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Commentary

Standardization of exercise intensity and consideration of a dose–response is essential. Commentary on "Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models", by Lourenco et al., published 2019 in *Nature Medicine*

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Over the past decade, several biochemical pathways have been investigated to understand the underlying mechanisms involved in the beneficial effects of physical exercise on cognition.[1,2] Lourenco et al.,[3] in an elegant study published in *Nature Medicine*, examined the relationship between exercise training and hippocampal memory function. Mechanistically, the authors showed that FNDC5/irisin is an important mediator of beneficial effects of physical exercise in a mouse model of Alzheimer's disease.

The recently updated Physical Activity Guidelines for Americans states that the regular practice of physical activity and exercise is one of the best things people can do to improve their health.[4] The guidelines stress that the beneficial effects of physical exercise are highly dependent on overload, progression, and specificity. This requires that researchers describe in detail the exercise regimes[5] they use when the protocols are intended to produce a certain health effect, in this case, enhancing cognition in experimental Alzheimer's disease. Without the correct prescription of physical exercise, the translational value of the exercise protocol can be lost.[6,7]

The researchers who originally proposed that irisin was an exercise hormone also observed (as Lourenco et al.[3]) increased levels of the PGC-1α regulated hormone in the plasma and skeletal muscle from mice submitted to 3 weeks of free-wheel running and humans after 10 weeks of supervised endurance exercise training.[8] In these cases, the exercise protocols used were partially defined as aerobic or endurance protocols. For humans, rehabilitation and physical exercise prescriptions rely on different exercise intensities and dose–response relationships, factors that will induce diverse effects on disease/health states.[9] Unfortunately, Lourenco et al.[3] did not specify the exercise intensity the animals performed, omitting details that would allow for the definition of the dose of physical exercise applied to elicit the desired psychophysiological response, which would in turn allow for a comparison across different strains of mice or rodent species.[10] Therefore, this drug-free treatment will require a specific dose and administration time to achieve its maximal therapeutic effect. Furthermore, it is not clear whether physical activity, physical exercise, or exercise training (definitions commented in[5]) drives the cognition-enhancing responses. In this scenario, a reproducible physical exercise protocol should include: (1) an indicator of the achieved exercise intensity: external load markers (or the work completed independent of internal characteristics), internal load markers for the assessment of individual demands, i.e., blood lactate levels at the end of the session, oxygen consumption, heart rate, *etc.* (individual biological responses to the external load); (2) the desired therapeutic dose of physical exercise to counterbalance, for example in this case, memory impairment in Alzheimer's disease pathology. An incremental loading test with an increasing workload as a percentage of the animal's body weight until exhaustion would determine the animal's maximal workload. Then, intensity could be calculated, for example, 65% of the maximal capacity, as shown in Boström et al.;[8] (3) the adaptation protocol for exercise should be also defined and standardized. Because mice are aversive to water and environmental stress, shorter habituation periods

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might influence the results across exercise protocols, mouse strains, and rodent species.[10]

The exercise paradigm presented in Lourenco et al.[3] involved the use of different mouse strains submitted to swimming exercise, 1 h/day, 5 days/week, for 5 weeks, with a habituation protocol set at 10 min/day for 2 days. Most protocols in the literature have shown that mice require about 1 week for the habituation to the acute stress induced by physical exercise.[8,10,11] In addition, each parameter needs to be defined for a specific mouse strain. Indeed, C57BL/6 mice are smaller than Swiss mice and less resistant to long exercise sessions. The intensity of the swimming exercise regime could be set up by determining, for example, the maximal lactate steady state,[10] which also needs to be determined in all mouse strains and exercise protocols involved in a particular study. Thus, it is difficult to conclude whether the mice in the Lourenco et al.[3] study were submitted to aerobic exercise as claimed by the authors. Using the appropriate exercise regimes for each strain might have allowed Lourenco et al.[3] to identify the dose of physical exercise required to boost irisin-dependent cognition.

We believe that studies involving physical activity, physical exercise, or exercise training should be precisely described in detail so that they can be reproduced in other research laboratories, and, more important, can be assessed for their translational impact.[5] An accurate physical exercise prescription aims to provide a comparable exercise dose, that is, for use in clinical trials, considering that higher intensities and repetitions are often recommended to promote beneficial effects on the neurobiological system.[4,12] For cognition-enhancing strategies with exercise-based approaches, it is necessary to analyze the specific dose−response relationship in animals to extrapolate their data to the human cognitive impairment. Finally, studies should also determine whether the exercise-induced effects last for a considerable amount of time or whether they decrease after days or weeks of not exercising.

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Authors' contributions

TG, ACdBA, EMR, AL, JS, and HB wrote the paper; TG and ACdBA contributed equally to this work. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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