

Original Article (short paper)

Moderate-intensity exercise training improves long-term memory in fructose-fed rats

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Abstract – Aim: Animal disease model studies are widely used to show the effectiveness of physical exercise to improve cognitive function. Thus far, few studies are investigating the effects of exercise training on memory performance in fructose feed animals. **Method:** The present study investigated the effects of physical exercise protocol carried out with three weekly sessions, on the short and long-term memory performance of animals fed with fructose. Male Wistar rats were divided into sedentary (SD); sedentary+fructose (SDF); trained (TR); trained+fructose (TRF). Treadmill running sessions consisted of a five-minute warm-up at 20% maximum speed (MS) followed by 40 minutes at 40% MS and a 5-minute cool-down at 20% MS. Sessions were carried out three days a week (Monday, Wednesday, and Friday) for six weeks. Object Recognition Test was used to evaluate short and long-term memory. **Results:** The access to fructose altered food intake and drinking volume, as fructose-fed animals had lower food intake (SDF: -27% and TRF: -24%) and higher drinking volume (SDF: +49% and TRF: +45%) than an animal which drank water. Trained groups had lower epididymal fat pad compared to their sedentary counterparts (TR: -30% and TRF: -11%). In addition, TR and TRF had an improvement in glucose tolerance. Regarding memory performance, neither fructose intake nor exercise training influenced short-term memory. On the other hand, long-term memory was enhanced by exercise training. An improvement of about 39% was observed for TR and the largest effect was seen for TRF, which improved long-term memory in 76%. **Conclusion:** In conclusion, moderate-intensity exercise training, carried out three days a week, for six weeks was effective to improve long-term memory in fructose-fed rats. This result was related neither to the visceral fat amount nor to the glucose metabolism. Further studies should consider the investigation regarding cerebral areas, associated with memory that might be adapted facing physical exercise.

Key words: physical exercise, fructose, cognitive function

Introduction

The increase in processed food intake, which has high fructose content, has been linked to a higher prevalence of cardiovascular diseases, non-alcoholic fatty liver disease, type 2 diabetes, and obesity^{1,2}. Excessive fructose consumption induces oxidative stress, insulin resistance, high blood pressure, and impaired appetite hormone signaling³, features that could be associated with changes in cognitive function, which comprises the phases of the information process, perception, learning, memory, attention, surveillance, reasoning and problem solving, psychomotor functioning, reaction time, movement time and performance speed⁴⁻⁶.

The mechanisms in which excessive fructose intake might lead to cognitive impairment are not yet fully elucidated⁷. The hypotheses include insulin resistance that would lead to the functional decline of hippocampus^{8,9}, increased blood pressure, oxidative stress, and inflammation that impairs short and long-term working memory¹⁰.

On the other hand, the beneficial effects of exercise training to prevent or manage cardiovascular¹¹ and metabolic diseases¹² is well recognized. Animal model studies carried out in our laboratory have shown that moderate-intensity aerobic exercise, performed five days a week, preserved endothelial function in rats fed a highly palatable diet rich in sugar and fat¹³, prevented weight gain and the accumulation of visceral fat¹⁴.

Regarding the impact of exercise training on cognitive performance, the majority of studies have investigated the effects of aerobic exercise training to revert memory impairment. Aerobic exercise, performed five days a week, was effective to counteract neurodegeneration, improve spatial learning and long-term memory in a rat model of Alzheimer¹⁵. Improvement in short-term memory and spatial learning was seen in rats that suffered cortex injury and were submitted to daily exercise sessions¹⁶, a similar result was seen in an intracerebral hemorrhage model¹⁷. Type 1 diabetic rats have also performed better in spatial memory testing after physical training¹⁸. One of the few studies carried out with healthy animals showed that Wistar

rats submitted to aerobic exercise training had working memory and spatial memory improved¹⁹.

Nevertheless, an emerging question in sports science is related to the establishment of a minimal amount of physical exercise, which might cause improvement in different physiological systems function. It is already known that physiological adaptations, including cerebrovascular, are dependent on physical exercise intensity²⁰.

Animal disease model studies are widely used to show the effectiveness of physical exercise to counteract neurodegeneration and improve cognitive function. These studies were carried out using exercise training protocols with five weekly sessions that take up to 60 minutes per session. Taking into account the prevalence of insufficient physical activity in adults this training protocol might not be feasible, as most people do not accumulate this amount of exercise per week²¹. Considering the importance of translational research, the present study investigated the effects of physical exercise protocol carried out with three weekly sessions, on the short and long-term memory performance of animals fed with fructose.

Methods

Animals and procedures

Forty male Wistar rats (444 ± 46 g; 70 days old) were divided into 4 groups according to the protocol of exercise training (sedentary or trained) and drink offered (water or fructose solution) as follows: sedentary (SD, n=9), sedentary + fructose (SDF, n=9), training (TR, n= 11), training + fructose (TRF, n=11). The animals were randomized into groups after a one-week treadmill familiarization. Only the rats, which were able to maintain a running behavior, were randomly allocated in trained groups.

Animals were housed in collective polypropylene cages (41×34×30 cm) (five animals/cage) and kept under a 12h light/dark cycle. For the duration of the experiment (7 weeks), animals had free access to standard chow and drinking tap water or fructose solution (10%). Food intake was measured daily by weighing the remaining chow and subtracting the chow amount placed the day before on the cage top. The values were divided by the number of rats maintained in the cage. Water/fructose intake was also measured subtracting the remaining amount of liquid from the amount placed into the drinker. Body weight was also measured once a week. After 48h of the last exercise session, animals were submitted to overnight fasting followed by decapitation under anesthesia with Urethane (25%, 1.25 g/kg). Epididymal fat was excised and weighted. During fasting, the fructose solution was replaced by tap water.

All procedures were reviewed and approved by the Ethics Committee on Animal Use in Research (CEUA/PUSP-RP protocol number 2016.1.462.90.7) in compliance with the "Principles of laboratory animal care" (NIH publication N° 86-23, revised 1985) and the national law (CONCEA publication N° 11.794, 2008).

Incremental maximal treadmill test and exercise training protocol

Before the incremental maximal test and training protocol, animals were submitted to a familiarization period with increments in running speed and minutes along the week (Table 1). After this period, rats underwent an incremental treadmill test (adapted from²²), beginning at 11.6 m/min followed by progressive increases of 1.6 m/min every 2 minutes until 20 m/min. Subsequently, the speed was increased by 3.2 m/min until exhaustion (determined when the animal touched the bottom of the bay five times within one minute). The exhaustion speed was used to determine maximal speed (MS) using the following equation: $MS = W1 + (W2 \times t/120)$, where W1= exhaustion speed, W2= speed increase (1.6 m/min or 3.2 m/min), t= duration of the incomplete test stage²³.

Table 1 - Scheme of running familiarization

Days of familiarization	1st	2nd	3th	4th	5th
Speed (m/ min)	5	5	10	10	IMT
Exercise time (minutes)	30	60	30	60	

IMT: Incremental Maximal Test

Exercise training protocol

Physical exercise sessions were carried out on Mondays, Wednesdays, and Fridays, in the same period of the day (11 a.m to 2 p.m.) for six weeks. Running sessions consisted of a five-minute warm-up at 20% MS followed by running at 40% MS for 40 minutes and a cool-down at 20% MS for 5 minutes. At the final of the 3rd week, trained rats underwent Incremental Maximal Test, as previously described, to adjust speed training and guarantee the maintenance of exercise intensity during the six weeks.

Short and Long-term memory evaluation

Object Recognition Test was used to evaluate memory performance as previously described²⁴. Briefly, on the first day, rats were submitted to a habituation session in an open field (45 × 40 × 60 cm), during which they were placed in the empty arena for 5 min. On the following day, rats were given one 5-min training trial in which they were exposed to two identical objects (A1 and A2). The objects were positioned in two adjacent corners, 9 cm from the walls. Ninety minutes after the training trial, rats were allowed to explore the open field for 5 min in the presence of two objects: the familiar object A and a novel object B, which are placed in the same locations as in the training trial. In this trial, short-term memory was evaluated. On the long-term memory testing trial (24 h after the training trial), rats were allowed to explore the open field for 5 min in the presence of two objects: the familiar object A and a third novel object C. All objects presented similar textures, colors, and sizes, but distinctive shapes. Object exploration was measured

using two stopwatches to record the time spent exploring the objects during the experimental sessions. Sniffing or touching the object with the nose was considered as exploration behavior. The recognition index (RI) for each animal was determined using the following equation: $RI = TB / (TA + TB)$, as TA: time spent exploring the knowing object; TB: time spent exploring the novel object.:

Glucose Tolerance Test

Being fasting for 8 hours, glycaemia was determined before and 30, 60, 90, and 120 minutes after intraperitoneal glucose injection (2g/kg) (25). Blood samples were collected from the animal tail to determine blood glucose using test strips (Accu-CheckAdvantage- Roche). The area under the curve was calculated using GraphPad Prism software.

Statistical procedures

Data are presented as means \pm standard error of the mean (SEM). All data were assessed for normality using Kolmogorov and Smirnov test. Analysis of variance (two-way ANOVA) followed by Bonferroni post-hoc test was used to identify differences between groups. Factors analyzed were exercise (yes/no) and diet (fructose or water). The strength of association between independent variables (memory performance, glucose tolerance, and epididymal fat mass) was determined by the Pearson correlation coefficient. Data analysis was done using GraphPad Prism software. Statistical significance was considered at 5% ($P < 0.05$).

Results

Body weight gain was not altered either by fructose ($F_{(1,38)} = 0.43, p = 0.51$) or physical exercise ($F_{(1,38)} = 2.08, p = 0.16$). However, epididymal fat mass was affected by either fructose intake ($F_{(1,38)} = 11.65, p = 0.002$) or physical exercise ($F_{(1,38)} = 5.32, p = 0.03$) without interaction between factors. Trained groups had diminished fat mass compared with their sedentary counterparts (about 30% for TR and 11% for TRF). The results are in figures 1A and 1B. Fructose influenced food intake and drinking volume, as fructose-fed animals had lower food intake ($F_{(1,38)} = 33.35, p < 0.001$, fig 1C) and higher drinking volume ($F_{(1,38)} = 24.01, p < 0.001$, fig 1D) than an animal which drank water. Interaction between physical exercise and diet was observed for drinking volume ($F_{(1,38)} = 7.07, p = 0.02$), highlighting the different effects of physical exercise on drinking volume between trained groups. While SD and TR had also the same drinking volume in the 6th week, TRF tends to drink less than SDF (fig 1D).

Physical exercise prevented the raise of fasting glucose ($F_{(1,38)} = 4.83, p = 0.04$, fig 3A) and provided a better glucose tolerance, as demonstrated by a lower area under the curve in TR and TRF ($F_{(1,38)} = 8.15, p = 0.01$, fig 2B and 2C).

Regarding memory performance, neither fructose intake ($F_{(1,38)} = 0.22, p = 0.64$) nor exercise training ($F_{(1,38)} = 0.00, p = 0.99$) influenced short-term memory. On the other hand, long-term memory is enhanced by exercise training. An improvement of about 39% was observed for TR and the largest effect was seen for TRF, which improved long-term memory by 76% (figure 3).

A weak correlation was observed between long-term memory performance and glucose tolerance in trained animals ($r = 0.39, p = 0.08$). A similar result was verified between long-term memory performance and epididymal fat mass ($r = -0.11, p = 0.63$) (figure 4).

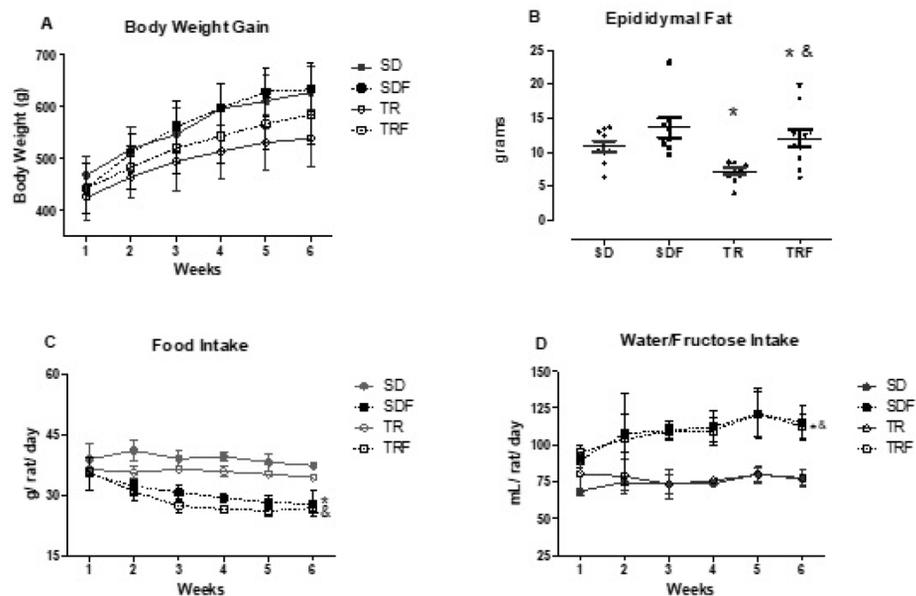


Figure 1 - Body weight gain (A), epididymal fat (B), food intake (C) and water or fructose intake (D) from Sedentary (SD), Trained (TR), Sedentary-Fructose (SDF), Trained-Fructose (TRF). Data are mean \pm SEM for n=9-11 each group. Two-way ANOVA followed by Bonferroni post hoc ($p < 0.05$). *physical exercise effect; &fructose effect.

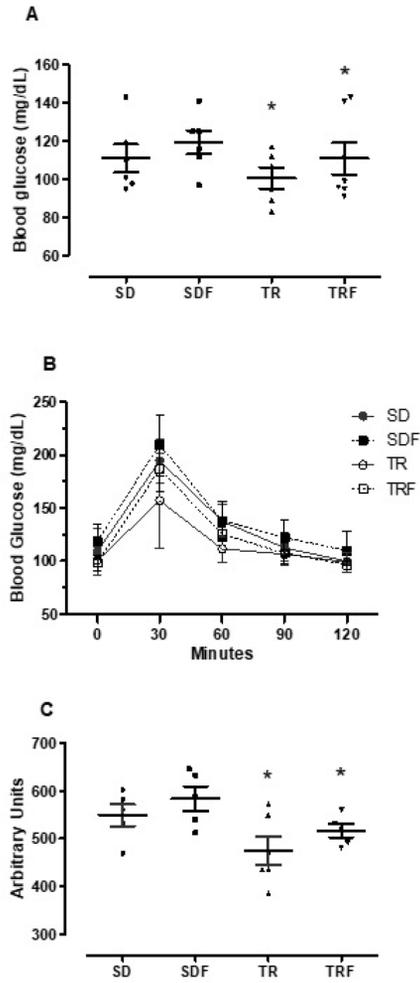


Figure 2 - Fasting Glucose (A), blood glucose kinetics during glucose tolerance test (B) and area under the curve from glucose tolerance test (C) from Sedentary (SD), Trained (TR), Sedentary-Fructose (SDF), Trained-Fructose (TRF). Data are mean ± SEM for n=6-7 each group. Two-way ANOVA followed by Bonferroni post hoc (p<0.05). *physical exercise effect.

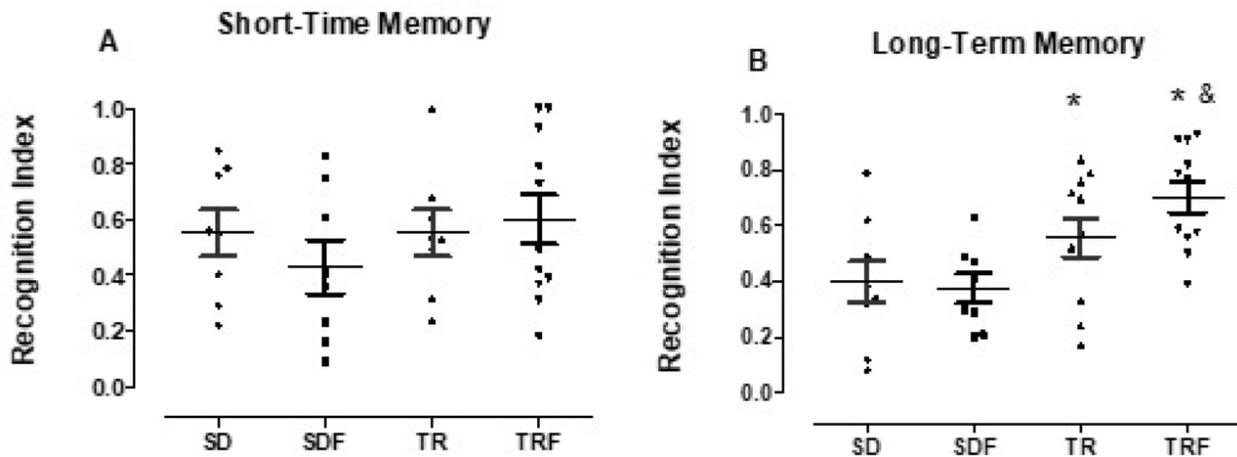


Figure 3 - Recognition Index for Object Recognition Test, carried out 90 minutes after previous object exposition (panel A) and Object Recognition Test carried out 24 hours after previous object exposition (panel B) from Sedentary (SD), Trained (TR), Sedentary-Fructose (SDF), Trained-Fructose (TRF). Data are mean ± SEM for n=9-11 each group. Two-way ANOVA followed by Bonferroni post hoc (p<0.05). *physical exercise effect; &fructose effect.

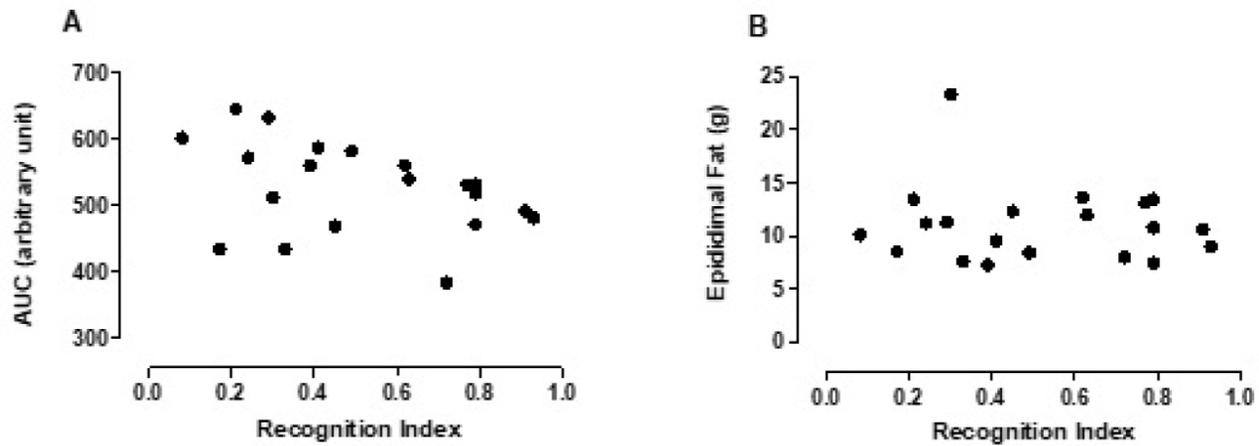


Figure 4 - Pearson correlation coefficient between the long-term memory performance and area under the curve from glucose tolerance test (panel A) and epididymal fat mass (panel B).

Discussion

Modern humans live in an environment that demands very low daily physical activity, as a result, chronic diseases prevalence raises as sedentary behavior is increased²⁶. In addition, our environment is full of food cues that may promote overeating of high-sugar, high-fat palatable foods which in turn increases cardiometabolic disease²⁷. The negative impact of physical inactivity and poor nutritional habit on cognitive performance are poorly studied^{5,28}.

Our results have shown that fructose intake, per se, did not provoke major body weight or epididymal fat gain. Similar results were seen in Fisher rats fed with a 60% fructose diet²⁹ and C57BL/6 mice fed with a 40% fructose diet³⁰. As expected, trained groups had lower epididymal fat amounts compared to their sedentary counterparts. The effects of exercise training on the prevention of fat gain have already been demonstrated in rats fed with either standard chow or a high-fat diet^{14,31}. Eating behavior was modified by fructose intake as SDF and TRF had lower food intake and higher drinking than SD and TR, which had water to drink. A similar result was observed in a previous study carried out with the same animal lineage and fructose solution concentration³². Exercise training carried out three days a week, did not affect eating behavior. However, other studies that submitted Wistar rats to five days a week treadmill training had demonstrated exercise effect to lower food intake^{33,34}.

Regarding fructose-fed effects on cognitive function, Sprague-Dawley rats fed with fructose (10%) during eight months had impaired performance in spatial memory test⁹. A similar result was seen in C57BL/6J mice fed with fructose (15%) during eight weeks³⁵. However, this study failed to demonstrate

the detrimental effect of fructose-fed on memory performance. It might be related to the lower fructose concentration offered (10%) and/or the short-term duration of the experimental protocol (6 weeks).

On the other hand, the exercise training protocol proposed in the present study, which was carried out during six weeks with three days per week sessions was sufficient to enhance working memory performance in both trained groups. Improvement in spatial memory was seen in rats fed with a high-fat diet and submitted to treadmill running five days per week during eight weeks³⁶. Mice fed with high fat or high fructose diets and submitted to treadmill running five days per week, during 23 weeks, did not have impairment on spatial memory and working memory³⁷.

Our results demonstrated that trained animals had improvement in memory performance as well as better glucose metabolism and lower epididymal fat. Therefore, we investigate if peripheral factors influenced memory performance. It is well known that impaired peripheral glucose uptake and metabolism, due to insulin resistance, extends to impairment of insulin signaling within the hippocampus and impairs learning and memory³⁸. A recent study demonstrates that insulin resistance, induced by LPS intracerebral injection, promotes memory impairment, which is nullified by intracerebral injection of insulin³⁹. In addition, obesity appears to have a deleterious effect on cognition as low-grade systemic inflammation precipitates local inflammation within the hypothalamus that alters synaptic plasticity, contributes to neurodegeneration, and even initiates brain atrophy⁴⁰.

However, a non-significant association between the area under the curve (from GTT) and the long-term memory recognition index was observed. A similar result was detected between

epididymal fat, which is the indirect measure of visceral fat, and memory performance. Thus, in the present study, neither systemic glucose metabolism nor fat amount was factors that affect memory performance.

Probably, local mechanisms would have a greater association with this response. The impairment of cognitive function has been attributed to cerebral microvascular complications⁴¹ as it was observed an inverse association between cerebral blood flow and cognitive performance in Alzheimer's patients⁴² and hypertensive middle-aged adults⁴³. Endothelial dysfunction in brain capillaries would lead either to an increase in tau protein phosphorylation or its aggregation⁴⁴. In addition, the increase of blood-brain barrier permeability, observed in high-fat diet mice, is related to inflammation and leucocyte recruitment precedes neurodegeneration and the memory performance decline⁴⁵.

Physical exercise has long been recognized as a non-pharmacological approach that improves vascular function^{31,34}, insulin signaling, and glucose metabolism^{14,46}. The anti-inflammatory effect of physical exercise has also been described⁴⁷. Recently, the existence of muscle-brain crosstalk was proposed. Myokines such as cathepsin B and irisin have been recognized as promoters of brain neurotrophic factor (BDNF)⁴⁸. Physical exercise induces astrocytic plasticity and enhances cognitive performance in either healthy or diabetic rats¹⁸. The type and intensity of exercise training are a factor that might modulate brain adaptation response. In older rats, both moderate-intensity aerobic training and strength training improved spatial memory through distinct molecular mechanisms of neuroplasticity, showing that the effects of physical exercise on brain plasticity and spatial memory occur in an exercise type-dependent manner⁴⁹. A recent study shows that Wistar rats, with cognitive impairment induced by scopolamine, submitted to treadmill running at moderate intensity (70% of maximal speed) exhibit better memory performance and higher expression of BDNF and synaptophysin in the hippocampus than rats trained at a lower intensity (40% of maximal speed) (CEFIS et al., 2019). However, this dose-response effect appears to be limited. Female mice submitted to treadmill running at high intensity had no improvement in spatial discrimination and had a lower response in terms of the increase in neurotrophic factors compared with mice that ran at moderate intensity⁵⁰.

In conclusion, moderate-intensity exercise training carried out three days a week, for six weeks was effective to improve long-term memory in fructose-fed rats. This result was neither related to the visceral fat amount nor glucose metabolism. Further studies should consider the investigation regarding cerebral areas, associated with memory that might be adapted facing physical exercise.

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