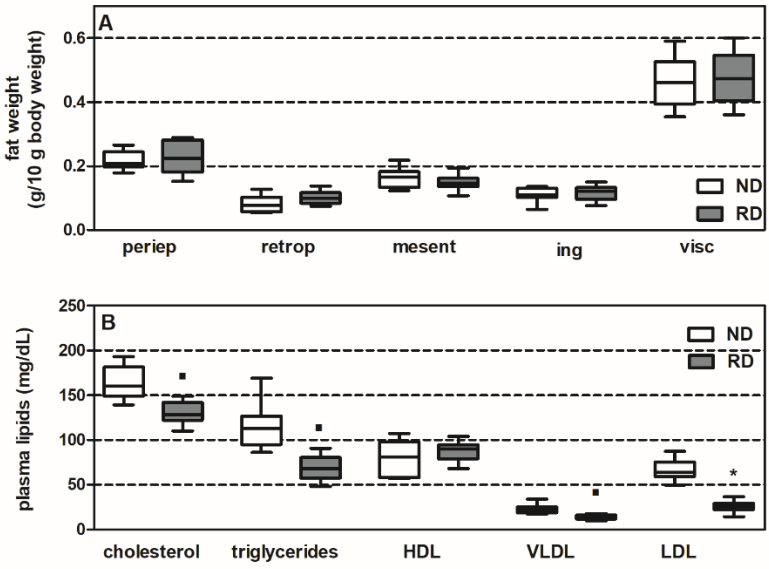

Figure 4. Relative fat weights (A) and lipid profile (B) of male Swiss mice from groups ND and RD after eight weeks of interval resistance training. (B) *p<0.0001, ▪p<0.001, t test. Data shown as box and whiskers, n=8-11/group at each data set.
periep: periepididymal fat, retrop: retroperitoneal fat, mesent: mesenteric fat, ing: inguinal fat, visc: visceral fat.

The atherogenic index was 2.18±0.16 in group ND (n=7) and 1.49±0.04 in group RD (n=11) (mean±standard error, p<0.0001, t test).

Figure 5 illustrates the results of the glucose (Figure 5A) and insulin (Figure 5B) tolerance tests. At time zero of the GTT (time course graph in Figure 5A), blood glucose was higher in group RD than in group ND, but they did not differ at the end of the test (time 60 minutes). Blood glucose variation during the test (shown as AUC on the right in Figure 5A) was not different between the groups. Blood glucose was on average 95.76 mg/dL higher at 60 minutes than at time zero in group ND and 46.8 mg/dL in group RD. The highest blood glucose was recorded at 20 minutes in group ND (276.3 mg/dL) and 45 minutes in group RD (239.9 mg/dL).

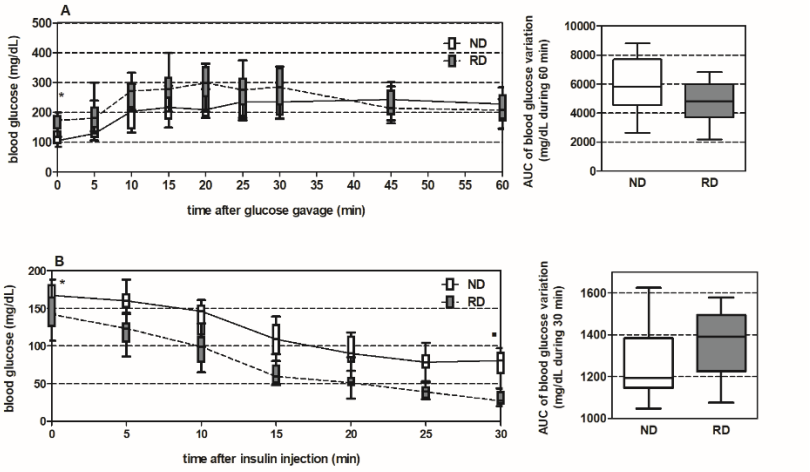

Figure 5. Glucose tolerance test (A) and insulin tolerance test (B) of male Swiss mice from groups ND and RD after eight weeks of interval resistance training. (A) *p<0.01, t test. (B) *p<0.05, ▪p<0.0001, t test. Data shown as box and whiskers, n=8-10/group at each time point.

At time zero of the ITT (time course graph in Figure 5B), blood glucose was higher in group ND than in RD and remained so until the end of the test (30 minutes). Despite the seemingly higher AUC of the ITT of group RD (on the right in Figure 5B), it was not statistically different from group ND. Blood glucose decayed by about 90.67 mg/dL in group ND and 113.6 mg/dL in group RD during the 30 minutes of the test.

Figure 6 brings the results of the *in situ* liver perfusion as peak glucose outputs. During perfusion with KH buffer (basal), lactate 4 mM and alanine 4 mM, the values of group RD were much lower than those of group ND, while they were similar with adrenaline 1 μM.

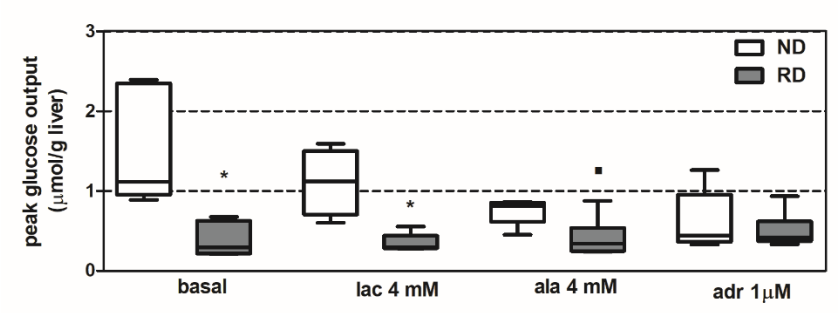

Figure 6. Peak glucose outputs during *in situ* liver perfusion of male Swiss mice from groups ND and RD after eight weeks of interval resistance training. *p<0.01, ▪p<0.05, Mann-Whitney test. Data shown as box and whiskers, n=5-7/group at each perfusion period.

DISCUSSION

This work combined caloric restriction (CR) and high-intensity resistance training in adult Swiss mice (group RD) to see whether biometric and biochemical parameters would be affected in comparison with age-matched freely fed trained mice (group ND). The following outcomes were recorded: body weight was decreased, but relative fat mass was preserved, in the RD mice; training performance was not impaired by CR; CR had a positive lowering effect on plasma lipids; systemic glucose metabolism was not affected by CR, but liver glucose metabolism was diminished.

The slight body weight gain of group RD (about 2 g) during the 12 weeks of the experimental period in comparison with that of group ND (about 8 g), together with the similarity of both groups in relative fat weight, might be directly related to the relative food ingestion of group RD. As the 30% CR was calculated from age-matched (not weight-matched) freely fed mice, it was smoothed by the smaller growth of the RD animals during the experimental period. This was probably decisive for the training performance of the RD group: its relative maximal load increased 15 g, while that of group ND increased 11 g. In addition, group RD made more climbing trials than group ND during all the eight weeks of training.

Decreased adiposity, especially of visceral fat, is often found in rodents, non-human primates and humans under CR and/or regular exercise[4,5,7,9,11,12,14,17,20]. It is possible that, designed as it was, CR arrested body growth as a whole, sparing fat from being more markedly decreased and preserving body composition in the RD mice. The lower levels of total cholesterol, triglycerides, VLDL, LDL and atherogenic index in group RD, as well as its unaffected adiposity, suggest that the metabolic processes of the mice had adapted to training under this restrictive nutritional condition with beneficial effects on plasma lipids. Similar reports were found in exercised humans[6].

The glucose and insulin tolerance tests are interrelated in the sense that they record the blood glucose variation in response to an acute overload of glucose or insulin, respectively, to assess whole-body glucose tolerance and insulin action[21,22]. These parameters were not affected in this study. Rodents and humans are often reported to improve glucose tolerance and insulin action after CR or regular physical exercise, but mostly when having overweight or excess adiposity – instances that compromise these metabolic indicators[23,24] – and that underwent CR or regular physical exercise aiming at the reversal of the negative outcomes of these conditions[5,7].

Glucose output during the basal period of the *in situ* liver perfusion represents residual glucose from intracellular stores; during perfusion with lactate or alanine, glucose is mostly derived from

gluconeogenesis from these substrates; and in the presence of adrenaline, glucose output comes from glycogenolysis[25-28].

Except for adrenaline, glucose output was lower in group RD than in ND, suggesting that CR decreased the storage of glycogen (the source of glucose during basal and adrenaline-stimulated perfusion) as well as the liver gluconeogenic capacity. However, as adrenaline-stimulated glucose output was similar in both groups, there is the possibility that some gluconeogenesis-derived glucose, instead of being released from the hepatocytes, was stored as glycogen through the indirect pathway of glycogen synthesis[25,26], which was later degraded by adrenaline stimulation.

The combination of CR and high-intensity interval training had surprising outcomes: the decreased food ingestion of the RD mice did not reduce adiposity or training performance, and liver glucose metabolism also responded differently from what was expected. Therefore, it is important to take into account the specific physiological, biochemical and biological aspects of the animal model under investigation, instead of taking findings from other models for granted. Once these initial aspects are known, additional information can be obtained, and complementary or modified interventions can be implemented.

CONCLUSION

High-intensity interval training had no compromising effects in mice under caloric restriction, and both interventions were successfully combined. However, liver glucose output was markedly reduced, an observation that should be considered when liver glucose metabolism is targeted.

ACKNOWLEDGEMENTS

The authors thank CAPES for the scholarship of the co-author – Finance Code 001, the Program of Graduate Studies in Physiological Sciences and the Department of Physiological Sciences for their infrastructural and administrative support. They also thank the technical contribution of V.S.R. Carrascoza and M. Fabricio

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