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ORIGINAL CONTRIBUTION

Short-term moderate exercise provides long-lasting protective effects against metabolic dysfunction in rats fed a high-fat diet

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Abstract
Introduction A sedentary lifestyle and high-fat feeding are risk factors for cardiometabolic disorders. This study determined whether moderate exercise training prevents the cardiometabolic changes induced by a high-fat diet (HFD).
Materials and methods Sixty-day-old rats were subjected to moderate exercise three times a week for 30 days. After that, trained rats received a HFD (EXE-HFD) or a commercial normal diet (EXE-NFD) for 30 more days. Sedentary animals also received the diets (SED-HFD and SED-NFD). Food intake and body weight were measured weekly. After 120 days of life, analyses were performed. Data were analysed with two-way ANOVA and the Tukey post-test.
Results Body weight gain induced by HFD was attenuated in trained animals. HFD reduced food intake by approximately 30 % and increased body fat stores by approximately 75 %. Exercise attenuated 80 % of the increase in fat pads and increased 24 % of soleus muscle mass in NFD animals. HFD induced a hyper-response to glucose injection, and exercise attenuated this response by 50 %. Blood pressure was increased by HFD, and the beneficial effect of exercise in reducing blood pressure was inhibited by HFD. HFD increased vagal activity by 65 % in SED-HFD compared with SED-NFD rats, and exercise blocked this increase. HFD reduced sympathetic activity and inhibited the beneficial effect of exercise on ameliorating sympathetic activity.
Conclusion Four weeks of moderate exercise at low frequency was able to prevent the metabolic changes induced by a HFD but not the deleterious effects of diet on the cardiovascular system.

Keywords Exercise · High-fat diet · Obesity · Cardiometabolic syndrome · Autonomic nervous system

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Introduction

Obesity is a major public health problem that can be related to a sedentary lifestyle and a western diet, which is rich in calories including fatty acids [1]. One consequence of obesity is metabolic syndrome, which is defined as a cluster of dysfunctions including central adiposity, dyslipidemia, elevated blood pressure and impaired glucose homeostasis. The clustering of risks factors for metabolic syndrome may depend on stressful factors in early life [2]. The prevalence of metabolic syndrome in young adults, which covers the transition period from adolescence to adulthood, has increased in recent years [3] and may depend on shifts in dietary and lifestyle patterns due to environmental and social pressure [4]. Therefore, strategies for risk factor management are needed in early adulthood, but the preventive effect of physical activity on cardiometabolic outcomes remains unclear.

A high-fat diet (HFD) is linked to many of the metabolic and cardiovascular changes that are characteristic of obesity and related to metabolic syndrome [5, 6]. Animals readily accumulate adipose tissue and develop higher

blood pressure and insulin resistance when they consume a short-term HFD [7, 8]. These changes may involve the autonomic nervous system (ANS) [9–11]. Studies have shown that HFD increases plasma norepinephrine, renal sympathetic nerve activity and norepinephrine turnover in the heart, which may lead to cardiovascular changes [8, 12, 13]. Interestingly, vagus nerve activity is increase by HFD [7, 14] suggesting an increase in the activity of the parasympathetic nervous system which may be related to impairment of parasympathetic-dependent insulin action in animals exposed to HFD [15].

Studies have reported the beneficial effects of moderate exercise in preventing obesity and metabolic syndrome. Moderate exercise that is started after weaning appears to induce better protection against metabolic disorders than exercise that is started later in life [16], emphasising the importance of interventions during the period of active brain development [17]. Furthermore, it has been shown that moderate exercise stimulates neuronal plasticity, which may contribute to its protective effect [18–20]. Recently, we demonstrated that the early adulthood period may be susceptible to dietary insults, such as protein restriction which induces long-lasting hallmarks of metabolic malfunctions leading to changes in fat deposition, glucose homeostasis and ANS later in life in rats [21]. Additionally, spontaneous exercise that is performed in early adulthood has also been shown to have a protective effect on metabolism [22].

Most of the studies on the mechanisms underlying the protective effect of exercise evaluate exercise that is performed concurrently with the obesity-inducing factor. However, the long-lasting protective effect of exercise remains controversial [23, 24]. Furthermore, post-weaning exercise benefits are still present when the exercise intensity is low [25]. It is important to consider the duration, frequency and type of exercise that are necessary to obtain the protective and beneficial effects of exercise [26]. We hypothesised that short-term moderate exercise at low frequency performed in young adult rats may provide long-lasting protection against the cardiometabolic changes induced by HFD.

Materials and methods

Experimental model and diet

Fifty-day-old male Wistar rats were housed three animals per cage and were provided water and food ad libitum in a room that was maintained at 22 ± 2 °C with a 12/12 h light/dark cycle. After 10 days of environmental adaptation, a group of 60-day-old rats underwent an exercise training protocol for 30 days. The control rats remained sedentary. During this period, all animals were fed a normal-fat diet (NFD). After this period (from 90 to 120 days of life), the animals were fed with a NFD or HFD and remained sedentary. The protocol design is shown in Fig. 1. Four groups were obtained: sedentary rats subjected to a NFD (SED-NFD), sedentary rats subjected to a HFD (SED-HFD), exercised rats subjected to a NFD (EXE-NFD) and exercised rats subjected to a HFD (EXE-HFD). The four groups in the present study included a total of 80 rats: 20 rats for each of the two groups that were fed with a NFD and 20 rats for each of the two groups that were fed with a HFD. All protocols were approved by the Ethics Committee of the State University of Maringá.

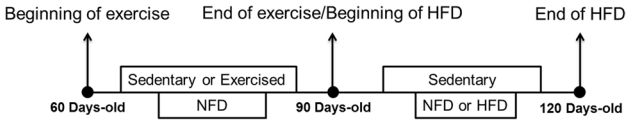

Fig. 1 Timeline describing the protocol design. *NFD* period when animals were exposed to normal-fat diet. *NFD or HFD* period when animals were exposed to normal-fat diet or high-fat diet

The NFD was a commercial diet with 3.801 kcal/g (AIN 93 M, Nuvital-Curitiba, PR), and the HFD was a hypercaloric home-made diet with 5.817 kcal/g and 35 % lard. The composition of the NFD and HFD was described previously [14].

Short-term moderate exercise treadmill protocol

The rats were trained on an animal treadmill (model ET-2000 Insight; RibeirãoPreto, SP, Brazil) three times a week for 4 weeks (12 sessions from 60 to 90 days of life), always in the morning. A plastic ball that was 10 cm in diameter was placed on the back end of the treadmill as a contact stimulus to keep the animal moving. The training started with sessions of 10 m/min for 10 min and finished with sessions of 16 m/min for 60 min by the end of the fourth week. This protocol was modified from a moderate physical exercise protocol proposed by Negrão et al. [27]. The intensity of the training was confirmed using a maximum effort test performed at 58, 75 and 94 days of life, corresponding to the times before, at the middle and at the end of the exercise period. The velocity proposed by the exercise protocol was considered as a percentage of the peak velocity obtained in the maximum effort test for each age. At the three tested ages, 58, 75 and 94 days of life, the proposed protocol velocity was 50, 66 and 68 %, respectively, of the peak velocity obtained in the maximum effort test, confirming the moderate intensity of the training.

Caloric intake and body weight gain

The food was weighed once a week from 60 to 120 days of life. The food intake was calculated as the difference

between the amount of food remaining and the total provided, which was divided by the number of days and the number of rats in the box [28]. Because the energetic values between the diets were different, the values in grams were converted into caloric values. The animals were weighed once a week during the experimental period.

Intravenous glucose tolerance test

A silicone cannula was implanted into the right jugular vein of 120-day-old rats, which were under anaesthesia (ketamine/xylazine, 0.5 mg/100 g of body weight each). After 12 h of fasting (from 8 PM to 8 AM), the animals received a bolus of glucose (1 g/kg of body weight). Blood samples were collected via the implanted cannula 0 min prior to the glucose infusion and 5, 15, 30 and 45 min after the infusion. Plasma was used to determine glycaemia via the glucose-oxidase technique (Gold Analisa® Belo Horizonte, MG, Brazil). The glucose responses during the glucose tolerance test were calculated by estimating the total area under the glucose curve using the trapezoidal method [29].

Cardiovascular parameters

After 12 h of fasting, catheters (PE-10) filled with 5 % heparinised saline were implanted into the femoral artery of rats that were anesthetised with thiopental (45 mg/kg of body weight). The arterial cannula was connected to a fluid-filled blood pressure transducer (MLT0699, ADInstruments, Dunedin, New Zealand), which was connected to a signal amplifier (Insight, RibeirãoPreto, SP, Brazil). Direct recordings of the arterial pressure (AP) were performed over 10 min using a microcomputer equipped with an analogue-to-digital converter board (CODAS, 1-kHz sampling frequency, Dataq Instruments, Inc., Akron, OH). Each recording was visualised to select segments without erratic fluctuations and with sufficient duration (1 min) [30]. Analyses were performed on a beat-to-beat basis over two periods of one min per animal to quantify the changes in the mean AP and heart rate (HR) [31].

Parasympathetic and sympathetic activity

After the blood pressure recordings, a longitudinal surgical incision was made on the anterior cervical region of the animals. The left vagus superior branch was isolated and placed over a silver electrode inside a faraday cage, as previously described [6]. After 12 min of vagus nerve electrical recordings, a laparotomy was performed to isolate the branch of the sympathetic nerve that is located in the splanchnic region; this branch originates in the lumbar plexus at the level of L2 and extends to the retroperitoneal adipose tissue.

The neural signal output was acquired using the Insight interface (Insight®, RiberãoPreto, SP, Brazil) for 12 min, from which 20 recorded frames of 5 s from each animal were randomly chosen for spike counting. Spikes >0 mV were considered. The average number of spikes was used as the nerve firing rate.

Evaluation of obesity and muscle mass

After the exercise period, 90-day-old animals were euthanised by decapitation. Blood samples were collected, and the fat pads (retroperitoneal and periepididymal) were removed and weighed. After autonomic nerve recording, 120-day-old anaesthetised animals were euthanised by decapitation. Retroperitoneal and periepididymal fat pads and the right soleus muscle were removed and weighed. The percentage of fat relative to the total animal body weight was used as an estimation of the total fat accumulation; the weight of the soleus muscle was used to determine muscle mass.

Statistical analysis

Data were expressed as the mean ± SEM. GraphPad Prism version 6.01 for Windows (GraphPadSoftware, La Jolla, CA, USA) was used for statistical analyses and developing graphs. Statistical analysis was performed using Student's *t* test for animals at 90 days of life, and two-way analysis of variance (ANOVA) followed by the Tukey multiple comparisons test was used for 120-day-old animals. A p value <0.05 was considered significant when considering the main effect of diet (D), exercise (E), their interaction (I; diet vs exercise) and the differences between groups.

Results

Caloric intake and body weight

During the physical exercise period, from 60 to 90 days of life, exercise did not impact caloric consumption. After this period, the HFD animals showed a significant decrease in caloric intake ($p_d < 0.001$; Fig. 2a). At the first week of HFD, the weekly average caloric intake was decreased by 10 %, and this effect persisted until the end of the HFD exposure, at 120 days of life. The physical exercise performed prior to the HFD exposure did not influence energy consumption.

Body weight gain was attenuated by exercise only at the last week of the training period, finishing at 90 days of life (Fig. 2b). Furthermore, the HFD induced a greater body weight gain, which was continually attenuated by the prior exercise in EXE-HFD rats after the second week of the diet resulting in a significant diet versus exercise interaction ($p_i < 0.001$).

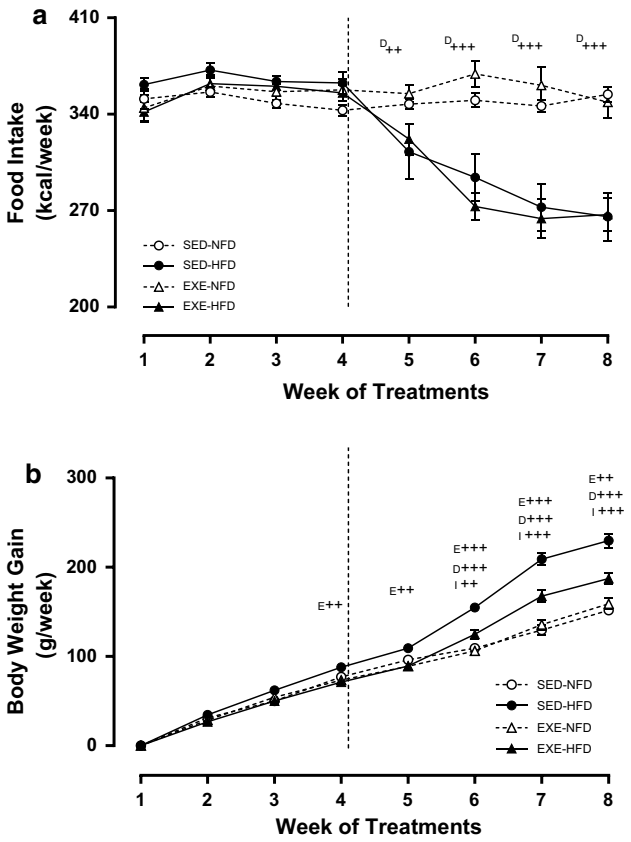

Fig. 2 Caloric intake (**a**) and body weight gain (**b**) from 60 to 120 days of life (n = 7–13 and 22–30, respectively). *SED-NFD* sedentary rats subjected to a normal-fat diet, *SED-HFD* sedentary rats subjected to a high-fat diet, *EXE-NFD* exercised animals subjected to a normal-fat diet and *EXE-HFD* exercised animals subjected to a high-fat diet. *E* exercise factor, *D* diet factor and *I* interaction between exercise and diet factors. $^{+++}p < 0.001$, $^{++}p < 0.01$ and $^{+}p < 0.05$ for the probability based on a two-way analysis of variance

Fat deposition and muscle mass

Fat deposition was evaluated in 90- and 120-day-old animals (Table 1). At 90 days of life, before the start of the HFD, the EXE animals showed approximately 15 % lower retroperitoneal and periepididymal fat deposition than the SED rats ($p < 0.05$). At 120 days of life, HFD induced approximately 75 % greater retroperitoneal fat deposition in the SED-HFD and EXE-HFD animals than in those exposed to NFD ($p_d < 0.001$). Interestingly, the previous exercise attenuated the body fat gain in approximately 20 % of the EXE-NFD and EXE-HFD animals compared with the sedentary animals ($p_e < 0.001$). No interaction was observed between diet and exercise ($p_i = 0.47$). The periepididymal fat showed a similar profile. The HFD reduced muscle mass in the sedentary and exercised animals (13 and 26 % in SED-HFD and EXE-HFD compared with SED-NFD and EXE-NFD, respectively, $p_d < 0.001$). Interestingly, exercise increased only the muscle mass in the EXE-NFD animals (24 % increase compared with SED-NFD, $p < 0.01$), leading to a significant diet versus exercise interaction ($p_i < 0.05$).

Glycaemia and insulinaemia

Fasting glycaemia was not affected by exercise or HFD (Table 1). During the ivGTT, the SED-HFD animals showed greater glycaemia (Fig. 3a) and insulinaemia (Fig. 3c) over the 45 min after the glucose bolus injection. This pattern led to an increase in the AUC of glycaemia (SED-HFD vs SED-NFD: 41 %; EXE-HFD vs EXE-NFD: 22 %; $p_d < 0.001$; Fig. 3b) and insulinaemia (SED-HFD vs SED-NFD: 69 %; EXE-HFD vs EXE-NFD: 13 %; $p_d < 0.001$; Fig. 3d). Interestingly, the previous exercise

Table 1 Biometric and biochemical parameters in 90- and 120-day-old rats

Parameters	90-day-old			p
	SED-NFD	EXE-NFD		
Retroperitoneal fat (n = 17–20)	1.44 ± 0.06	1.17 ± 0.07		<0.05
Periepididymal fat (n = 17–19)	1.10 ± 0.04	1.01 ± 0.03		<0.05
Fasting glucose (n = 18–20)	103 ± 1.9	102 ± 2.0		0.45

	120-day-old				Factors		
	SED-NFD	SED-HFD	EXE-NFD	EXE-HFD	E	D	I
Soleus muscle (n = 8–13)	0.17 ± 0.01	0.14 ± 0.01	0.21 ± 0.01	0.15 ± 0.01	++	+++	+
Retroperitoneal fat (n = 18–20)	1.65 ± 0.05	2.81 ± 0.1	1.28 ± 0.06	2.31 ± 0.11	+++	+++	ns
Periepididymal fat (n = 17–20)	1.44 ± 0.4	2.41 ± 0.1	1.09 ± 0.1	1.92 ± 0.1	+++	+++	ns
Fasting glucose (n = 12–20)	100 ± 1.5	101.8 ± 2.4	98.3 ± 1.5	95.2 ± 2.8	ns	ns	ns

SED-NFD sedentary rats subjected to a normal-fat diet, *SED-HFD* sedentary rats subjected to a high-fat diet, *EXE-NFD* exercised animals subjected to a normal-fat diet, *EXE-HFD* exercised animals subjected to a high-fat diet, *NFD* normal-fat diet, *HFD* high-fat diet, *EXE* exercised animals, *SED* sedentary animals, *E* exercise factor, *D* diet factor and *I* interaction between exercise and diet factors

$^{+++}$ $p < 0.001$ and ns (not significant) for the probability based on an analysis of variance

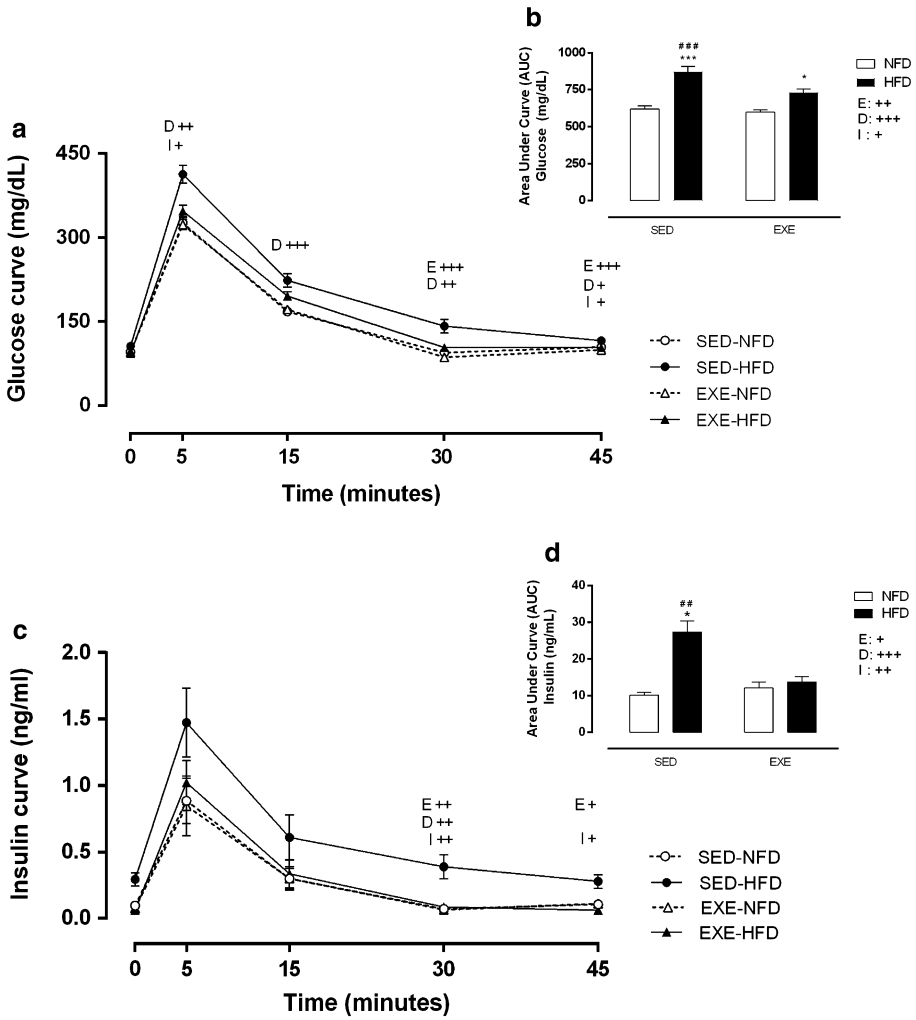

Fig. 3 Glucose curve and area under curve for glycaemia (**a**, **b**) and insulinaemia (**c**, **d**) evaluated during ivGTT in 120-day-old rats ($n = 18$–26 per group). *SED-NFD* sedentary rats subjected to a normal-fat diet, *SED-HFD* sedentary rats subjected to a high-fat diet, *EXE-NFD* exercised animals subjected to a normal-fat diet and *EXE-HFD* exercised animals subjected to a high-fat diet. *E* exercise factor, *D* diet factor and *I* interaction between exercise and diet factors. $^{+++}p < 0.001$, $^{++}p < 0.01$ and $^{+}p < 0.05$ for the probability based on a two-way analysis of variance. $^{***}p < 0.001$ and $^{*}p < 0.05$ statistical significance of the differences between NFD and HFD, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ statistical significance of sedentary versus exercised animals for the probability based on a Tukey multiple comparisons test

attenuated the AUC of glycaemia by 16 % and insulinaemia by 50 % in the EXE-HFD compared with the SED-HFD animals, which led to a significant exercise versus diet interaction (glycaemia: $p_i < 0.05$; insulinaemia: $p_i < 0.001$).

Blood pressure

The SED-HFD and EXE-HFD animals showed 7 and 26 % greater systolic blood pressure than the SED-NFD and EXE-HFD animals, respectively (Fig. 4a). A similar pattern was observed in diastolic blood pressure (Fig. 4b). This pattern was evidenced by the main effect of HFD on increased blood pressure ($p_d < 0.001$). Interestingly, previous exercise reduced systolic and diastolic blood pressure by 12 % only in the EXE-NFD compared with the SED-NFD animals (Tukey post-test: $p < 0.01$), but the HFD inhibited this reduction in the EXE-HFD animals. This pattern was reflected by a significant diet versus exercise interaction ($p_i < 0.01$; Fig. 4a, b).

The HFD increased HR by 18 % ($p_d < 0.01$). The previous physical exercise did not affect the HR (Fig. 4c).

Parasympathetic and sympathetic activity

The HFD increased the vagal tone by 65 % in the SED-HFD animals (Tukey post-test: $p < 0.001$; Fig. 5a). However, previous exercise blocked the HFD-induced increase in vagal activity in the EXE-HFD animals leading to a significant diet versus exercise interaction ($p_i < 0.01$).

The sympathetic nerve activity was reduced in the HFD-fed animals ($p_d < 0.001$; Fig. 5b) and increased in the exercised animals ($p_e < 0.001$; Fig. 5b). The exercise-induced increase in sympathetic activity was attenuated by 50 % in the EXE-HFD animals leading to a significant diet versus exercise interaction ($p_i < 0.05$).

Discussion

The major finding of this study was that previous exercise that was performed during young adulthood protected

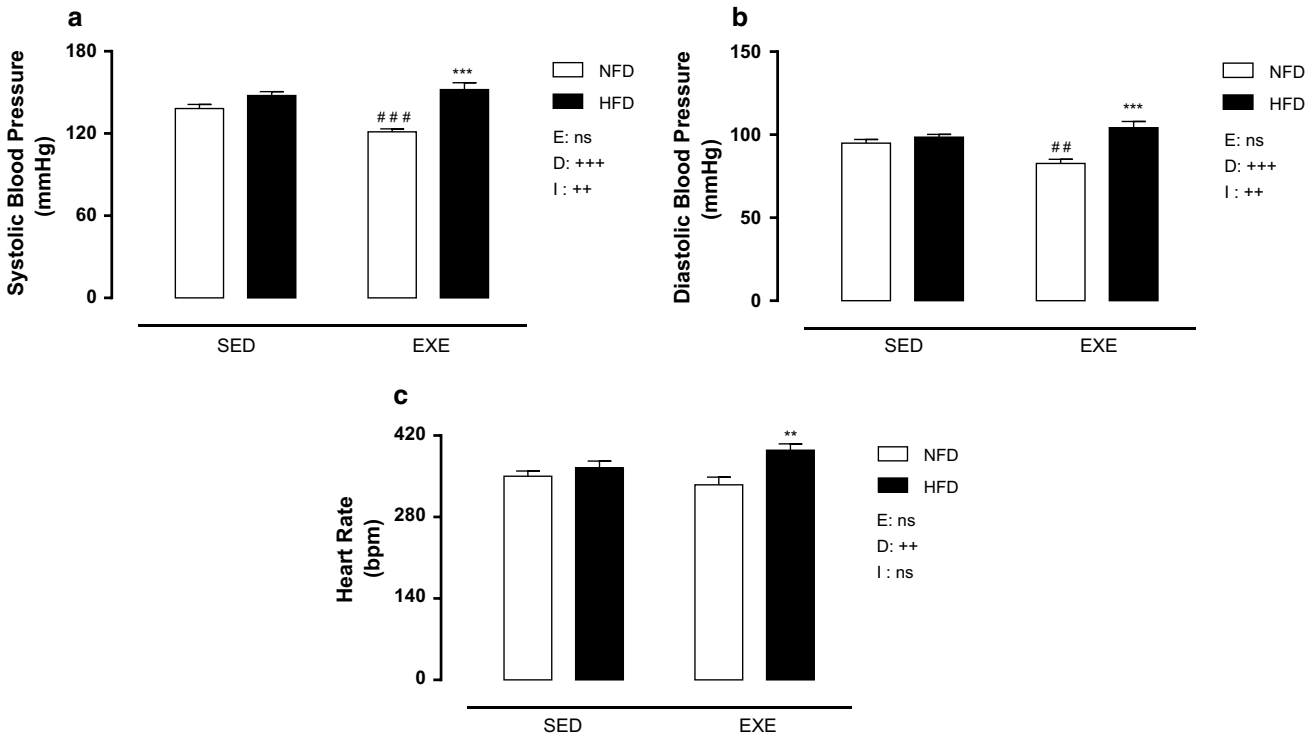

Fig. 4 Systolic blood pressure (**a**), diastolic blood pressure (**b**) and heart rate (**c**) in 120-day-old rats ($n = 7$–14 per group). *NFD* normal-fat diet, *HFD* high-fat diet, *EXE* exercised animals, *SED* sedentary animals, *E* exercise factor, *D* diet factor and *I* interaction between exercise and diet factors. $^{+++}p < 0.001$, $^{++}p < 0.01$ and ns (not significant) for the probability based on a two-way analysis of variance. $^{***}p < 0.001$ and $^{**}p < 0.01$ statistical significance of the differences between NFD and HFD. $^{###}p < 0.001$ and $^{##}p < 0.01$ statistical significance of sedentary versus exercised animals for the probability based on a Tukey multiple comparisons test

metabolism but not the cardiovascular system against the deleterious effects of a HFD. Earlier studies have shown that performing exercise during the post-weaning period protects animals from developing the full obesity phenotype [32, 33]. These and other studies suggested that the long-lasting protective effect of exercise performed early in life on energy homeostasis may implicate the nervous system via both their function and their organisation [7, 18]. Interestingly, the present findings suggest that the young adulthood period may also offer long-lasting beneficial effects from exercise.

The rats that were pre-exposed to exercise during their young adult life showed attenuated body weight gain and reduced body fat deposition after consuming a HFD. These findings contrast with a study that used a genetic model of obesity with congenital deficiency of the cholecystokinin 1 receptor (implicated in satiety), the Otsuka Long-Evans Tokushima fatty (OLETF) rats, which are already overweight at 8 weeks of life [22]. In that study, Chao et al. [22] showed that the long-lasting protective effect of spontaneous exercise, which was performed during a period similar to that of the present study, was no longer evident when the animals consumed a HFD. The animals that consumed a HFD after exercise regained their body weight and fat deposits; this effect may depend on hyperphagic behaviour that is modulated centrally [22]. Conversely, in the present study, the HFD animals showed reduced food intake (data not shown) and reduced energy intake, which is consistent with previous studies from our group and others [14, 34]. It has been proposed that rats fed with a HFD gain more weight even if energetic intake is not high, and the high amount of lipids in the diet are arguably one of the most influential factors for the induction of obesity [35, 36]. The balance between intake and oxidation is not accurate for fat [37], which may contribute to body weight gain as well. Interestingly, the present results show a greater body weight gain and fat deposition in animals exposed to HFD. Furthermore, the present reduction in energy intake observed in the HFD animals was independent of previous exercise, suggesting that the present beneficial effect of previous exercise on body weight and fat deposition may depend on factors other than energy intake.

Rinaldi et al. [38] described the chronic effect of exercise on increases lean mass by skeletal muscle hypertrophy. In this context, the current work shows that previous exercise in animals exposed to NFD increases muscle mass but that HFD exposure reduced the muscle mass increased by exercise. This pattern was associated with reduced fat

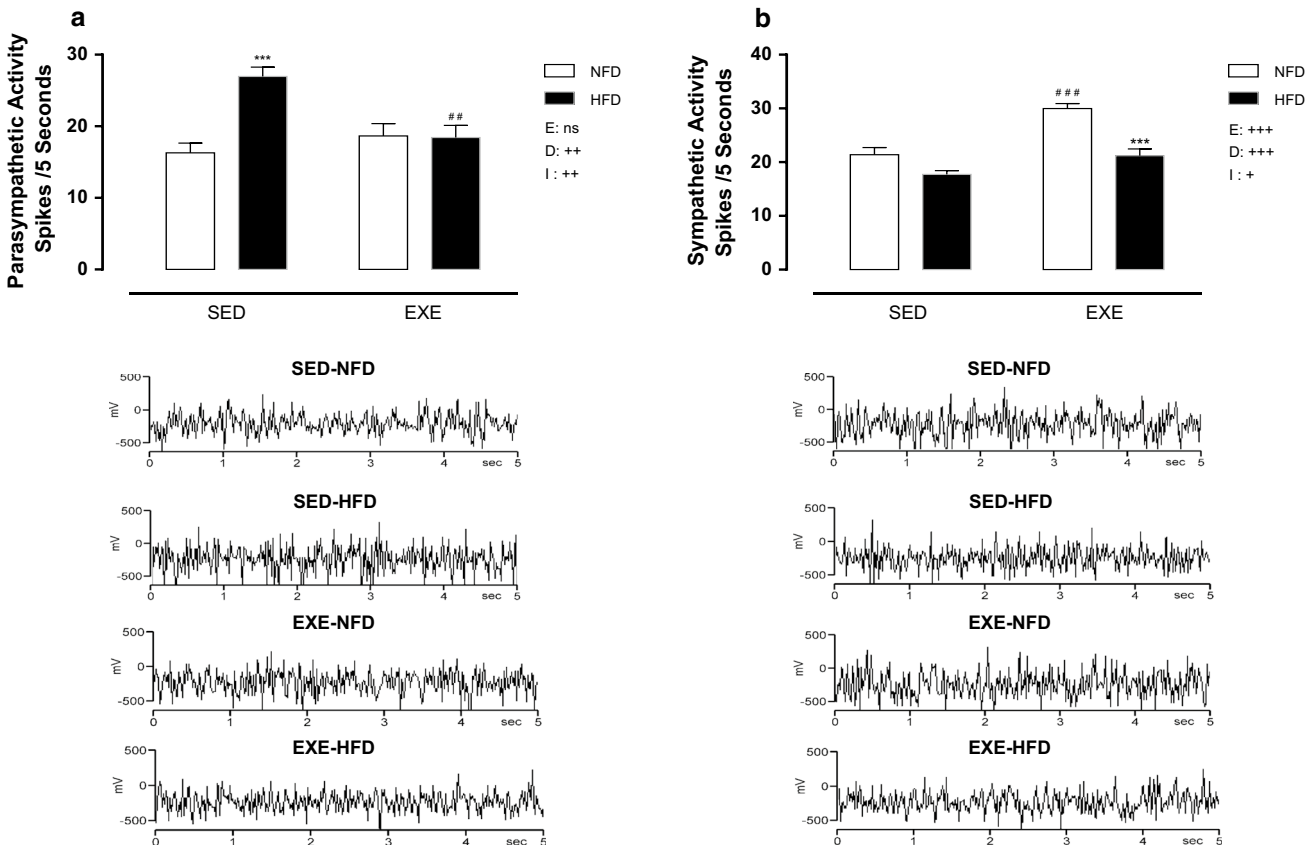

Fig. 5 Parasympathetic (**a**) and sympathetic (**b**) nerve activity evaluated in 120-day-old rats (n = 15–17 and 12–17, respectively, per group). *NFD* normal-fat diet, *HFD* high-fat diet, *EXE* exercised animals, *SED* sedentary animals, *E* exercise factor, *D* diet factor and *I* interaction between exercise and diet factors. $^{***}p < 0.001$ statistical significance of the differences between NFD and HFD. $^{\#\#\#}p < 0.001$ and $^{\#\#}p < 0.01$ statistical significance of sedentary versus exercised animals for the probability based on a Tukey multiple comparisons test. $^{+++}p < 0.001$, $^{++}p < 0.01$, $^{+}p < 0.05$ and ns (not significant) for the probability based on a two-way analysis of variance

deposits in EXE-HFD animals and may contribute to their reduced body weight gain compared with SED-HFD animals. In contrast, the control EXE-NFD animals did not show changes in body weight gain, with reductions in fat deposits and increased soleus mass. These findings suggest that the balance between lean and fat mass may be determinant of body weight gain. Sasaki et al. [39] also evaluated the best combination of daily timing of HFD feeding and aerobic exercise. They showed that HFD eating followed by exercise minimised increases in body and fat weight while increases in skeletal muscle weight were maximised [39]. The divergent findings in both studies should take into consideration animal age and duration of exercise and diet, as well the order of treatment introduction.

Previous studies show that 2 days of HFD-induced insulin hyper-secretion partially related to a decreased sympathetic tone, which was followed by glucose intolerance 7 days after the diet and persisted until 8 weeks of HFD exposure [40]. The present results are in accordance with those of that study as 4 weeks of HFD induced greater glycaemia and insulinaemia in response to glucose bolus at 4 weeks with HFD. Interestingly, the present findings show that the exercise programming protected against HFD-induced changes in glucose tolerance and hyperinsulinaemia. These findings are consistent with a recent study showing that mice subjected to exercise from 9 weeks of life had improved glucose tolerance at 20 weeks of life [41]. Furthermore, the preventive effect against the development of non-insulin-dependent diabetes mellitus has been shown to last for at least 3 months after the cessation of exercise in OLETF rats [42]. Conversely, exercised obese OLETF rats that consumed a HFD became glucose intolerant and insulin insensitive to the same degree as the sedentary OLETF rats on a HFD [22]. Together, these studies suggest that the protective effect of exercise is more evident when the exercise exposure happens before obesity. Early life exercise training in rats that were born small, which suggests a tendency for developing diabetes, restored beta-cell mass in adulthood [43]. Additionally, previous studies from our group have shown that the beneficial effect of exercise on glucose metabolism may depend on an improvement in pancreatic islet function and ANS activity in different models of metabolic syndrome [7, 25, 44, 45].

Previously, we showed that exercise performed early in life ameliorates the balance between autonomic nerve activity and catecholamine content in the adrenal gland in a model of programmed metabolic syndrome with monosodium L-glutamate (MSG) [44, 45]. Additionally, this benefit of exercise on the ANS may last for several weeks [16] with increased sympathetic and reduced parasympathetic nerve activity related to metabolism regulation in obese MSG rats that performed exercise during post-weaning and the pubertal period (unpublished data). This pattern is also observed in the present study in which Wistar rats exposed to exercise training during the young adulthood period showed a long-lasting protective effect against HFD-induced autonomic changes. Barella et al. [14] showed that a HFD increases vagus nerve activity independent of the period of life when the diet is offered. Recently, we showed that the present exercise protocol starting post-weaning and lasting until early adulthood restores vagus nerve activity in animals exposed to HFD [7]. Interestingly, the present findings show that this pattern is maintained when the exercise training is performed in early adulthood and followed by a HFD, reinforcing the long-lasting beneficial effect of this exercise training on glucose metabolism.

It is important to consider that in contrast to the present findings, several studies focused on the implication of the ANS on hypertension related to obesity have suggested that the sympathetic nervous system is increased and the parasympathetic nervous system inhibited by HFD [8, 12, 46, 47]. Interestingly, previous studies suggest that obesity induced by HFD is associated with the preservation of leptin's ability to increase blood pressure despite the resistance to the metabolic effects of leptin [48, 49]. They showed that the renal sympathetic nervous activity response to intracerebroventricular leptin was preserved, whereas lumbar and brown adipose tissue sympathetic nervous activity responses were attenuated in rats fed a HFD, suggesting a regional sympathetic sensitivity to leptin [48, 49] which may implicate the brain renin angiotensin system to selectively facilitate renal sympathetic nerve responses to leptin while sparing effects on food intake [50].

The current study also shows that a HFD increases blood pressure and HR; these findings were previously demonstrated in different animal models [6, 8, 12]. In contrast to the present findings on metabolism and the data from the literature [51], exercise did not protect the animals from the HFD-induced deleterious effect on cardiovascular parameters. Recent studies have shown that performing exercise concomitant with the consumption of a high-fructose diet, which leads to hypertension, prevented cardiovascular disorders [52–54]. Furthermore, long-term exercise (up to 10 weeks) showed a long-lasting protective effect on the cardiovascular and autonomic dysfunction observed in streptozotocin-diabetic or infarcted rats, thus also reducing mortality [55–57]. This beneficial effect of exercise on cardiovascular parameters may indicate a role of central mechanisms and their modulation of the ANS, mainly the parasympathetic nervous system [56, 58, 59]. Neurotropic factors, mainly brain-derived neurotrophic factor, whose levels are increased centrally by exercise and remain elevated [60, 61], may modulate the ANS control of blood pressure and HR via central baroreflex pathways [19, 59]. The present study showed a beneficial effect of exercise on blood pressure only in the control animals. However, a protective effect of exercise on the HFD-induced disturbance of blood pressure and HR was not observed. The deleterious HFD-induced effect may indicate a role of central pathways and their capacity to stimulate the kidney and muscles through the sympathetic nervous system [10, 12, 62]; this effect may predominate over the protective cardiovascular pathways modulated by exercise. Furthermore, 4 weeks of moderate exercise at low frequency may not be sufficient to initiate the long-lasting cardiovascular protection mechanism as most benefits of exercise have been associated with longer-term training [63].

In conclusion, a HFD disturbs metabolism and the cardiovascular system, but 4 weeks of moderate exercise at low frequency is able to protect against metabolic dysfunctions induced by a dietary insult. The mechanism underlying the long-lasting protection of glucose metabolism and body weight may depend, at least in part, on the ANS. The benefits of this exercise pattern are not sufficiently strong to protect the cardiovascular system against the HFD insult. Thus, the ideal physical exercise that will lead to a long-lasting protective effect against cardiometabolic syndrome remains unclear; however, early adult life may be a susceptible period during which permanent preventive actions can be established.

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