

RESEARCH

Open Access

Effects of acute exercise on spontaneous physical activity in mice at different ages



Ana Carolina Silveiras Quintanilha, Izabelle Dias Benfato, Robson Luiz Oliveira Santos, Hanna Karen Moreira Antunes and Camila Aparecida Machado de Oliveira*

Abstract

Background: Exercise is often used to obtain a negative energy balance. However, its effects on body weight reduction are usually below expectations. One possible explanation is a reduction in spontaneous physical activity (SPA) after exercise since the increase in energy expenditure caused by the exercise session would be offset by the decrease in SPA and its associated energy cost. Thus, we evaluated the effects of a single bout of moderate exercise at individualized intensity on spontaneous physical activity. The impact of the single bout of exercise was determined in early adulthood and at the transition to middle age.

Methods: Male C57bl/6j ($n = 10$) mice were evaluated at 4 (4 M) and 9 (9 M) months of age. One week after a treadmill Maximal Exercise Capacity Test (MECT), mice performed a 30-min single bout of exercise at 50% of the maximal speed reached at MECT. An infrared-based system was used to determine locomotor parameters (SPA and average speed of displacement, ASD) before (basal) and immediately after the single bout of exercise for 48 h (D1, 0-24 h; D2, 24-48 h). Food intake was measured simultaneously. Data were analyzed by GEE and statistical significance was set at $p < 0.05$.

Results: Basal SPA declined from 4 M to 9 M ($p = 0.01$), but maximal exercise capacity was similar. At both ages, SPA and ASD decreased significantly ($p < 0.0001$) on day 1 after exercise. On D2, SPA returned to basal levels but ASD remained lower than basal ($p < 0.001$). The magnitude (% of basal) of change in SPA and ASD on D1 and D2 was similar at 4 M and 9 M. Food intake did not change at 4 M but decreased on D2 at 9 M.

Conclusions: A single bout of moderate exercise decreases physical activity in the first 24 h and average speed of locomotion in the 48 h following exercise. This compensation is similar from early adulthood to the transition to middle age. The decrease in both the amount and intensity (speed) of SPA may compensate for the increase in energy expenditure induced by exercise, helping to understand the below-than-expected effect of exercise interventions to cause a negative energy balance.

Keywords: Energy homeostasis, Non-exercise activity, Physical activity, Ageing

* Correspondence: cam.oliveira@unifesp.br

Departamento de Biociências, Instituto de Saúde e Sociedade, Universidade Federal de São Paulo - UNIFESP, Campus Baixada Santista, sala 325, St. Silva Jardim 136 – Vila Mathias, SP CEP 11015-020 Santos, Brazil



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

New findings

What is the central question of this study?

Does spontaneous physical activity (SPA) decrease in response to an acute bout of moderate exercise at individualized intensity and does this compensation change as mice age from early adulthood to the transition to middle age?

What is the main finding and its importance?

- SPA, but not exercise capacity, declines from early adulthood to the transition to middle age;
- Acute exercise decreases SPA quantity and intensity in the following 24–48 h;
- The magnitude of the fall in SPA is similar from early adulthood to the transition to middle age;
- The fall in SPA can contribute to both body mass increase as a result of aging and to the below-than-expected effects of exercise on energy balance.

Background

Physical exercise is widely used as a strategy to induce body weight loss. However, its effects on energy balance are commonly disappointing due to a process referred to as compensation [1]. Among the mechanisms which may be involved in the exercise below-than-expected energy deficit are increased energy intake [1] and decreased energy expenditure, including decreased basal metabolic rate and spontaneous physical activity [2, 3].

Spontaneous physical activity (SPA) consists of daily life activities excluding structured, purposeful exercise. It generally comprises low-intensity physical activities (LIPA), with low energetic costs [4]. Recent studies showed that LIPA is associated with higher total brain volume [5] and inversely associated with all-cause mortality [6], highlighting the importance of SPA on health. The contributions of SPA to energy balance, however, are less clear, despite studies demonstrating protective effects against weight gain in response to overfeeding [7] and an inverse correlation with the rate of body weight change [8].

In humans, there is no consensus on the role of SPA in the compensation in response to exercise [1]. In rodents, the results are more consistent. We [9] and others [10–12] have shown that exercise decreases SPA. Lark et al. [12] found that this reduction was predicted to attenuate the expected change in energy balance by approximately 45%. All of the above studies, however, used running wheel as a model of exercise, which does not allow for the control of either volume or intensity of exercise.

To gain further insight into the effects of exercise on compensation we have investigated in mice the effects of an acute session of moderate exercise at individualized intensity on 48 h SPA (amount and intensity) and energy

intake, simultaneously. Moreover, as we have previously demonstrated, SPA decreases from early adulthood to the transition to middle age [13], so we also investigated whether compensation in either SPA or energy intake following exercise changes with increasing age.

Methods

Experimental design

C57Bl/6j male mice ($n = 10$), obtained from the Center for Development of Experimental Models (CEDEME), Federal University of São Paulo (UNIFESP), were first acclimatized to the animal house of the Department of Bioscience. They were evaluated when they were 4 (4 M) and 9 (9 M) -month-old. A separated set of mice ($n = 8$) was used to perform a control experiment, as explained below. According to Flurkey et al. [14], this lifespan corresponds to the beginning of adult life to the transition to middle age.

Food intake

Food intake was determined individually in the 48 h before and in the 48 h immediately after the acute exercise session, simultaneously with the measurement of SPA. Daily food consumption was determined by subtracting the weight of the remaining food after 24 h from the weight of food given, with care taken to account for spillage. Before each acute exercise session (basal) food intake was calculated as the mean of the two 24 h periods whereas food intake after the exercise was separated in day 1 and day 2.

Maximal exercise capacity test

Mice were familiarized with the treadmill for five days before each maximal exercise capacity test (MECT), which was performed at 4 and 9 months. The acclimatization consisted of placing the mice for 30 min on a static treadmill on day 1 and, in the following days, the speed was set at 8 cm/s, which is a very low speed aimed to make mice familiar with any noise a turned-on treadmill can produce. On days 4 and 5 the mice spent an additional 10 min in the treadmill at 12 cm/s.

For the MECT, mice were placed in the treadmill for an 8-min warm-up at 12 cm/s. The test started immediately after the warm-up with an initial speed of 15 cm/s increased by 15 cm/s every 45 s until mice were not able to keep the pace even after gentle prodding by hand (adapted from [15]). The maximal speed (cm/s) at which mice completed the 45 s stage (maximal stage completed) was used to calculate the speed for the acute exercise session. The total distance (cm) and the maximal speed reached (not necessarily completing the 45 s stage) were also recorded. No electrical shock was applied for either the MECT or the acute exercise session.

Acute exercise session

The acute exercise session was done one week after the MECT. It was performed for 30 min at 50 % of the maximal speed (cm/s) at which mice completed the 45 s stage (adapted from de [16]). When necessary, mice were gently prodded by hand. Two mice at 4 and 9 months of age were not included in the posterior analysis of spontaneous physical activity and food intake for either refusing to run for the stipulated time or for getting a small injury in the finger during the session, avoiding any interference on locomotor parameters. As a control experiment, a separated set of mice was placed in the treadmill for the same 30 min but without exercising (non-moving treadmill). They were submitted to the same locomotor (SPA and speed of displacement) and food ingestion analysis, before and after exposure to the treadmill. Additionally, on a different occasion, mice were placed in the actimeter and analyzed for 5 consecutive and uninterrupted days.

Spontaneous Physical Activity (SPA)

Activity was measured individually by infrared beam sensors using an IR actimeter system composed of a 2 dimensional (X and Y axes) square frame (25 × 25 cm), each frame containing 16 × 16 infrared beams separated 1.3 cm from each other (Panlab-Harvard Apparatus, Barcelona, Spain). SPA was recorded in the 48 h before and in the 48 h immediately after the acute exercise session at 4 and 9 months of age. The software ActiTrack v2.7 (Panlab-Harvard Apparatus, Barcelona, Spain) also generated data on average speed of displacement. Mice were allowed 2 h of acclimatization in the actimeter cage before basal measurements. SPA consisted of the sum of stereotypes and locomotion. The software determines stereotypes by the number of samples where the position of the mouse is different from its position during the previous sample and equal to its position from the second sample, back in time; and locomotion by the number of samples where the position of the mouse is different from its position during the previous sample and different to the position of the second sample, back in time. Average speed of displacement (cm/s) is calculated as locomotion (expressed in centimeter instead of counts) divided by the time mice spent in locomotion. For basal SPA and average speed, we calculated the mean of the two 24 h periods (48 h) before the acute exercise session. After exercise, the 48-h analysis was separated in day 1 and day 2.

Statistics

Results are presented as mean and standard deviation (SD). To evaluate the effect either age (4 and 9 months) or exercise (basal, day 1 and day 2 post-exercise), data were analyzed using Generalized Estimating Equations

(GEE) on SPSS, version 20 (IBM). A pairwise Bonferroni comparison was used if necessary. The probability distribution and correlation matrix structure were chosen based on the Quasi Likelihood under Independence Model Criterion (QIC). A significance level of $p < 0.05$ was adopted.

Results

The results of the maximal exercise capacity test are shown in Table 1. No effect of age was observed for any of the parameters evaluated at 4 and 9 months.

Figure 1 shows the effects of aging on SPA, average speed of displacement, food intake, and body mass. There was a significant effect of age on SPA ($p = 0.01$), which reduced significantly at 9M compared to 4M (Fig. 1A). Average speed of displacement did not differ significantly in the timespan studied (Fig. 1B). Food intake was also similar from 4 to 9 months of age (Fig. 1C). Body mass increased significantly ($p = 0.0001$) from 4M to 9M (Fig. 1D).

A separated set of mice was submitted to the same evaluations, but without exercising. Instead, they remained for the same 30-min in the non-moving treadmill. No difference in either SPA, speed of displacement, or food intake was observed before compared to after exposure to the treadmill (Supplementary Fig. 1A-C). In an additional analysis, mice remained for 5 consecutive and uninterrupted days in the actimeter and again, no difference was observed for either locomotor parameters or food intake (Supplementary Fig. 1D-F).

The effects of an acute exercise session on SPA, average speed of displacement, and food intake in 4-month-old mice are shown in Fig. 2. There was a significant effect of exercise on SPA ($p = 0.0001$). Exercise decreased SPA ($p = 0.0001$) in the 24 h immediately after the acute session (day 1). On day 2, SPA returned to pre-exercise levels (Fig. 2A). Exercise also had a significant effect on average speed of displacement ($p = 0.0001$). The speed dropped significantly on day 1 ($p = 0.0001$) and despite increasing toward basal levels on day 2, it was still lower ($p = 0.036$) than before exercise (Fig. 2B). For food

Table 1 Maximal exercise capacity test and acute exercise session at different ages

	4 M	9 M
Maximal exercise capacity test		
Distance (cm)	546.0 ± 105.1	603.0 ± 128.8
Total time (s)	168.7 ± 19.3	168.6 ± 20.3
Maximal speed reached (cm/s)	55.5 ± 10.1	58.5 ± 8.5
Maximal stage completed (cm/s)	52.5 ± 7.9	54.0 ± 7.7
Acute session		
Speed (cm/s)	26.5 ± 3.7	27.0 ± 3.9

Results are mean ± SD; Mice (n = 10) were followed from 4 to 9 months of age

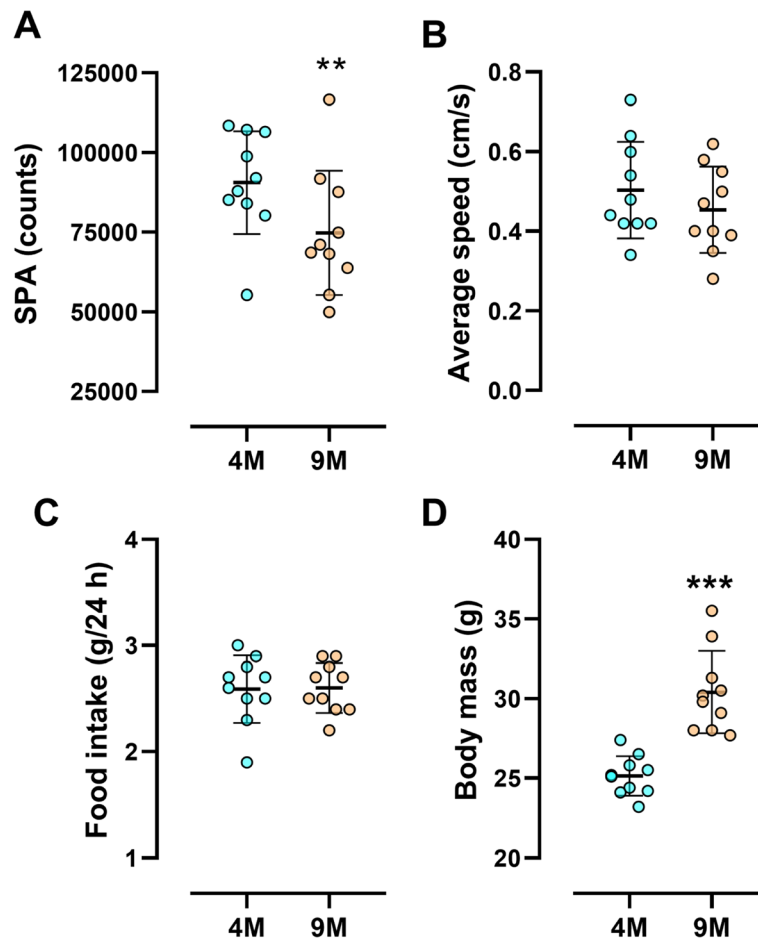


Fig. 1 Spontaneous physical activity, average speed, food intake, and body mass through the time. Basal spontaneous physical activity (A), average speed of locomotion (B), food intake (C), and body mass (D) at different ages. Results are mean \pm SD. ** $p < 0.01$; *** $p < 0.001$

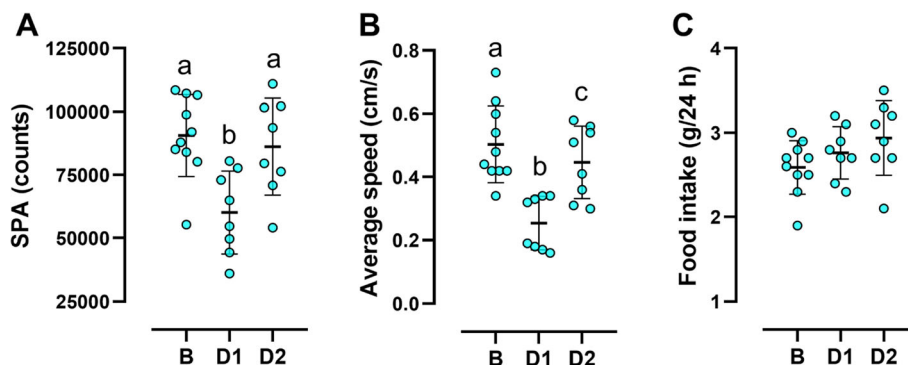
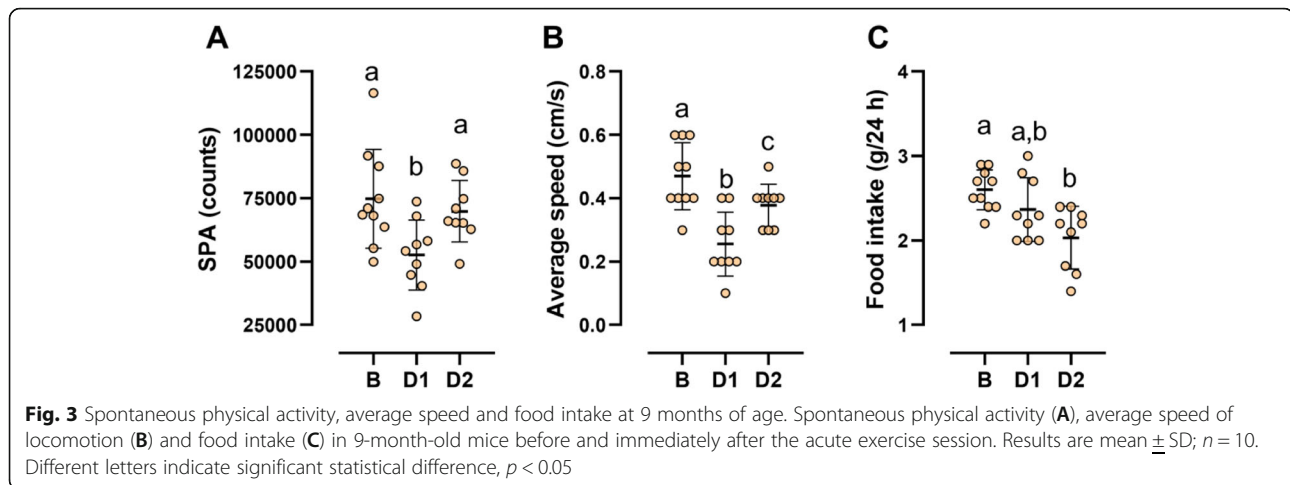


Fig. 2 Spontaneous physical activity, average speed and food intake at 4 months of age. Spontaneous physical activity (A), average speed of locomotion (B), and food intake (C) in 4-month-old mice before and immediately after the acute exercise session. Results are mean \pm SD; different letters indicate significant statistical difference, $p < 0.05$



intake, despite GEE analysis indicated a significant effect of exercise ($p = 0.041$), no difference among the times (basal, day 1, and day 2) was found in the pairwise comparisons (Fig. 2C).

As in the younger age, the acute exercise in nine-month-old mice significantly affected SPA ($p = 0.0001$). SPA reduced significantly on day 1 compared to basal ($p = 0.0001$) but was similar to pre-exercise levels on day 2 (Fig. 3A). Likewise, there was a significant effect of exercise on average speed of displacement ($p = 0.0001$). The speed fell significantly on day 1 in relation to basal ($p = 0.0001$) but, even though it increased on day 2, the average speed was still significantly lower ($p = 0.001$) than before exercise (Fig. 3B). Exercise also had a significant effect on food intake ($p = 0.0001$) but with a different temporal pattern. Compared to basal, food intake was not different on day 1 but decreased significantly ($p = 0.0001$) on day 2 (Fig. 3C).

Next, we determined whether the magnitude of changes (% in relation to basal) in SPA, average speed of locomotion, and food intake in response to exercise was affected by age. There was no effect of age on the magnitude of change for SPA and average speed of locomotion either on day 1 (Fig. 4A) or day 2 (Fig. 4B) after exercise. For the magnitude of food intake change, there was an effect of age in response to acute exercise only on day 2 ($p = 0.001$). Whereas food consumption increased to values higher than pre-exercise at 4 M, it decreased at 9 M (Fig. 4B).

Discussion

In our study, we found that an acute exercise session at individualized intensity consistently decreased both SPA and average speed of displacement and that the magnitude of the fall did not increase from young adulthood to the transition to middle age. Moreover, we showed

that food intake was not a significant contributor to exercise compensation, favoring a role for reduced activity amount (SPA) and intensity (speed of displacement) in decrease exercise effectiveness to cause a negative energy balance.

Analyzing separately the effects of aging, we found a decrease in SPA at 9 months, as previously observed by our group [13]. During the same period, no change in absolute food intake (basal) was observed. Body mass, however, increased from 4 to 9 months of age. Different mechanisms participate in body mass gain as age increases, including decreased activity of the somatotrophic axis which begins as early as after puberty, increased fat to lean muscle mass ratio [17], and reduction in resting energy expenditure that cannot be fully explained by changes in body composition [18]. Remarkably, the latter was found to be more pronounced at early adulthood in men [18]. Importantly, physical activity is a critical contributor to total daily energy expenditure [19]. Bjursell et al. [20] showed that exposure to a high-fat diet led to increased body weight gain throughout the 21 days of experiment. However, while energy intake was higher only in the first 24 h, locomotor activity reduced as early as after 3–5 h and remained lower all over, being the most important factor for body weight gain induced by the diet. Thus, taking into account that SPA comprehends all mice movement in the cage, its relevance on energy balance becomes more evident as well as the role of the decreased SPA on body mass gain with age.

The results of the maximal exercise capacity test indicate that mice at the transition to middle age have similar exercise capacity than at the beginning of adult life. SPA, as previously said, was lower at 9 M compared to 4 M, thus, suggesting that, at least in mice, the mechanism controlling SPA is more sensitive to aging and declines earlier than the function of cardiorespiratory/

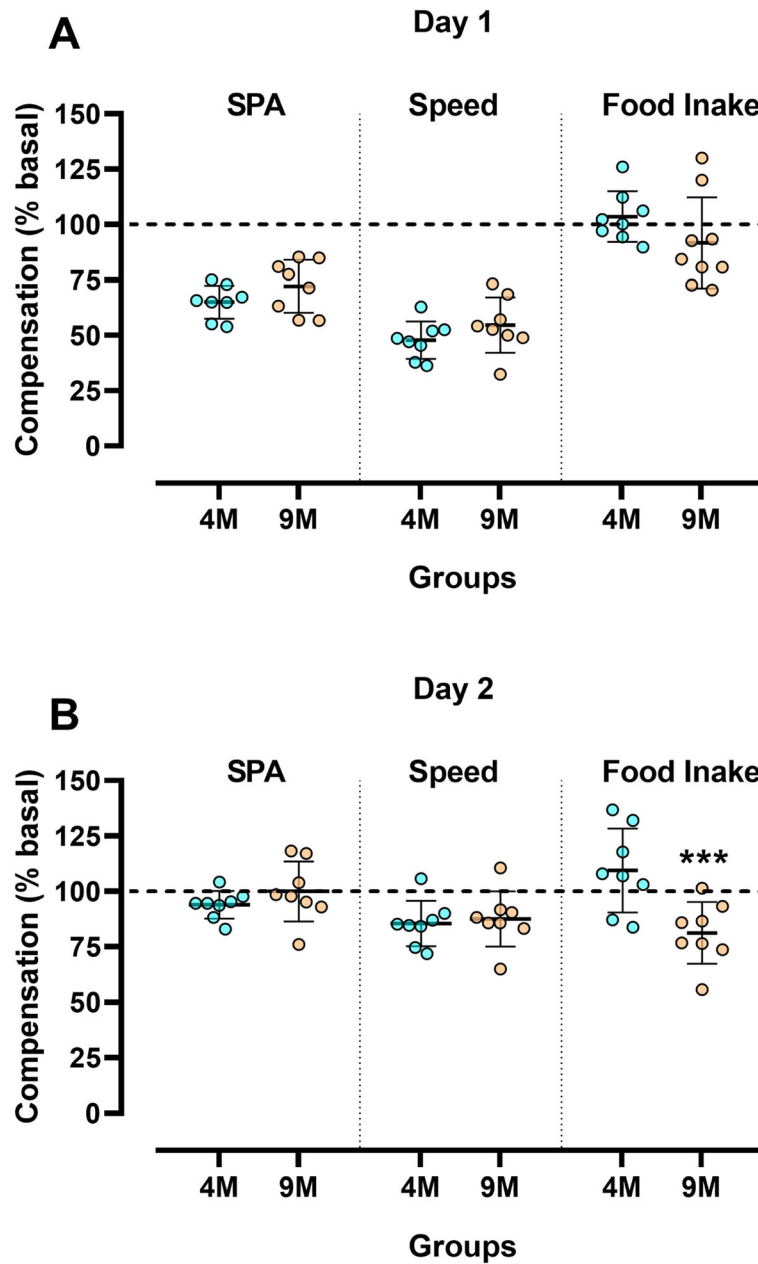
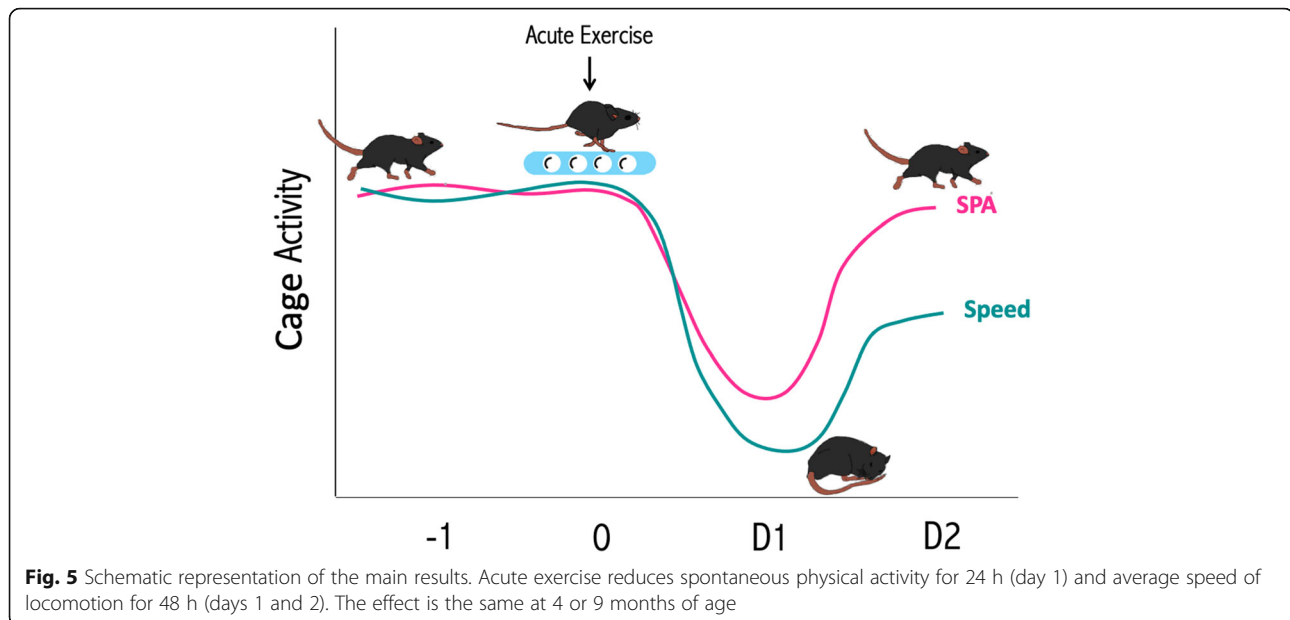


Fig. 4 Magnitude of changes in the parameters studied at 4 and 9 months of age. Magnitude of change in spontaneous physical activity, average speed of locomotion, and food intake in the first (A) and second (B) day immediately after the acute exercise session at the different ages. Results are mean \pm SD. *** $p < 0.001$

musculoskeletal systems. Scariot et al. [21] found that both SPA and exercise capacity declined from 2 to 5-month-old Wistar rats. Swimming exercise at individualized intensity for 12 weeks, though, avoided the decrease in SPA but not in aerobic and anaerobic capacity. Despite the differences between ours and Scariot et al. [21] study, which include distinct animals, age, exercise type, and method of SPA measurement, they both have in common the finding that SPA and exercise capacity seems to be uncoupled.

The inherent drive for movement responsible for SPA is controlled centrally and several structures and neurobiological modulators have been proposed to its regulation [22]. In a previous study, we found that leptin signaling was decreased in hypothalamus by the time SPA first started to fall, at 6 months [13]. How exercise modulates the circuitry leading to a compensatory decrease in SPA, though, needs further investigation. Exercise can, directly and indirectly, be sensed by the brain. Peripheral factors released from skeletal muscle, known



as myokines, could mediate this muscle-brain crosstalk [23]. Pontzer et al. [24] proposed the “constrained-energy expenditure” theory, in which physical activity does not increase total energy expenditure in a dose-dependent manner, as an evolved mechanism to maintain energy expenditure within a physiological narrow range. In line with this theory, some myokines and other exercise mediators change in plasma according to the acute metabolic stress induced by exercise [23], which could signal to the central nervous system to decrease other energy-demanding behavior/function in order to minimize the impact on energy balance.

Different than expected, the compensation in either locomotion parameters or food intake was not more pronounced when mice were older. In humans, a compensatory decrease in SPA in response to exercise training has been observed in individuals with 56 years or more [25, 26]. However, in these studies, the results were not compared with a younger group. We did not find any study performed with rodents comparing the effects of exercise on SPA at different stages of life. Concerning food intake, a minor to lack of effects of an acute exercise session is commonly observed in humans, as reviewed by Caudwell et al. [27]. In mice, contrasting results can be found, probably, due to varying volumes of exercise and duration of the energy consumption measurement [28, 29]. Nevertheless, in Wistar rats, as they aged from 4 to 11 and from 25 to 27 months, there was an increase in the effects of appetite-suppressing factors and a decrease in the appetite-stimulating factors [30]. If similar alterations take place in mice, it could help to explain the reduction in food intake in 9-month-old mice 2 days after the acute exercise session.

A limitation of our study is that we evaluated SPA only in response to a single bout of exercise, and not after training. A compensatory decrease in cage activity has been seen in mice even after 10 weeks of wheel-running [9], implying that exercise training might not mitigate this behavior. Other authors also reported decreased SPA after chronic 3 to 8 weeks-exposure to running wheel mice are free to exercise as they will, our study advances as our protocol allowed for the control of both volume and intensity of exercise, which are key parameters for exercise prescription. Also, it would be interesting to evaluate the same compensatory behaviors in obese mice, since they would benefit the most from negative energy balance.

Conclusions

In conclusion, as summarized in Fig. 5, a single bout of moderate exercise decreases spontaneous physical activity amount and intensity in the subsequent 24–48 h with minor effects on energy intake. The magnitude of this compensatory reduction in SPA is similar from early adulthood to the transition to middle age. The decrease in both the amount and intensity of SPA may compensate for the increase in energy expenditure induced by exercise, helping to understand the below-than-expected effect of exercise interventions in causing a negative energy balance.

Abbreviations

ASD: Average speed of displacement; GEE: Generalizing estimating equation; LIPA: Low intensity physical activity; MECT: Maximal exercise capacity test;

QIC: Quasi likelihood under independence model criterion;
SPA: Spontaneous physical activity

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13102-021-00311-2>.

Additional file 1: Supp. Fig. 1. Spontaneous physical activity, average speed of locomotion and food intake in mice before and after 30-min in a non-moving treadmill (A-C) or evaluated for five consecutive and un-interrupted days (D-F). Results are mean + SD; $n=8$.

Acknowledgements

Not applicable.

Authors' contributions

CO and IB conceived the study, designed the experiments, and wrote the manuscript. AQ, RO and IB performed the experiments. AQ contributed with the first draft of the manuscript. HA contributed with acquisition of data and performed a critical revision of the manuscript. CO analyzed the data and obtained the funding. All authors have read the manuscript and approved its contents.

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, São Paulo Research Foundation (FAPESP) (grant 2011/05932-3; 2017/04528-0), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brasília, DF, Brazil (123028/2018-3).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was carried out in compliance with the ARRIVE Guidelines and according to the Arouca Law (nº 11.794/ October 8, 2008) and the Normative Resolutions of the National Council for Animal Experiments Control - CONCEA, both regulated by Brazilian Federal Constitution. All experiments in this manuscript were approved by the Institutional Ethics Committee on Animal Use (CEUA n. 5541040218) of the Federal University of São Paulo (UNIFESP), Brazil. Male C57Bl/6 mice were obtained from the Center for Development of Animal Models for Medicine and Biology (CEDE ME, Federal University of São Paulo). They were kept from 3 to 9 months of age at the animal house of the Department of Bioscience in a temperature-controlled room (22 °C) with a 12:12-h light-dark cycle (7:00–19:00 h) and free access to water and AIN-93 M diet (Rhoister Indústria e Comércio LTDA, São Paulo, Brazil). At the end mice were anesthetized with a mixture of ketamine (75 mg/Kg), xylazine (10 mg/kg), fentanyl (0.5 mg/Kg) and acepromazine (1 mg/Kg) administered intraperitoneally and euthanized by cardiac perfusion.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 29 March 2021 Accepted: 10 July 2021

Published online: 27 July 2021

References

- Martin CK, Johnson WD, Myers CA, Apolzan JW, Earnest CP, Thomas DM, et al. Effect of different doses of supervised exercise on food intake, metabolism, and non-exercise physical activity: The E-MECHANIC randomized controlled trial. *Am J Clin Nutr.* 2019;110(3):583–92.
- Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA. Resistance to exercise-induced weight loss: compensatory behavioral adaptations. *Med Sci Sports Exerc.* 2013;45(8):1600.
- Doucet E, McInis K, Mahmoodianfard S. Compensation in response to energy deficits induced by exercise or diet. *Obes Rev.* 2018;19:36–46.
- Kotz CM, Perez-Leighton CE, Teske JA, Billington CJ. Spontaneous physical activity defends against obesity. *Curr Obes Rep.* 2017;6(4):362–70.
- Spartano NL, Davis-Plourde KL, Himali JJ, Andersson C, Pase MP, Maillard P, et al. Association of accelerometer-measured light-intensity physical activity with brain volume: the framingham heart study. *JAMA Netw Open.* 2019;2(4):e192745-e.
- Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ.* 2019;366:14570.
- Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science.* 1999;283(5399):212–4.
- Zurlo F, Ferraro RT, Fontvielle A, Rising R, Bogardus C, Ravussin E. Spontaneous physical activity and obesity: cross-sectional and longitudinal studies in Pima Indians. *Am J Physiol Endocrinol Metab.* 1992;263(2):E296–300.
- De Carvalho FP, Benfato ID, Moretto TL, Barthichoto M, de Oliveira CAM. Voluntary running decreases nonexercise activity in lean and diet-induced obese mice. *Physiol Behav.* 2016;165:249–56.
- Copes LE, Schutz H, Dlugosz EM, Acosta W, Chappell MA, Garland T Jr. Effects of voluntary exercise on spontaneous physical activity and food consumption in mice: results from an artificial selection experiment. *Physiol Behav.* 2015;149:86–94.
- O'Neal TJ, Friend DM, Guo J, Hall KD, Kravitz AV. Increases in physical activity result in diminishing increments in daily energy expenditure in mice. *Curr Biol.* 2017;27(3):423–30.
- Lark DS, Kwan JR, McClatchey PM, James MN, James FD, Lighton JR, et al. Reduced nonexercise activity attenuates negative energy balance in mice engaged in voluntary exercise. *Diabetes.* 2018;67(5):831–40.
- Benfato ID, Moretto TL, de Carvalho FP, Barthichoto M, Ferreira SM, Costa Junior JM, et al. Spontaneous physical activity and mediators of energy homeostasis in the hypothalamus of mice from 4 to 10 months of age. *Exp Physiol.* 2017;102(11):1524–34.
- Flurkey K, Curren JM, Harrison DE. The mouse in aging research. In: Fox JG, et al, editors. *The mouse in biomedical research*, 2nd Ed. Burlington: American College Laboratory Animal Medicine (Elsevier); 2007. p. 637–72.
- Rezende EL, Garland T, Chappell MA, Malisch JL, Gomes FR. Maximum aerobic performance in lines of *Mus* selected for high wheel-running activity: effects of selection, oxygen availability and the mini-muscle phenotype. *J Exp Biol.* 2006;209(1):115–27.
- de Andrade LHS, de Moraes WMAM, Junior EHM, de Moura EdOC, Antunes HKM, Montemor J, et al. Aerobic exercise training improves oxidative stress and ubiquitin proteasome system activity in heart of spontaneously hypertensive rats. *Mol Cell Biochem.* 2015;402(1):193–202.
- van den Beld AW, Kaufman J-M, Zillikens MC, Lamberts SW, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol.* 2018;6(8):647–58.
- Alfonzo-González G, Doucet E, Bouchard C, Tremblay A. Greater than predicted decrease in resting energy expenditure with age: cross-sectional and longitudinal evidence. *Eur J Clin Nutr.* 2006;60(1):18–24.
- Villablanca PA, Alegria JR, Mookadam F, Holmes DR Jr, Wright RS, Levine JA. Nonexercise activity thermogenesis in obesity management. *Mayo Clin Proc.* 2015;90(4):509–19.
- Bjursell M, Gerdin AK, Lelliott CJ, Egecioglu E, Elmgren A, Törnelli J, et al. Acutely reduced locomotor activity is a major contributor to Western diet-induced obesity in mice. *Am J Physiol Endocrinol Metab.* 2008;294(2):E251–60.
- Scariot PP, Manchado-Gobatto FdB, Torsoni AS, Dos Reis IG, Beck WR, Gobatto CA. Continuous aerobic training in individualized intensity avoids spontaneous physical activity decline and improves MCT1 expression in oxidative muscle of swimming rats. *Front Physiol.* 2016;7:132.
- Teske J, Billington C, Kotz C. Neuropeptidergic mediators of spontaneous physical activity and non-exercise activity thermogenesis. *Neuroendocrinology.* 2008;87(2):71–90.
- Pedersen BK. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol.* 2019;15(7):383–92.

24. Pontzer H. Energy constraint as a novel mechanism linking exercise and health. *Physiology*. 2018;33(6):384–93.
25. Goran MI, Poehlman ET. Endurance training does not enhance total energy expenditure in healthy elderly persons. *Am J Physiol Endocrinol Metab*. 1992;263(5):E950–7.
26. Morio B, Montaurier C, Pickering G, Ritz P, Fellmann N, Coudert J, et al. Effects of 14 weeks of progressive endurance training on energy expenditure in elderly people. *Br J Nutr*. 1998;80(6):511–9.
27. Caudwell P, Gibbons C, Finlayson G, Näslund E, Blundell J. Physical activity, energy intake, and obesity: the links between exercise and appetite. *Curr Obes Rep*. 2013;2(2):185–90.
28. Gaspar RC, Muñoz VR, Kuga GK, Nakandakari SCBR, Crisol BM, Lenhare L, et al. Acute physical exercise increases APPL1/PI3K signaling in the hypothalamus of lean mice. *Eur J Neurosci*. 2019;50(7):3181–90.
29. Bunner W, Landry T, Laing BT, Li P, Rao Z, Yuan Y, et al. ARCAgRP/ NPY Neuron Activity Is Required for Acute Exercise-Induced Food Intake in Un-Trained Mice. *Front Physiol*. 2020;11:411.
30. Akimoto S, Miyasaka K. Age-associated changes of appetite-regulating peptides. *Geriatr Gerontol Int*. 2010;10(Suppl 1):S107-19.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

