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ORIGINAL

Continuous or interval aerobic exercise training reduces daily fructose intake in female Wistar rat

Exercício físico aeróbio contínuo ou intervalado reduz ingestão de frutose em ratas Wistar

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ABSTRACT

Objctive

Fructose consumption has increased worldwide. Excessive fructose intake has been a risk factor for the increased metabolic syndrome disorder incidence. This study aimed to investigate the possible influence of two different exercise training methods, continuous and interval, on fructose intake.

Methods

Thirty two-months-old female Wistar rats were divided into six groups: sedentary + water ; sedentary + fructose ; continuous training + water ; interval training + water ; continuous training + fructose ; interval training + fructose . Fructose was given in drinking water (10%). Continuous (40 minutes at 40% maximal speed) or interval training (28 minutes, 1 minute at 70%; 3 minutes at 35% maximal speed) sessions were carried out 3 days/week for 8 weeks.

Results

Fructose consumption decreased food intake with a concomitant increase in fluid intake. Continuous and interval training did not modify food intake but progressively reduced fructose ingestion. In the 8th week, interval training + fructose and continuous training + fructose groups drank less fructose solution, 35% and 23%, respectively, than sedentary + fructose group.

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Conclusion

The findings indicate that both continuous and interval aerobic exercise training seem to modulate food behavior, possibly by mitigating the craving for sweetness, with interval training being more effective in reducing fructose intake than continuous exercise.

Keywords: Appetite. Exercise. Female. Fructose.

RESUMO

Objetivo

O consumo de frutose aumentou em todo o mundo. A ingestão excessiva de frutose tem sido implicada como um fator de risco do aumento da incidência de distúrbios da síndrome metabólica. Nesse contexto, este estudo teve como objetivo investigar a possível influência de dois métodos diferentes de treinamento físico, contínuo e intervalado, na ingestão de frutose.

Metodos

Trinta ratas Wistar foram divididas em seis grupos: sedentário + água, sedentário + frutose, treinamento contínuo + água, treinamento intervalado + água, treinamento contínuo + frutose, treinamento intervalado + frutose. A frutose foi dada na água potável (10%). Foram realizadas sessões contínuas (40 minutos a 40% da velocidade máxima) ou intervaladas (28 minutos, 1 minuto a 70%; 3 minutos a 35%) três dias por semana durante oito semanas.

Resultados

A ingestão de frutose diminuiu a ingestão alimentar, com um aumento concomitante da ingestão hídrica. O treinamento contínuo e intervalado não modificou a ingestão alimentar, mas reduziu progressivamente a ingestão de frutose. Na oitava semana, treinamento intervalado + frutose e treinamento contínuo + frutose beberam menos solução de frutose, 35% e 23%, respectivamente, do que sedentário + frutose.

Conclusão

Os achados indicam que tanto o treinamento aeróbico contínuo quanto o intervalado parecem modular o comportamento alimentar, possivelmente por meio da mitigação do desejo por sabor doce, sendo o treinamento intervalado mais eficaz para reduzir a ingestão de frutose do que o exercício contínuo.

Palavras-chaves: *Apetite. Exercício físico. Feminino. Frutose.*

INTRODUCTION

Obesity and its comorbidities are considered a public health concern worldwide with severe economic impact. Therefore, in the last years, strategies either to prevent or treat obesity have been the focus of science [1]. Obesity is a multicausal disease that includes many factors such as genetic, metabolic, and environmental interactions that lead to a positive energy balance, thereby increasing body weight [2]. Over the last decades, the rise in obesity prevalence was related, at least partially, due to the excessive consumption of fructose presented in sweetened beverages and processed foods, known as fast foods [3,4].

Fructose is a monosaccharide derived from natural sources, and when combined with a molecule of glucose, generates sucrose that is used in beverages and processed foods [5]. In the United States, fructose consumption increased more than 30% from 1977 to 2004, mainly due to the widespread use of high-fructose corn syrup as a sweetener in soft drinks, candy, and other processed foods. On the other hand, the consumption of natural sources of fructose has decreased [3]. Several studies show that this increased fructose consumption could be related to the rising incidence of non-alcoholic fatty liver disease, type II diabetes mellitus, dyslipidemia, and metabolic syndrome [6-13]. These deleterious effects may be due to fructose hepatic metabolism through glycolytic metabolism, leading to an accumulation of fructose that is converted into lipids by *de novo* lipogenesis [14,15].

In addition to metabolic disorders, sweetened foods or drinks could induce addiction similar to those observed with drugs such as cocaine or alcohol [16,17]. The mechanisms underlying this response are the same: either sugar or drugs stimulates reward systems modulated by dopaminergic and opioid pathways, which leads to a feeling of comfort [18,19] and even alter the sensibility of the dopaminergic and opioidergic systems that regulate reward [20]. Reward responses to food are closely related to food choice and may lead to caloric overconsumption [21]. Then, it seems plausible to speculate that the reward system can override the metabolic regulatory system, which in turn is responsible to control the hunger satiety cycle.

Recent studies have demonstrated that physical exercise exerts a beneficial effect and could be an effective approach to treating chemical dependence [22,23]. It seems that exercise-induced protective roles in drug addiction promote synaptic plasticity and neurogenesis, reducing apoptosis in mesocorticolimbic brain regions [24]. Most studies showing the beneficial effects of exercise training were carried out using the continuous training method [17]. However, the intermittent training method is emerging as a possible strategy to conduct exercise training programs for overweight people as it is more challenging and breaks the monotony of training reducing perceived exertion [25]. Moreover, this training method seems to be more enjoyable than the continuous method, which is relevant for improving exercise compliance [26]. Although aerobic exercise training responses in different organ systems are well documented in male experimental models, studies on whether exercise training affects non-ovariectomized females are still scarce.

Despite these findings on physical exercise effects on drug addiction, the influence of physical exercise on sweetened foods or drinks consumption remains unclear. Moreover, the effects of exercise on the reward system and also sweet craving behaviors are sex-dependent phenomena [27-29]. Thus, this study aimed to investigate the possible influence and differences of two different exercise trainingww methods on fructose intake in female Wistar rats.

METHODS

Thirty female Wistar rats (60 days old) were housed in collective polypropylene cages (41×34×30 cm) with five animals each and kept under a 12-hour light/dark cycle. During the experiment, which lasted 8 weeks, animals had free access to standard chow and drinking tap water or fructose solution (10%) [30]. Caloric intake was calculated based on the daily animal's cage chow intake using the caloric information provided by the manufacturer. To determine the caloric value of fructose, it was considered 4 kcal per gram of fructose intake. Food consumption and water/fructose solution intakes were daily assessed between the first and eighth week of the study, as body weight was measured once a week. At the end of the training protocol, animals were submitted to fasting for 8 hours, followed by euthanasia under anesthesia with Thiopental Sodium 35 mg/kg, *i.e.* Retroperitoneal and perirenal fat pads were excised, weighed, and the values were summed and considered as visceral fat. During fasting, fructose solution was replaced by drinking tap water (Figure 1).

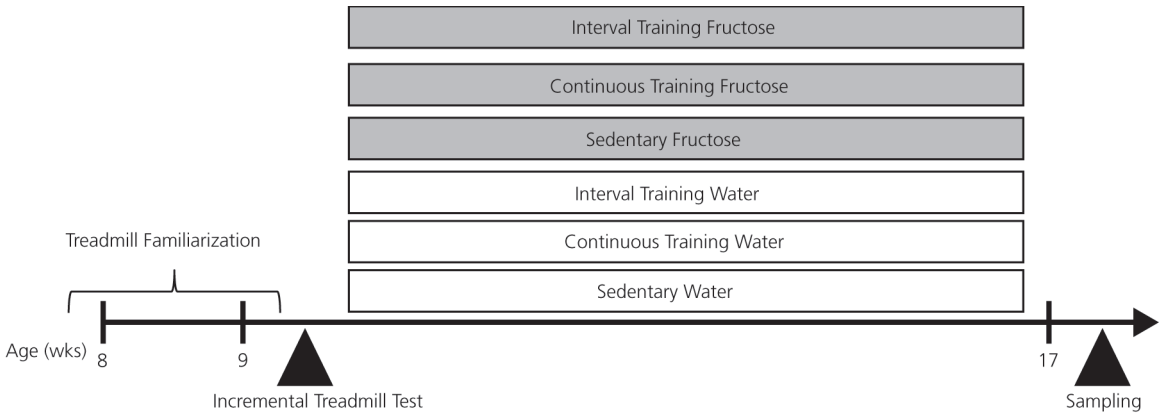

Figure 1 – Study design.

All procedures were reviewed and approved by the *Comissão de Ética no Uso de Animais* (Ethics Committee on Animal Use) *Prefeitura do Campus USP de Ribeirão Preto* (City Hall of the USP Campus of *Ribeirão Preto*) Protocol nº 14.1.874.53.7, in compliance with the "Principles of laboratory animal care" (NIH publication nº 86-23, revised 1985) and the Brazilian law (*Conselho Nacional de Controle de Experimentação Animal* (Brazilian National Council for Animal Experimentation Control) (Publication nº 11.794, 2008).

Maximum incremental test on treadmill and exercise training protocol

Rats were divided into six groups, according to the protocol of exercise training (interval and continuous) and drink offered (water or fructose solution), as follows: Sedentary + Water (SW); Sedentary + Fructose (SF); Continuous Training + Water (CTrW); Interval Training + Water (ITrW); Continuous Training + Fructose (CTrF); Interval Training + Fructose (ITrF).

Prior to maximal incremental test and training protocols, animals underwent a period of familiarization with treadmill running, consisting of one week of running exercise at 10 m/min for 30 minutes daily. After this period, all rats underwent an incremental test on treadmill, beginning at 11.6 m/min, followed by progressive increases of 1.6 m/min every 2 minutes until 20 m/min. Subsequently, speed was increased by 3.2 m/min with rats running 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: $MS=W_1 + (W_2 \times t/120)$, where W_1= exhaustion speed, W_2= speed increase (1.6 m/min or 3.2 m/min), t = incomplete test stage duration [31]. Only the rats that managed to maintain the running behavior were randomly allocated to trained groups, keeping five animals per group, with no sample loss during the physical training protocol.

Aerobic continuous and aerobic interval exercise training protocols

Both exercise regimens were based on and adapted from a previous study and were carried out for 8 weeks, 3 times a week (Monday, Wednesday, and Friday), in the morning [32]. Aerobic Continuous Exercise Training (CTr) consisted of a five-minute warm-up (running at 30% of MS) followed by 40 minutes of running and a 5-minute cooldown. Running velocity was progressively increased over the weeks of training, beginning at 30% until 40% of MS. The aerobic Interval Exercise Training (ITr) consisted of a five-minute warm-up (running at 30% of MS) followed by 28 minutes of running (7 cycles of 1 minute at 70% of MS and 3 minutes of active rest at 35% of MS) and a 5-minute cooldown. Running velocity was also progressively increased over the weeks of training. Table 1 shows exercise training details regarding intensity progression during the weeks. All animals completed the 8 weeks of physical training.

Table 1 - Exercise intensity progression in Continuous Training and Interval Training during the experimental protocol.

Weeks	Continuous Training (40-min)	Interval Training (28-min, 1:3)
	Running speed (% MS)	Running speed (% MS)
1	30	50-30
2	30	50-30
3	35	60-30
4	35	60-30
5	40	70-35
6	40	70-35
7	40	70-35
8	40	70-35

Note: CTr: Aerobic continuous exercise training; ITr: Aerobic interval exercise training; MS: Maximal Speed.

Data are presented as means ± standard error of the mean (SEM). All data were assessed for normality using Kolmogorov and Smirnov tests. MANOVA followed by Tuckey posthoc test was carried out considering exercise (no exercise, continuous exercise and interval exercise) and fructose (yes/no) as fixed factors, and dependent variables were weekly food and water/fructose intake. Data analysis was done using IBM®SPSS® Statistics 20. Statistical significance was considered at 5% (p<0.05).

RESULTS

Food intake was not greatly modified either by continuous or interval aerobic exercise training either in water or fructose groups. However, all fructose groups fed less than their peers who had access to drinking water (reduction of about 37% for SF, 40% for ITrF, and 32% for CTrF at the 8th week) (Figure 2, panel A).

To verify if this reduced food intake in fructose-fed animals was related to fructose intake, the fluid intake of these animals was analyzed. From the first week of protocol, fructose-fed groups presented increased fluid intake of 239% for SF, 266% for ITrF, and 196% for CTrF compared with their peers who had access to drinking water (SW, ITrW, and CTrW). Both exercise regimens did not modify fluid intake in water access groups (SW, ITrW, and CTrW). An interesting result was observed for fructose access groups. Interval or continuous aerobic exercise progressively reduces fructose intake from the 3rd until the 8th week. From the 5th week, the difference between interval and continuous training group was observed, and ITrF had lower fructose intake than CTrF. In the 8th week, ITrF drank 35% and CTrF drank 23% less than SF (figure 2, panel B). Despite eating less, the daily caloric intake of fructose groups (SF, ITrF, and CTrF) was similar to their water peers, due to increased fructose solution intake (Figure 2, panel C).

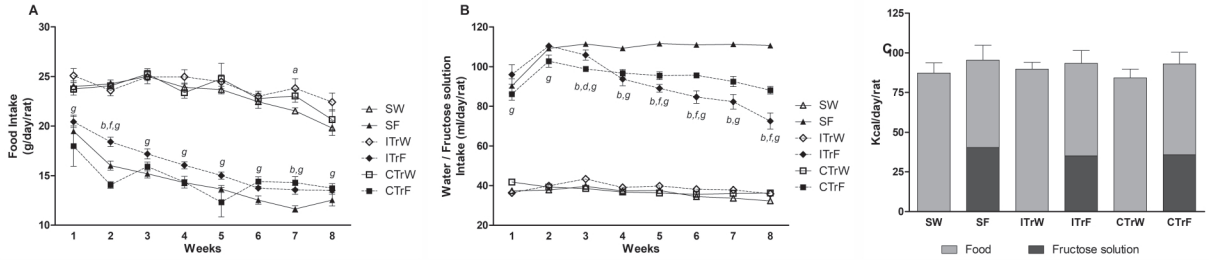

Figure 2 - Food intake (panel A), water/fructose solution intake (panel B) and calories source (panel C) in experimental goups.
Note: Data are mean±SEM (MANOVA two-way; p<0.05), a,b,c,d,e, and f different from SW, SF, ITrW, ITrF, CTrW, and CTrF, respectively, g difference between fructose groups and water groups. CTrF: Continuous Training+Fructose; CTrW: Continuous Training+Water; ITrF: Interval Training+Fructose; ITrW: Interval Training+Water; SF: Sedentary+Fructose; SW: Sedentary+water.

Body weight gain was not different among groups (Figure 3, panel A). Although the visceral fat pad of SF was 46% higher than in SW, statistical significance was not reached. Interval or continuous aerobic exercise training had the same effects for either water or fructose access groups (Figure 3, panels A and B).

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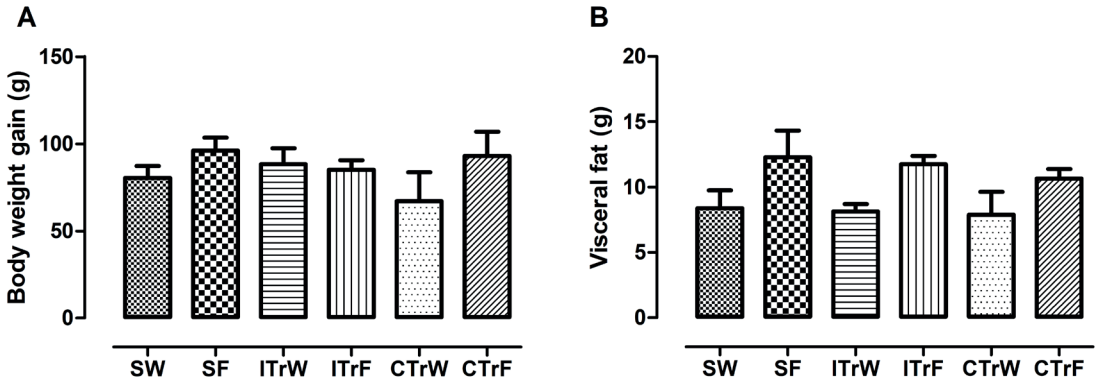

Figure 3 – Body weight gain (panel A) and visceral fat pad (panel B) in Sedentary+water (SW), Sedentary+Fructose (SF), Interval Training+Water (ITrW), Interval Training+Fructose (ITrF), Continuous Training+Water (CTrW), Continuous Training+Fructose (CTrF).
Note: Data are mean±SEM (MANOVA two-way; $p<0.05$).

DISCUSSION

An investigation was carried out on whether different training methods could influence fructose intake in female Wistar rats. The main findings demonstrate that fructose consumption decreased food intake with a concomitant increase in fluid intake during 8 weeks of both training regimes. In addition to this, both exercise training regimens reduced fructose ingestion from the 3rd until the 8th week, being interval training more effective. The results suggest that both continuous and interval aerobic exercise training could modulate food behavior.

It has been shown that fructose has a high sweet taste that can stimulate reward pathways [33,34] similar to some drugs of abuse such as cocaine [17]. Changes in food behavior found in the groups are consistent with those found by Kanarek and Orthen-Gambill [35], in which Sprague-Dawley rats increased fructose solution intake (32%) even when they had free access to drinking water. Therefore, it suggests that increased fluid intake in fructose-fed groups in the present study was not due to thirst reflex, but it seemed to be caused by a change in food behavior per se, since the animals prefer the bottle containing fructose instead of drinking water.

Since increased fructose intake seems to stimulate reward systems similar to other drugs, physical exercise training was used as a non-pharmacological tool in an attempt to understand how it could affect this pattern of food behavior [33]. A recent review showed that treadmill and voluntary wheel running are the most common types of exercise training used to treat cocaine, alcohol, and nicotine abuse in male animals [24]. Furthermore, an experimental study with C57BL/6J female mice using voluntary wheel running found that exercise decreased alcohol consumption by modulating the expression of genes involved in the mesolimbic dopaminergic pathway regulation (Slc18a2, VTA, Bdnf, and Drd1a) [36]. Similar mechanisms could be involved in the decrease in fructose intake observed in this study. However, such a possibility remains to be tested in further experiments. In addition to this, recent human studies showed that exercise can influence taste perception of sweet flavors and sweet taste per se can alter food intake [37,38]. These two phenomena can also explain, at least partially, the main results found in this present study.

Another possible explanation for the role of exercise in reducing the severity of drug addiction is its neuroplasticity effect. Exercise can change neuroplasticity in mesolimbic reward pathways by increasing the protein content of FosB in the nucleus accumbens, enhancing mRNA tyrosine hydroxylase levels in the ventral tegmental area and reducing mRNA levels of dopamine D2 receptor in the nucleus accumbens, thus improving neurotransmission of dopaminergic pathways. All these molecular changes induce neuroplasticity in different areas of the brain related to reward pathways, and this effect is associated with a reduced incidence of drug abuse disorder [39]. In addition, this mechanism of neuroplasticity due to exercise training has been shown not to differ between voluntary and forced training [40].

The limitation of this study refers to the experiment duration and the lack of direct measures of the reward system in brain tissues. Furthermore, the animals' detailed body composition was not assessed, thus decrease in fructose intake and changes in body composition could not be fully explained by current data, although the changes in fat tissue shown here suggest that the exercise groups may exhibit increased muscle mass. Therefore, the measurements of these parameters are an area for further research. Since it was not used another sweet-taste beverage besides fructose solution, further studies are needed to assess whether the effects found here are reproducible with other drinks such as sucrose solution. Finally, since this experiment was conducted in an animal model, the findings here should be extrapolated to humans with caution.

In conclusion, the findings indicate that both continuous and interval aerobic exercise training seem to modulate food behavior in females, possibly by mitigating the craving for sweetness, with interval training being more effective in reducing fructose intake than continuous exercise. It is worthy to note that a previous study conducted by the authors of this study using a very similar protocol did not find the same drinking behavior changes in males as found here [30], thus emphasizin the sex-dependent effect of exercise on sweet cravings. Further studies investigating physical exercise effects on food behavior and possible molecular mechanisms signaling in the brain could help to improve and understand intervention strategies for obesity treatment and/or prevention.

CONTRIBUTORS

LK OHAROMARI, P CHIMIN, and CD DE MORAES analyzed and interpreted the data, and were major contributors in writing the manuscript. ML MANFREDI and AG JOAQUIM performed the exercise training, incremental test and collected daily animal data. All authors read and approved the final manuscript.

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