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Original Research

Can Exercise Ameliorate Memory Impairment via PPAR Gamma Activation in Rats Fed A High–Fat Diet?

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ABSTRACT

Objective: This study aimed at determining the molecular effects of exercise on obesity treatment and cognitive impairment by examining the relationship between exercise (one of the non-pharmacological approaches) and PPAR-γ.

Methods: We classified 32 rats into four experimental groups: random control (C), obese (Ob), control exercise group (C+Ex), and obese exercise (Ob+Ex). The experimental groups were fed with a high-fat diet (45% fat) and standard rodent chow. The exercise program commenced after obesity diagnosis (30 min/day) and continued until the end of the study. At the end of the study, all rats underwent a learning–memory test in a Morris water tank, and the hippocampus of all rats were removed under anesthesia to study the PPAR gamma gene expression level.

Results: The escape latency was significantly different between the exercise groups and non-exercise groups ($p<0.05$). Molecular analysis revealed an increase in PPAR-γ gene expression levels in the exercise groups compared with that observed in the non-exercise groups, but no significant difference was found when comparing the gene expression levels between the groups ($p>0.05$).

Conclusion: PPAR-γ gene expression levels were upregulated in the exercise groups. In addition, the exercise groups performed better with regards to cognitive functions. This result provides a clue about the impact of exercise on the molecular pathway with respect to performance differences in cognitive function due to obesity.

Keywords: Experimental obesity model, exercise, learning–memory, PPAR gamma

INTRODUCTION

Obesity is mainly a preventable, complex, multifactorial disease that affects more than one third of the world's population (1). Based on World Health Organization's 2016 data, obesity has tripled worldwide since 1975 (2). While obesity is more common in developed countries, years, its incidence has also significantly increased in developing countries in recent years (3). If obesity continues to rise at the same rate, 2.16 billion people (38%) will reportedly be overweight and 1.12 billion people (20%) obese by 2030 (3).

Recent studies have shown that obesity affects the central nervous system spanning learning and memory centers in the brain (4). As mechanisms that cause cognitive impairment, obesity is responsible for systemic or chronic low-grade inflammation caused by increased levels of adiposity and cytokines (such as IL-6, TNF α, and CRP) (4).

Exercise reduces body weight, prevents obesity, reduces systemic inflammation and improves insulin resistance (5). In addition, physical exercise increases the levels of brain-derived neurotrophic factor (BDNF) and IGF-I in the hippocampus, leading to regeneration of neurons therein. This promotes differentiation of progenitor cells in the hippocampus and increase in BDNF gene expression. Both BDNF and IGF-1 (which provides stimulation of proliferation and differentiation of hippocampal progenitor neurons), are raised by astrocytes in hippocampus after exercise (6). Physical activity is an important factor that increases neuroplasticity (7).

PPAR-γ is a member of the nuclear receptor superfamily and a transcription factor (8). PPAR-γ plays a role in the differentiation of adipocytes, fatty acid storage and regulation of glucose metabolism (8). PPAR-γ is the target of antidiabetics, and its agonists (such as TZD; thiazolidinediones) improve insulin resistance against the effects of cytokines such as TNF-α (8). PPAR-γ agonists act as negative regulators of monocytes and macrophages and inhibit the production of proinflammatory cytokines (such as TNF-α, IL-β, IL-6), which cause neuroinflammation (9). Furthermore, PPAR-γ activation promotes BDNF expression level in the hippocampus, therefore improving cognitive deficit in diabetes patients (10).

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In this study, the experimental rats were deliberately fed a high-fat diet to become obese. The rats were then subjected to swimming exercise for treating obesity and improve their cognitive functions. This study intends to determine the molecular effects of exercise in the treatment of obesity and cognitive impairment by examining the relationship between exercise (a non-pharmacological approach) and PPAR-γ.

METHODS

Animals and Experimental Groups

Due to ease of care, resistance to diseases, and a universal acceptance in inducing experimental obesity model, Wistar albino rats (Rattusnovergicus var. albinus, Rodentia, Mammalia) were used in the study. Thirty- two male rats were randomly distributed into four experimental groups (eight rats in each group): Control (C), Control+Exercise (C+Ex), Obese (Ob) and Obese+Exercise (Ob+Ex). All rats were housed in standard plastic cages and maintained under 12 hourly light-dark cycle at constant temperature and humidity (23 ± 1°C and 40-50 %, respectively) in the Experimental Animals Research Center of Gaziantep University. The Local Ethics Committee of Animal Experiments for all surgical and experimental protocols approved our study through approval no:2017/16 and protocol no:32. All procedures were in compliance with NIH Guide for the Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals issued by the Local Ethics Committee of Animal Experiments of Gaziantep University. C and C+Ex groups were fed with standard laboratory feed while Ob and Ob+Ex groups were fed with a high-fat diet (45 % kcal fat) to induce obesity (Table 1). All groups were given *ad libitum* access to tap water throughout the study (for sixteen weeks) (ArdenIncCo., Ankara) (11). The body masses of all rats were measured weekly.

Exercise Protocol

Rats in the C+Ex and Ob+Ex groups were trained by swimming for 30 minutes per day, seven days a week (12). Morris water maze tank was used as a swimming pool. Each group swam separately. If a rat did not complete the 30 min-exercise, it was removed from the tank, after 30 min-exercise protocol, it swam for remaining time.

Morris Water Maze Test

The Morris water maze is a round pool of 180 cm in diameter and 70 cm in height. The reference memory of all animals was tested by applying spatial acquisition at the end of the 16th week (13). The tank was filled with tap water at 22 ± 2°C opacified with powder black food coloring (14). All rats performed four trials per day for four consecutive days. After the acquisition days, rats underwent a probe trial (15). Escape latency was recorded to assess memory by Etho Vision XT 11.5 video tracking system.

Main Points:

- We have found statistically significant difference between C – Ob and C+Ex -Ob+Ex.
- The escape latency was significantly different between the exercise groups and non-exercise groups.
- Molecular analysis revealed an increase in PPAR-γ gene expression levels in the exercise groups compared with that observed in the non-exercise groups, but no significant difference.

Hippocampus Isolation

The animals were anesthetized with ketamine and xylazine (80 mg/kg and 15 mg/kg, respectively), and hippocampus tissues were dissected from the whole brain.

Gene Expression Analysis

We extracted the total RNA from the hippocampus tissue using RN easy Mini kit (QIAGEN, No:74104) according to the manufacturer's protocols. RNA concentration was determined using Epoch Micro-Volume Spectrophotometer System (BioTech, Winooski, United States). The RNA samples were converted to cDNA using the Qiagen RT2 First Strand Kit (QIAGEN Cat No: 330404). Expression of the PPAR-γ gene was determined by using the Qiagen RT^{2}q PCR kit and primer assay for rat PPAR-γ gene (Cat No: PARN-149Z) GAPDH were used as housekeeping gene (Cat No: PPR06557B).

Gene expression data was obtained as ct values (ct = the cycle number at which logarithmic PCR plots cross a calculated threshold line). CT values were used to calculate ΔCT values (ΔCT =ct of the target gene - ct of the housekeeping gene). We obtained fold changes according to the transformation $2^{-\Delta CT} \times 10^{-4}$ and were expressed as arbitrary units.

Data Evaluation

To statistically analyze the weight values for the first eight weeks, the Student's t-test was applied using the Statistical Package for Social Sciences version 20.0.0 (IBM SPSS Corp.; Armonk, NY, USA)

Table 1. The Composition of High–fat diet

Component	% (Gr)
Casein	200.00
L–Cystin	3.00
Cornstarch	72.8
Maltodextrin	100.00
Sucrose	172.8
Soya oil	25.00
Cellulose	50.00
Lamb tail oil	177.5
Mineral Mix (S10026)	10.00
Dicalcium Phosphate	13.00
Calcium Carbonate	5.5
Potassium citrate (H2O)	16.00
Vitamin Mix (W10001)	10.00
Choline	2.0
Sum	858.1

Table 2. Average weight figures for the first eight weeks

Group	C	Ob	C+Ex	Ob+Ex
Mean±SD	307.00±6.00	385.00±44.00[δ]	315.00±11.00	377. 00±37.00[β]

[δ]The statistical significance between the control group (C) and the obese group (Ob) is illustrated in the table: $p<0.05$. [β]The statistical significance between the control exercise (C+ Ex) and the obese exercise group (Ob+Ex) is illustrated in the table: $p<0.05$.

Table 3. Morris Water Tank Learning/Memory parameters

	C	Ob	C+Ex	Ob+Ex
t(s)	51.25±12.34	74.38±14.14[a]	27.00±5.23[bc]	42.25±5.20[de]

[a]Statistically significant difference observed between the control (C) and obese groups (Ob): $p<0.05$.
[b]Statistically significant difference between the control (C) and control – exercise (C+Ex) groups: $p<0.05$.
[c]Statistically significant difference between the obese (Ob) and control – exercise (C+Ex) groups: $p<0.05$.
[d]Statistically significant difference between the obese (Ob) and obese – exercise (Ob+Ex) groups: $p<0.05$.
[e]Statistically significant difference between the control exercise (C+Ex) and obese – exercise (Ob+Ex) groups: $p<0.05$.

Table 4. Summary table for the elevation of the PPAR–γ gene expression levels

Control and Obese Group	Control and Control Exercise Group	Obese and Obese Exercise Group	Control Exercise and Obese Exercise Group
reduction by 2,914	elevation by 1,344	elevation by 3,127	reduction by 1,253
p: 0.524	p: 0.322	p: 0.6	p: 0.0045

and the weight data of the control, control exercise, obese, and obese exercise groups were described as mean ± standard deviation (mean ± SD) values.

We performed a one-way ANOVA Analysis with SPSS 20.0.0 for the "escape latency" data obtained from the results of the learning–memory experiment. Tukey's HSD was used post-hoc for the comparison of all groups, and the "escape times to the platform" data were provided in mean ± standard deviation values.

We applied the student's t-test to analyze the genetic data and compare two independent groups with the same version software. In the comparison of the groups, the expression level of the PPAR-γ gene was expressed in terms of the fold change values.

RESULTS

The Effect of a High-Fat Diet on the Weight of Rats

We observed a significant difference between the mean values of the control – obese group and the control exercise – obese exercise groups in the evaluation of the group weights for the first eight weeks ($p<0.05$) (Table 2).

Morris Water Tank Test Results

The test revealed a significant difference in the escape of latency between the C and Ob groups, C and C+Ex groups, Ob and Ob+Ex groups ($p<0.05$) (Table 3).

A video tracking system recorded their tracks of the rats asleep during the intervention period. The Ob group spent more time to find the platform, while the C+Ex group spent less time for the test purpose (Figure 1).

Gene Expression Results

On comparing PPAR-γ gene expression across the groups, we used the first group as reference and the second group as the target gene. In the obese group, the PPAR-γ gene expression level was 2,914 times lower than that in the control group (down-regulated), though no significant difference observed ($p>0.05$) (Table 4). Comparisons between other groups are summarized in Table 4 below and illustrated in Figure 2.

DISCUSSION

One of the approach to establish an experimental obesity model is to feed the experimental animals with a high-fat diet (16). In this study, obesity was induced in Wistar Albino rats using a high-fat diet. The rats were fed for eight weeks with 45% of the calories coming from fat. In the eighth week of the diagnosis of obesity, there was a difference between the average weight of the C and Ob groups, with a higher average weight in the obese group. A statistical evaluation of the average weights showed a significant difference between the C and Ob groups. It was observed that body weight increased with longer administration duration of the high-fat diet (11). Hundreds of hormones and adipokines are secreted from adipose tissue, and adipokines influence the peripheral and central nervous systems (17). Obesity leads to oxidative stress and the development of insulin resistance. The development of insulin resistance also reportedly causes cognitive impairment (18). It has been shown that when rats are fed a high-fat diet, oxidative stress occurs in the CA1 region of the hip-

Figure 1. a-d. Heat maps of acquisition days (group means). a, b, c, d represents C, Ob, C+Ex, Ob+Ex, respectively

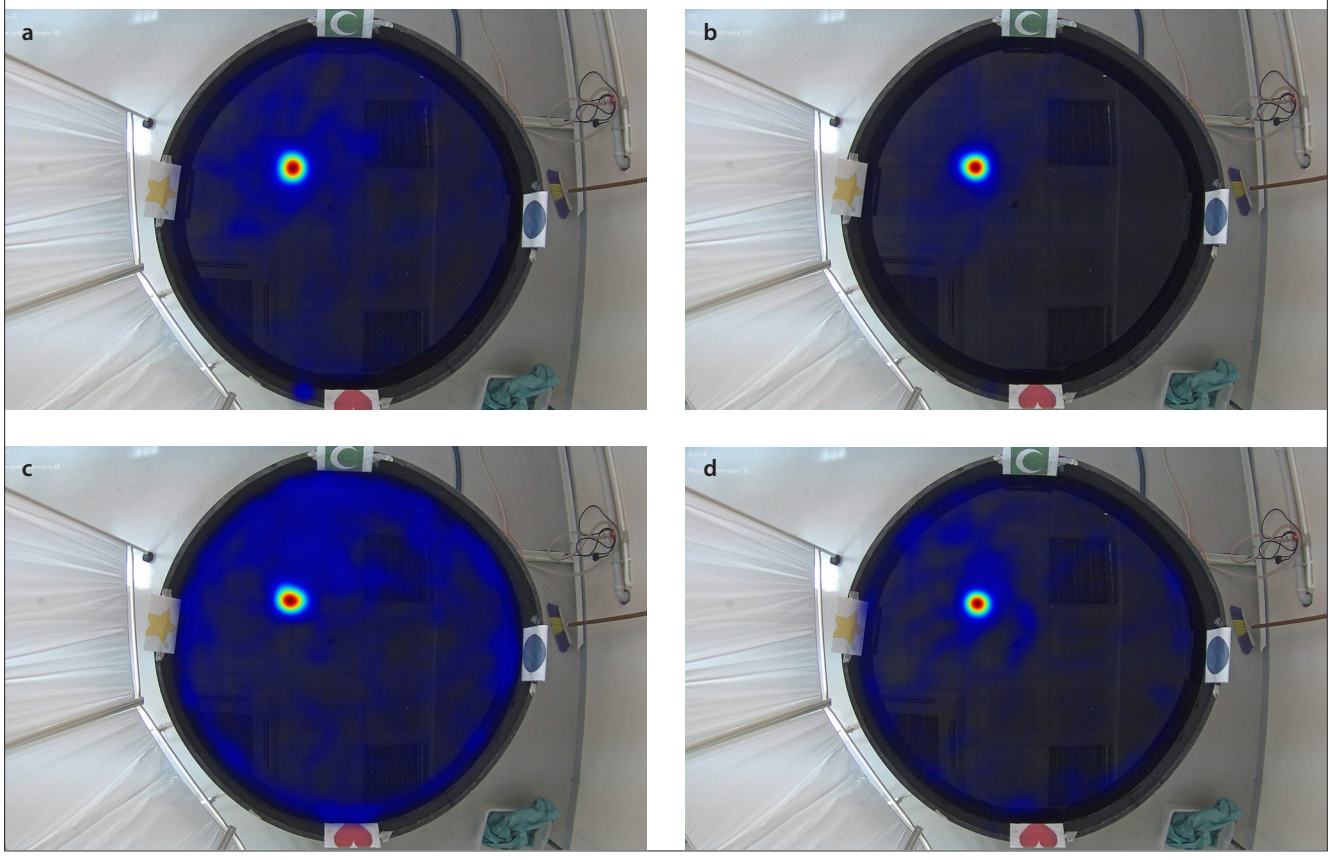
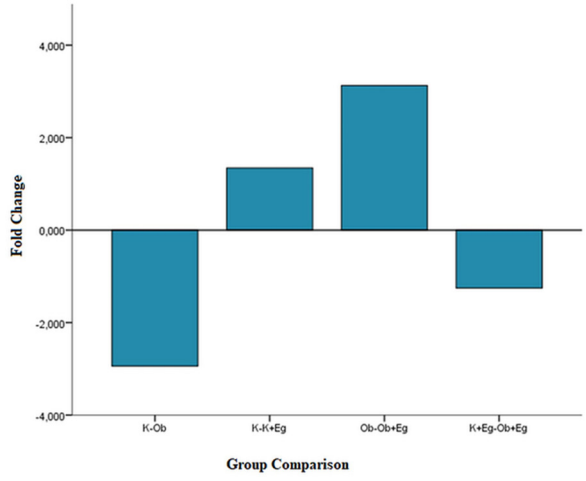


Figure 2. Chart showing the Fold changes of the PPAR γ gene expression level of the groups. C stands for control, Ob for obese, C+ Ex for control exercise and Ob + Ex for obese exercise groups



pocampus which is (important for learning and memory), and that the mitochondrial dysfunction of the brain worsens along with decreased synaptic plasticity and dendritic branching (19). In experimental epilepsy rat models, significantly elevated levels of proinflammatory cytokines such as L- 1β, IL-1Ra, IL-6, and TNF-α were observed in the hippocampus during epileptic episodes (20). Neuronal degeneration was observed in the dorsal and ventral CA1 and CA3 regions in the experimental animals of the same group (20).

Burning more calories is an effective strategy for treating obesity (21). With exercise, we accelerated glycogenolysis in the muscles and the liver, glycolysis in the muscles, citric acid cycle, and oxidative phosphorylation, lipolysis in the adipose tissue and the muscles, and fatty acid oxidation in the muscle (21). In a study in which an obesity model was developed, it was found that the adipocyte area was smaller in rats administered a swimming exercise compared with that observed in sedentary rats (22). We observed systemic low-grade inflammation as well as reduced neurodegeneration and cognitive impairment in rats that regularly exercised; furthermore, reduced levels of plasma IL-6, IL-8, CRP, and TNF-α in the central nervous system were also noted in them (23). Exercise alters the body's lipid profile, reduces obesity indicators, improves heart health, improves nutrient distribution and brain health by regulating cerebral blood flow, and also increases the volume of white and gray matter in the prefrontal, superior parietal, and temporal cortex (23). Physical activity improves hippocampal neurogenesis, increases synaptic plasticity, and significantly enhances hippocampal-based learning and memory (24). Many animal studies have demonstrated the functional benefits of exercise (25, 26). In addition, there are studies that show that treadmill and wheel running improve spatial learning and enhance hippocampal neurogenesis in experi-

mental animals. A study that examined the effect of exercise on synaptic plasticity and neurogenesis in rats found that exercise significantly increased BrdU-positive cells (bromodeoxyuridine) in the hippocampus of adult rats (25). Studies on humans have also shown that physical activity increases the volume of white and gray matter. One such study tested the association between a nine-year of physical activity and gray matter volume. We ultimately found that a greater frontal, occipital, entorhinal and hippocampal volume was associated with physical activity (26).

In the last week of this current study, the Morris Water Tank Spatial Memory Test revealed a significant difference between exercise and non-exercise groups in terms of the escape latency. Similarly, another experimental study applying a Morris water tank test to rats fed with a high-fat diet for eight weeks found that the escape latency was longer compared to the control group (27). Rats in which obesity was induced following a 13-week long high-fat diet performed a treadmill exercise. The memory test showed that the escape latency of the sedentary obese group fed with a high-fat diet was significantly longer than that of the sedentary group fed with a normal diet and the obese group fed a high-fat diet on an exercise regimen (28). In line with similar studies in the literature, obesity has been shown in this study to lead to changes in cognitive performance and that physical activity improves cognitive performance.

In this study, we isolated the hippocampus of animals from all experimental groups to better demonstrate the effect of this change in cognitive performance due to obesity and exercise. In this way, the change in the molecular level of the PPAR-γ gene expression for learning performance was studied for all groups. The activation of PPAR-γ has an important therapeutic potential in brain diseases playing a vital role in regulating proliferation, metabolism, differentiation, development, and the inflammatory response of the central nervous system. The genetic analysis in this current study showed that the PPAR-γ gene expression level in the hippocampal tissue reduced in the obese group compared to the control group. Alongside the problem of memory impairment due to obesity caused by a high-fat diet, the spatial reference memory test revealed a significant difference between the control and obese groups in terms of the escape times to the platform. In exercise groups, PPAR-γ gene expression levels increased in the control exercise group compared to the control group and in the obese exercise group compared to the obese group. Natural agonists for PPAR-γ activation include oleic, linoleic and polyunsaturated fatty acids (29). A study conducted using herring oil containing n-3 polyunsaturated fatty acids (PUFA) for PPAR-γ activation investigated the spatial learning performances and the hippocampal PPAR-γ gene expression of the groups (30). It was found that the PPAR-γ gene expression was significantly higher in rats administered with high doses of herring oil compared to rats administered with low or no doses at all. Having analyzed the escape times to the platform, it was found that it was significantly lower for the group that received high-dose herring oil than the group that received a low-dose and none at all (30). Another study investigated that activation of PPAR gamma by rosiglitazone (a synthetic ligand of PPAR-γ used in improvement of the cognitive impairment), improve spatial cognitive deficits by repairing expression of AMPA receptors in seipin knock out mice. Spatial memory deficits are caused by knocking out seipin gene in mice. The study has shown that seipin deficiency in neurons reduced the PPAR gamma level in the hippocampus compared with the wild type or control group but rosiglitazone repaired the spatial cognitive impairment caused by knocking out seipin and it has been shown in the Morris water maze by determining the escape latency compared to wild type. The escape latency was reduced in seipin knock out group treated with Rosiglitazone with respect to non-treated group and this decrease has shown a statistically significant difference between these two groups (31). The study by Gao et al. investigated the effect of pioglitazone, another synthetic ligand of PPAR gamma, on learning, and memory. They induced experimental type 2 diabetes mellitus and used pioglitazone to treat the animals. The results have shown that, pioglitazone treated group had lower Fasting Blood Glucose compared to non-treated diabetic and control group and the groups shown a statistically significant difference. In Morris water maze test, pioglitazone treated group revealed a significantly lower escape latency than non-treated diabetic group but higher than control group (32).

The synaptic function is based on special neural extensions called dendritic spine (33). These are the neurotrophins where BDNF is among the mediators that increase dendrite density and synaptic plasticity (30, 33). PPAR-γ agonists (such as rosiglitazone) increase synaptic plasticity, prevent loss of dendritic spine and improve synaptic function in the hippocampus (33). Exercises trigger expression of BDNF in the hippocampus (34). This way, BDNF regulates neuronal survival, neurogenesis, synaptogenesis and synaptic plasticity (34). In this study, we analyzed PPAR-γ gene expression levels from tissue samples obtained from the hippocampal tissues of the experimental groups. As a result, we observed an increase in gene expression in the exercise groups, though not significant (Table 4). Further studies are recommended to carry out extensive molecular investigations and to increase the number of samples to assess learning performance.

CONCLUSION

To conclude, our study revealed that impairment in cognitive functions (such as memory), occurs in obesity caused by a high-fat diet. According to the learning–memory test data from the experimental groups, exercise has a beneficial effect on cognitive functions. Hence, we observed in increase in the PPAR-γ gene expression level as well as better outcomes from the learning–memory test in the exercise groups.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (2017/16, 07.06.2017).

Informed Consent: All participants signed informed consent forms before study inclusion.

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