Egyptian Journal of Veterinary Sciences

https://ejvs.journals.ekb.eg/

The More Potent Favorable Effects of Swimming Exercise Versus Ketogenic Diet in Combatting Obesity-Induced Brain Damage in Rats

Hassnaa Benyamen[1], Mahran Mohamed Abd El-Emam[1], Yousef M. Shehata[1], Tarek khamis[2] and Mohamed Fouad Mansour[1]*

[1]*Department of Biochemistry and Molecular Biology, Zagazig University, Zagazig 44511, Egypt.*

[2]*Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Zagazig 44519, Egypt.*

Abstract

OBESITY is abnormal massive accumulation of fat in the body, which is cosidered one of the most common health problem worldwide. It is causing a state of oxidative stress and inflammation, which affects almost all body tissues including the brain. Obesity also affects cognitive development, executive function abilities, brain volume, and can increase the risk of dementia and Alzheimer's disease. Therefore, we assessed the effect of swimming exercise versus the ketogenic diet on the brain damage of obese rats. Thirty two rats were divided into 4 groups (8 rats each) include: Control group: Rats received standared rat diet, Obesity group: Rats received high fat diet, ketogenic diet group (KD): Obese rats received ketogenic diet/daily for 2 months and swimming exercise: Obese rats subjected to swimming (1 h/day/2 months). The results indicated that KD and swimming exercise improved waist circumference, total cholesterol, triacylglycerol, and HDL in comparison with obese group. Regarding oxidative status in the brain, Both KD and swimming exercise significantly reduced the level of MDA, while increased the level of total antioxidant capacity (TAC) and SOD. Both treatments downregulated the mRNA expression levels of TLR4/NF-κB signaling, mir-138-5p and mir-489-3p in the brain tissue of obese rats. However, KD and swimming exercise upregulated the mRNA expression levels of antioxidant-related genes (Nrf-2 and SIRT1), fission-related genes (Mfn1 and Mfn2), fussion-related gene (DRP-1), mitophagy-related genes (PINK1 and Parkin), mitochondrial respiratory chain-related genes (NDUFS1, SDHC, COQ8A, COX6A2 and ATP5F1A). Moreover, both tretments showed improvement in the brain tissue histopathology of obese rats. In conclusion, KD and swimming exercise restore the normal brain function in obese rats. Interestingly, the data of this study proved that swimming exercise showed higher potent effect than KD against brain damage in obese rats.

Keywords: Obesity, brain damage, ketogenic diet, swimming exercise, mitochonderial dysfunction.

Introduction

Obesity is a chronic condition characterized by abnormal fat accumulation. The body mass index (BMI), a weight-for-height index, is used to categorize adults who are overweight or obese. An individual is considered obese if it is 30.0 kg/m2 or higher. In 2015, over 600 million were obese [1]. Obesity increases noncommunicable diseases like metabolic, cardiovascular, cancer, musculoskeletal, and brain diseases, leading to premature mortality and disability [2]. Recent research shows that a high-fat diet can negatively impact learning and memory function, leading to mood disorders and decreased hippocampal plasticity over time [3].

An imbalance between the production of reactive oxygen species (ROS) and antioxidant defense is known as oxidative stress, which is a key factor in metabolic disorders [4]. Obese individuals exhibit dysregulation of fatty acid oxidation and lipid peroxidation [5]. Obesity-related neurodegenerative illnesses may be a significant factor due to the lower brain resistance to oxidative stress compared to other organs [6]. Oxidative stress caused by obesity leads to brain atrophy, inflammation, and impaired blood-brain barrier, potentially resulting in cognitive

*Corresponding authors: Mohamed Fouad Mansour, Email: mafouad@zu.edu.eg Tel: +201227420601
(Received 16 March 2025, accepted 03 October 2025)
DOI: 10.21608/ejvs.2025.368783.2704

decline [7]. Cognitive deterioration and oxidative stress were linked to downregulated level and activity of the Nrf2 [8].

Mitochondria dynamics are crucial for metabolic health, which are maintained through processes like mitophagy, biogenesis, fission, and fusion. Fission is a crucial process that regulates the quantity and location of mitochondria, adapts to a cell's energy demands, and eliminates damaged ones [9]. Fusion is a process that involves the exchange of mtDNA to preserve the operation of the mitochondria [9]. The Dynamin family of conserved GTPases regulate fission and fusion, with Fission 1 protein and/or Drp1 mediating fission and Mitofusin 1 and 2 and Opa1 mediating fusion. Furthermore, Mitophagy and biogenesis regulate mitochondrial function, with sirtuin-3 (SIRT3) playing a crucial role in affecting the acetylation status of over 165 proteins in the mitochondrial proteome [10]. Moreover, SIRT3 is crucial for controlling mitochondrial quality control in neural mitochondria [11].

The primary intervention techniques for reducing energy intake, improving energy expenditure, or decreasing energy absorption include exercise, diet, bariatric surgery and medication [12]. Exercise has the potential to promote neurogenesis in the hippocampus [13]. Increased physical activity through training in swimming can lessen stress-related conditions including anxiety and depression-related symptoms in several animal models, including type 2 diabetes, Alzheimer's disease, and activation of the maternal immune system [14]. Studies indicate that swimming can enhance learning and memory functions, and boost the level of hippocampal brain-derived neurotrophic factor [15]. In addition, Physical exercise can prevent age-related decline in the hippocampus and enhance the overall health of neurons [16]. Voluntary exercise can enhance the neuroplastic potential of the brain [17].

One dietetic approach that restricts carbohydrate intake is the ketogenic diet (KD), which is primarily based on fat consumption, with 80-90% of calories in a classical KD [18]. It causes a change in metabolism that allows ketone bodies to be used as an extra energy source [19]. Research has shown that the KD is more effective than other diet plans in weight reduction in obese subjects. The KD reduces obesity by simulating the metabolic alterations that occur during prolonged fasting and starvation, which enables cells to use extra lipids for energy production [20]. The KD was developed to treat epilepsy, particularly drug-resistant seizures [21]. Recent evidence suggests that KD has both pathophysiological and clinical benefits in neurodegenerative diseases, making it a potential treatment option for nervous diseases [22]. KD can potentially have ameliorative effects by altering certain neuroinflammatory pathways [23]. Furthermore, studies suggest that KD may enhance cognitive function performance [24].

In this experimental study, we attempt to compare the efficacy of physical exercise and KD on the modulation of mitochondrial dynamics and function in the brain tissue of obese rats. We tested this hypothesis by evaluating the serum lipid profile, mRNA expression levels of mitochondrial dynamics markers, antioxidant capacity and histopathological examination of brain tissue. To our knowledge, this is the first study highlighting the protective effects of exercise training versus KD supplementation on the brain of obese rats.

Material and Methods

Materials

Ketogenic diet was composed of water, Goat fat 70%, chicken egg yolk 19.45%, avocado 5.69%, roasted peanuts 4.86% [25]. High fat diet (40% fat) includes 40 g Fat (Beef thallow), 22 g casein, 13 g Cellulose, 18 g Starch, 3.4 g Cysteine, 1.5 g mineral mix, 0.3 g Choline chloride and 1.8 g vitamin mix [26].

Experimental animals

Thirty two male Sprague-Dawley rats weighing 250 ± 5 g were acquired from the research animal farm located at Zagazig University's Faculty of Veterinary Medicine. Each rat was housed in a stainless-steel cage that was maintained at a temperature between 21 and 24 °C, offering a clean, pathogen-free environment. To achieve ideal living circumstances, the rats were exposed to a 12-hour light-dark cycle and a 60% relative humidity. Commercial food pellets and unlimited water were provided to the rats. The research protocol was reviewed and approved by the ethics committee of Zagazig University's Faculty of Veterinary Medicine in Egypt. Laws and regulations were followed throughout the entire process (approval number: ZU-IACUC/2/F/15/2025). The study was carried out in accordance with the guidelines provided by ARRIVE.

Animals and experimental design

Four groups of eight rats each were randomly assigned. The first one is the control group, which received the standard rat diet. The second one was obese group, which received a HFD for 3 months. The third group was obese rats received ketogenic diet for 2 months. The fourth group was exercise group includes obese rats subjected to exercise by free swimming for 1 houre/day/2 months.

Sampling

Upon the conclusion of the experimental period, the rats were anesthetized by thiopental (120 mg/kg B.w i.p), and blood was drawn from the medial canthus. Part of the blood was put in test tubes

without anticoagulants, which were centrifuged, and a serum sample was used for biochemical analysis. The brain tissue sample was dissected into three parts for gene expression (RT-qPCR), histopathological examination, and part was homogenized for biochemical measurements.

Body mass index (BMI)

The final weight and length were recorded upon completion of the investigation for every animal group using an electronic balance and a ruler respectively to verify the rat's BMI.

Biochemical analysis

Triacylglycerol (TAG), high-density lipoprotein (HDL), and total cholesterol (TC) were measured in serum samples using Reactivos GPL kits (Barcelona, España). Malondialdehyde (MDA), total antioxidant capacity (TAC), and superoxide dismutase were determined in brain homogenate using the kits supplied by Chema Diagnostica (Monsano, Italy).

Real-Time Quantitative PCR (RT-qPCR) Analysis

Previous documentation of the real-time analysis was done by Abd El-Hakim et al. [27]. At the beginning, we utilized the Trizol Reagent from Thermo Fisher Scientific in Massachusetts to extract total RNA from brain tissue. As previously stated, 500 ng of total RNA was utilized for transcription, resulting in the production of mRNA. Ten ng of RNA were subjected to miRNA transcription using the TaqManTM Small RNA Assays in accordance with the manufacturer's instructions. Assay design software at http://genomics.dote.hu:8080/mirnadesigntool (viewed on 10 September 2020) was used to design miRNA-specific primers, stem-loop primers, and the universal reverse primer [28]. Table 1 displays the primer sequences. mRNA and miRNA were normalized to housekeeping GAPDH and U6, respectively, and gene expression was determined using the 2–ΔΔCt approach in real-time PCR using the Maxima SYBR Green/Rox qPCR 2× Master Mix.

Histopathological examination

The brain specimen was excised and handled with caution to minimize any damage to the delicate seminiferous tubules, and five shallow piercings to the tunica albuginea were performed using a 21-gauge needle before immersion in modified Davidson's solution for 24 hours. Next, the brain was processed for paraffin infiltration, and embedding, and 4-5 µm thick transverse tissue was prepared, stained with hematoxylin and eosin [29], and examined microscopically.

Statistical analysis

We utilized GraphPad INSTAT software (Version 2) to conduct the statistical analysis. Tukey's multiple range test and a one-way analysis of variance (ANOVA) were used in the statistical evaluation. The results are presented as mean and standard error. A p-value of 0.05 was taken into consideration for determining significance.

Results

Effects of KD supplementation and swimming exercise on body mass index (BMI) and waist circumference in obese rats.

We found that obese rats showed higher BMI and waist circumference (approximately 32% and 34%, respectively) than control rats. The KD supplementated group significantly decreased BMI and waist circumference by 7%, and 8%, respectively, compared to the obese group. On the other hand, rats exposed to swimming exercise displayed a 21% decrease in BMI and an 18% decrease in waist circumference compared to obese rats. The exercise group exhibited better effects than the KD group (Figures 1 A and B).

KD supplementation and swimming exercise modulate changes in serum levels of lipid profile in HFD-fed rats

Rats given an HFD had significantly lower HDL levels by 24% and higher serum TC and TG levels by 55% and 177%, respectively than the control group. Compared to the obese group, KD feeding significantly reduced TC and TG levels by 15% and 36%, respectively, and increased HDL by 22%. Compared to the obese group, swimming exercise resulted in a significant decrease in TC and TG levels by 27% and 50%, respectively, and an increase in HDL by 36%. Moreover, compared to the KD group, the physical training group's serum levels of the lipid profile were more drastically altered (Figures 2 A-C).

The effects of KD and swimming exercise on oxidant/antioxidant status in brain tissue

To evaluate the antioxidative qualities of swimming exercise or KD, the levels of MDA, TAC, and SOD in rat brain tissues were measured. The findings showed that whereas TAC and SOD levels decreased by 38% and 31%, respectively, obesity increased MDA levels by 47%. KD supplementation resulted in amelioration of oxidative capacity indicated by the decrease of MDA level by 21% and the increase in the levels of TAC, and SOD by 45%, and 47%, respectively. Comparing the obese group to the obese rats trained with swimming, the former dramatically decreased their MDA levels by 23% and increased their TAC and SOD levels by 51% and 41%, respectively. The exercise group exhibited effects similar to those of the KD group in all the forementioned parameters (Figures 3 A-C).

Effects of KD and swimming exercise on the mRNA expression levels of TLR4/NF-κB signaling pathway of the HFD-fed rats

Obesity significantly increased the levels of mRNA expression of TLR4 and NF-κB by 378% and 543%, respectively, in brain tissue, contrary to the control group. There was a significant downregulation in TLR4 and NF-κB by 41% and 36%, respectively, in the KD-supplemented group compared to the obese group. Furthermore, tats exposed to swimming exercise resulted in a considerable suppression of TLR4 and NF-κB mRNA expression levels by 65% and 58%, respectively, compared to the rats exposed to obese rats. there was a significant downregulation in TLR4 and NF-κB by 41%, and 36%, respectively in the KD-supplemented group compared to the obese group. Exercise-trained rats showed better results than the KD-fed rats in ameliorating TLR4/NF-κB in the brain tissue of obese rats (Figures 4 A and B).

Impact of KD and swimming exercise on mRNA expression of Nrf-2 and SIRT1 in the brain of obese rats

Compared to control rats, obese rats exhibited a significant decrease in Nrf-2 and SIRT1 in the brain of about 81% and 87%, respectively. After KD supplementation, we observed that the obese group's brain showed a 170% rise in SIRT1 and a 144% increase in Nrf-2 gene expression. Compared to obese rats, exercise-exposed obese rats showed increases in Nrf-2 and SIRT1 in the brain of about 329% and 427%, respectively. Compared to the KD group, the exercise group had better results (Figs. 5 A and B).

KD and swimming exercise modulate the expression of genes involved in mitochondrial dynamics in the brain of obese rats

We examined the effect of KD and swimming exercise on the mRNA expressions of the genes regulating mitochondrial fission and fusion. The obese group displayed marked lower mRNA levels for each gene evaluated, including the mitochondrial fusion genes Mfn1 and Mfn2 by approximately 88% and 83%, and the mitochondrial fission gene DRP-1 by approximately 83%. We also found roughly a 355% increase in Mfn1 gene expression, a 244% increase in Mfn2, and a 141% increase in DRP-1 in the brain following KD supplementation in the obese group. Obese rats exposed to swimming training showed a significant rise in Mfn1, Mfn2, and DRP-1 by approximately 515%, 374%, and 372%, respectively, in the brain. The exercise group exhibited superior results comparable to those of the KD group (Figs. 6 A-C).

Impact of KD and swimming exercise on the relative expression of mitophagy-related genes in the brain of obese rats

The expression of genes related to mitophagy is shown in Fig. 7. The mRNA levels of Parkin and PINK1 were notably downregulated by about 86% and 80% in the obese group compared with the control group. Following the addition of KD to the obese group, the expression of Parkin and PINK1 was significantly increased by about 378% and 217% compared with the obese group alone. Following the exercise in the obese rats, the expression of Parkin and PINK1 was significantly increased by about 648% and 399% compared with the obese group. The exercise group consistently exhibited superior improvement in mitophagy comparable to the KD group (Figures 7 A and B).

Effect of KD and swimming exercise on mitochondrial respiratory chain mRNA gene expression in brain tissues of obese rats

We analyzed the mRNA expression of mitochondrial respiratory chain complexes to examine the effects of KD and swimming exercise on obesity-induced mitochondrial dysfunction. We found inhibition of gene expression of NADH-ubiquinone oxidoreductase (NDUFS1), Succinate dehydrogenase complex subunit C (SDHC), Coenzyme Q8A (COQ8A), Cytochrome c oxidase 6A2 (COX6A2) and ATP synthase F1 subunit alpha (ATP5F1A) by about 84%, 81%, 86%, 96% and 86%, respectively in the obese group compared with the control group. KD feeding and Swimming exercise substantially raised the mRNA expression of NDUFS1, SDHC, COQ8A, COX6A2, and ATP5F1A by about (264%, 511%), (200%, 463%), (240%, 634%), (500%, 1000%) and (205%, 562%) when compared to the obese group. In addition, significantly higher upregulation in all the aforementioned respiratory chain genes was detected in the exercise group compared to KD one (Figs. 8 A-E).

KD and swimming exercise modulate miRNA expression levels of mir-138-5p and mir-489-3p in the brains of obese rats

The location of the 3′ UTR region for miRNA binding to the targeted mRNA is shown in (Fig. 9). The influence of KD and swimming exercise on miRNA expression levels of mir-138-5p and mir-489-3p in the brain was evaluated. Obesity resulted in a notable rise in the expression levels of mir-138-5p and mir-489-3p by 729% and 554% in the brain tissue compared to the control group. KD and swimming exercise resulted in a noteworthy downregulation in the mir-138-5p and mir-489-3p expression levels by (34%, 67% and (38%, 70%), respectively compared to the obese group. Furthermore, the obtained results obtained by the exercise group were superior to those obtained by the KD group (Figs. 9 A and B)

Histopathological findings

The control group showed a normal cerebral cortex with normal histological structures of neuronal cells, glial cells, neuropil, and cerebral blood vessels (Figure 10A). While the obese group showed vacuolated neuropil, numerous pyknotic neurons with dark basophilic nuclei, and satellitosis (Figure 10 B and C). Swimming exercise and KD gropus showed amelioration in histological structures of brain tissue. a few areas of vacuolated neuropil were in swimming exercise (Figure 10D) and a few pyknotic neurons and neuronophagia were seen in KD (Figure 10E). Lesions score of the severity extent in brain tissues among different experimental groups were shown in Table 2.

Discussion

Obesity is a health issue resulting from an unhealthy diet and insufficient exercise, and current best practices for treating it include a healthy lifestyle, increased physical activity, and behavioral changes [30]. The use of KD in weight loss therapy is proven to be highly effective [31]. Furthermore, even in the absence of weight loss, physical activity can lessen the detrimental effects of obesity [32]. The study looked into how swimming exercise or KD might lessen the brain damage that rats' high-fat diets caused.

In the present study, obese rats showed a significant increase in their BMI and waist circumference related to control values. The study of Arika et al. [33] revealed that the obesity index and waist circumference of the obese untreated rats fed high-fat meals for an extended period increased steadily between the first and sixth weeks of the study. The study suggests that rats' consumption of calorie-dense meals, which have high energy content, can lead to the development of belly fat [34]. KD feeding or swimming exercise training significantly decreased BMI and waist circumference, and superior results were obtained with the swimming exercise. KD may increase daily energy expenditure and hence decrease body mass [31]. Nevertheless, it decreases lean mass more than fat mass. Exercise interventions have been shown to enhance body composition, including lowering fat mass and maintaining or increasing lean mass [35, 36].

In the current study, the substantial rise in raised serum levels of TG, TC, and LDL-C, as well as the low concentration of HDL-C, validated the induction of obesity as previously described by El-Shial et al. [37], who showed that the HFD group had high serum levels of total cholesterol, TG, and LDL-C, while there was a noticeable decrease in the HDL–C of rats in the normal group. Furthermore, the study found that rats in the obese group showed significantly higher levels of TG and total cholesterol, indicating fat deposition in the liver tissue. Our results showed that swimming exercise significantly reduced TC and TG levels, increased HDL, and significantly impacted lipid profile in the training group compared to the exercise group. These findings may be attributed to two reasons. First, exercise increases the activity of enzymes that aid in the transfer of LDL from the circulation and blood vessel walls to the liver. The cholesterol is then either expelled or transformed into bile for digestion. Second, exercise makes lipoproteins bigger, and ultimately, LDL becomes HDL [38].

Exposure of polyunsaturated fatty acids to reactive oxygen species in the brain leads to the formation of harmful lipid peroxidation intermediates [39]. Oxidative stress leads to neurodegeneration in the brain due to the insufficient production of antioxidants to counteract the increase in reactive oxygen species. According to the results of the most current study, obese rats' brains had significantly higher MDA levels and lower SOD and catalase activity. A high-fat diet has been shown to raise the amount of lipid peroxidation in rat brains [40]. Additionally, obesity raises the brain's levels of superoxide and reactive oxygen species [41], which might explain the decreased activities of SOD, and catalase observed in obese rats. Exercise training significantly reduced the lipid peroxidation level and increased the activities of antioxidants in obese rats. Albrahim et al. [42] reported that exercise was successful in rebalancing oxidant/antioxidant levels in the brains of rats that had undergone ovariectomy, showing a non-significant increase in oxidative stress markers compared to control rats. Greco et al [43] found that oxidative stress is significantly reduced in both the cytosol and mitochondria of the brain by KD after traumatic brain injury in rats.

In order to initiate the inflammatory response and promote brain damage from cerebral ischemia-hypoxia, carbon monoxide poisoning, and brain trauma, the TLR4/NF-κB signaling pathway is essential [44, 45]. Through signaling pathways that are dependent on MyD88 and TRIF, LR4 causes the production of inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8, which in turn causes a variety of immuno-inflammatory reactions [46]. Animal studies have revealed that HFD increases TLR4 gene levels compared to normal chow [47]. The present study demonstrated that the expression levels of TLR4, and NF-κB were significantly reduced in the brain tissue of obese rats after swimming training. The results of Qi et al. [48] suggested that aerobic exercise may lower blood pressure in hypertensive rats by slowing the course of renovascular hypertension by lowering the activation of the pro-inflammatory cytokine via TLR4/MyD88/NF-κB signaling inside the

paraventricular nucleus. By blocking the TLR4 signaling pathway and lowering the activation and release of inflammatory cytokines in the brain, our research has shown that swimming exercise has an anti-inflammatory effect. Histopathological examination, which showed certain regions of vacuolated neuropil and a few pyknotic neurons, provided additional evidence of the anti-inflammatory and neuroprotective benefits of swimming exercise.

The multifunctional protein Nrf2 is an important antioxidant sensor whose activation is necessary for cellular defense systems. Once active, Nrf2 travels from the cytoplasm to the nucleus, where it manipulates the transcription of particular genes, such as hemeoxygenase 1 (HO-1), in conjunction with the antioxidant defense system. These genes' transcription increases resistance to oxidative stress and provide protection against inflammation [49]. Calorie restriction, metabolism, senescence, apoptosis, inflammation, and the deacetylation of histones and nonhistone proteins are all regulated by SIRT1, a nuclear histone deacetylase that is dependent on NAD [50]. SIRT1's capacity to deacetylate prevents NF-kB from transactivating [51]. SIRT1 has been found to decrease oxidative stress levels and inflammation levels in various studies [52]. Based on our research, obese rats showed a greater increase in Nrf-2 and SIRT1 expression in their brains following exercise. Nonato et al. [53] found that swimming training attenuated oxidative damage and increased enzymatic antioxidants in the rat brain. Our findings back up the previously mentioned results showing that swimming exercise significantly influenced the balance of oxidants and antioxidants, as well as the inflammatory response in the brains of high-fat diet rats.

Mitochondria are dynamic organelles that play a crucial role in cellular processes like quality control and apoptosis due to their equilibrium between fusion and fission events [54]. Mitochondrial dysfunction results in the production of free radicals after brain injury apoptosis [55]. In this study, we found that the levels of Mfn1, Mfn2, and DRP-1 genes related to mitochondrial fusion and fission were decreased following HFD intake, suggesting that obesity could lead to decreased levels of healthy mitochondria and hinder fusion and fission processes in the brain (Schmitt and Gaspar 2023). Furthermore, swimming exercise significantly upregulated low expression of Mfn1, Mfn2, and DRP-1 over KD feeding, which may be attributed to the activity of SIRT1. SIRT1 has been suggested as a crucial regulatory mechanism for mitochondrial function, apoptosis, and oxidative stress response in various cellular processes [49]. In addition, the stimulatory effect of swimming exercise on SIRT1 expression in our study was confirmed by a noteworthy downregulation in the mir-138-5p which targets the SIRT1 gene.

The PINK1/Parkin pathway is the most extensively studied underlying mechanistic pathway in mitophagy due to its crucial role in the process [58]. PINK1 stabilizes depolarized mitochondria, phosphorylates Parkin, an E3 ubiquitin ligase, and then moves to damaged mitochondria from the cytosol [59]. Parkin ubiquitylates mitochondrial substrates, triggering a p62/NDP52/OPTN aggregation of ubiquitylated proteins. This cargo is then recruited into the autophagosome by binding to LC3 [58]; these events in turn then promote the degradation of mitochondria by mitophagy [60]. The results of the current study indicated that the expression levels of mitophagy-related genes Parkin and PINK1 were downregulated in the brains of obese rats. However, these genes were further enhanced by swimming exercise, indicating that exercise stimulated mitophagy and the formation of autophagosomes by mediating the PINK/Parkin pathway. Also, this effect was confirmed by a noteworthy downregulation in the mir-489-3p, which targets the pink1 gene.

Mitochondrial respiratory complex dysfunction can lead to decreased ATP production and increased oxidative stress, causing metabolic and neurological disorders. In the present study, we demonstrated that HFD downregulated gene expression of NDUFS1, SDHC, COQ8A, COX6A2, and ATP5F1A in rat brains. In line with this, a previous investigation examining the impact of a high-fat diet on mitochondrial respiratory complexes showed that this diet was linked to changes in the protein expression of several complexes I, III, and V of the hypothalamus' mitochondrial respiratory complexes [61]. Interestingly, these effects are reversed by exercise and KD feeding with a more pronounced effect in the exercise group. De Sousa Fernandes, [62] demonstrated that exercise can trigger mitochondrial subunit biogenesis by demonstrating that the trained group's ATP5A levels were higher than the control group. Moreover, elevated activity of mitochondrial respiratory chain enzymes (SDH, complexes I, II, II-III, IV) and decreased hydroperoxide production in skeletal muscles were better achieved with five weekly training sessions [63]. Aerobic physical training is widely utilized for obesity prevention and treatment, as well as enhancing brain function through neuromuscular rehabilitation protocols [64]. Exercise enhances metabolic functions such as lipolysis, immunity, oxidative metabolism, neuroplasticity, mitochondria function, and oxidative stress resilience [65].

Conclusion

KD and swimming exercise restore the normal brain function in obese rats via regulation of brain oxidant/antioxidant status, improving mitochondrial functions and restoring the normal brain tissue structure. Interestingly, the data of this study proved that swimming exercise showed higher potent effect than KD against brain damage in obese rats.

Acknowledgments

Not applicable.

Funding statement

This study didn't receive any funding support

Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

The ethics committee of the Faculty of Veterinary Medicine at Zagazig University in Egypt examined and approved the research protocol. All procedures were carried out in compliance with the laws and regulations (approval number: ZU-IACUC/2/F/15/2025). The research was conducted in compliance with ARRIVE recommendations.

TABLE 1. Primers and stem-loop sequences of targeted genes.

Gene	Forward primer	Reverse primer	Accession no.
PrKn	GAACTGTGGCTGTGAGTGGA	GGTGTTTCCCATGAGGTCGT	NM_020093.1
mfn-1	CTGGGACGGAATGAGTGACC	CATGTGAGGGGCCCAATCTT	NM_138976.2
Pink-1	AGGAAAAGGCCCAGATGTCG	CTGTTTGCTGAACCCAAGGC	NM_001106694.1
mfn-2	ACCAGCTAGAAACGAGATGTCC	GTGCTTGAGAGGGGAAGCAT	NM_130894.4
ATP5F1A	TGCCATTGATGGGAAGGGTC	TGGTTCCCGCACAGAGATTC	NM_023093.1
COX6A2	GGAACCACACGCTTTTCCAC	GAGTCTTCAAGGCTGCTCGT	NM_012812.3
coenzyme Q8A	CTCAGCGTGTGGACTGAATA	CCAGGTTCTGCAGGTGAGTT	NM_001013185.1
SDHC	GCTCTTGCTGAGACACATCG	TTGCCATGGGAAGAGACCAC	NM_001005534.1
NADH	AGAGCCTCACAGACAATGGC	ATGGCTCCTCTACTGCCTGA	NM_001005550.1
Drp-1	GGCAACTGGAGAGGAATGCT	CTGTTCTCGGGCAGACAGTT	NM_053655.3
NF-κβ1	CCACTGTCAACAGATGGCCC	CTTTGCAGGCCCCACATAGT	NM_001276711.1
TLR4	ACTGGGTGAGAAACGAGCTG	CAGCAATGGCTACACCAGGA	NM_019178.2
Nrf-2	GGTTGCCCACATTCCCAAAC	CAGGGCAAGCGACTGAAATG	NM_001399173.1
sirt-1	GACAACCTCCTGTTGGCTGA	TGCGTGTGATGCTCTGTCAT	NM_001414959.1
mir-138-5p	AACAAGAGCTGGTGTTGTGAA	GTCGTATCCAGTGCAGGGT	
mir-489-3p	AGCCAGCGATGACATCACATAT	GTCGTATCCAGTGCAGGGT	
mir-138-5p stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCGGCCT		
mir-489-3p stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACGCTGCC		

TABLE 2. Lesions score of the severity extent in brain tissues among different experimental groups.

Organ	Lesions	Control	Obese	KD	Exercise
Brain	**vacuolated neuropil**	0	2	1	0
	Pyknotic neurons	0	3	1	1
	Satellitosis	0	2	0	1

Examined rats = 10 rats/group. Number of examined fields (five non-overlapped fields/rat, 400X). The lesions were graded by estimating severity of lesions among different groups: Lesions score system was as follows: 0 = absence of lesion, 1 = mild alterations, 2 = moderate alterations, and 3 = severe alterations.

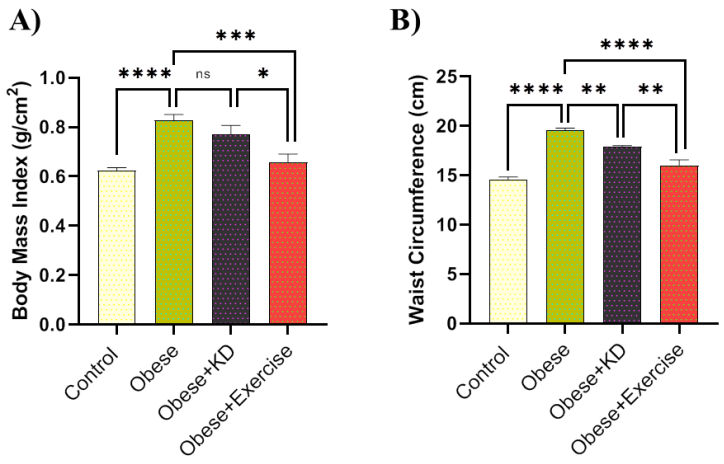

Fig. 1. Effect of KD supplementation and swimming exercise on body mass index (BMI) and waist circumference in obese rats. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

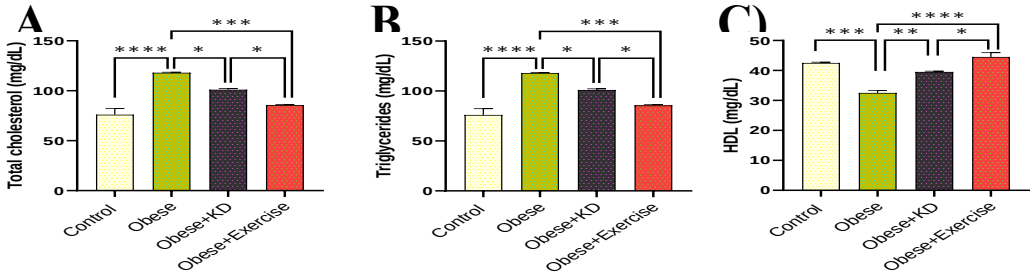

Fig. 2. Effect of KD supplementation and swimming exercise on the serum lipid profile in obese rats. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

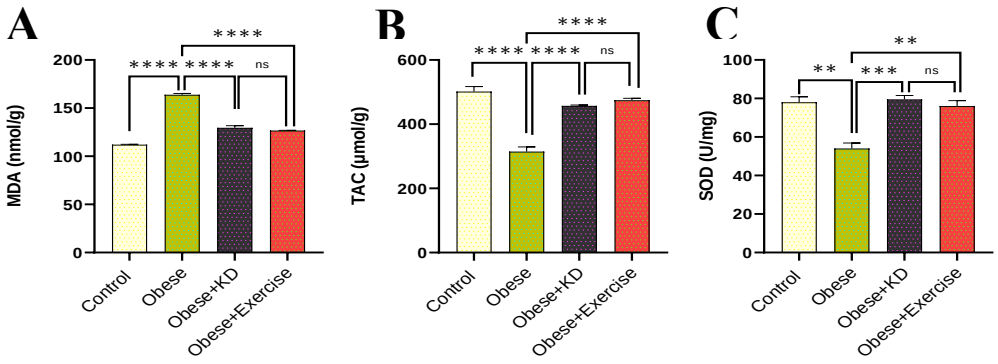

Fig. 3. Effect of KD supplementation and swimming exercise on oxidant/antioxidant status in brain tissue of obese rats: A) MDA: B) SOD: C) Catalase. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

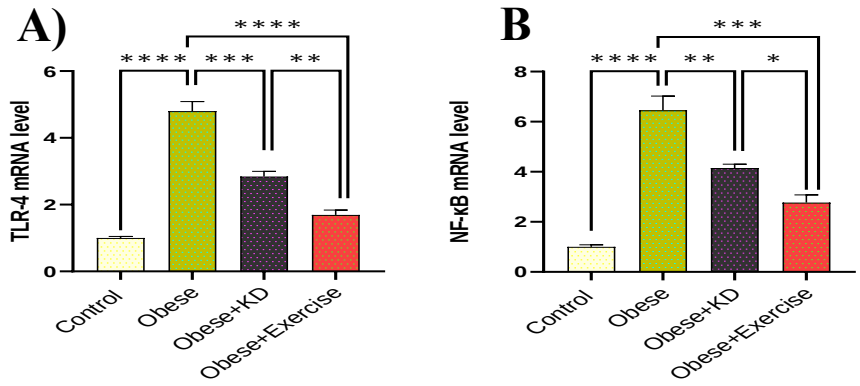

Fig. 4. Effect of KD supplementation and swimming exercise on the mRNA Expression Levels of TLR4/NF-κB Signaling pathway status in brain tissue of obese rats. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

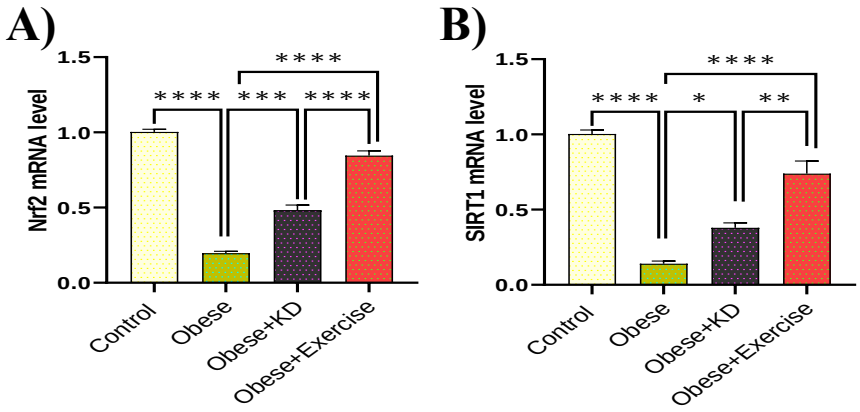

Fig. 5. Impact of KD supplementation and swimming exercise on mRNA expression of Nrf-2 and SIRT1 in the brain of obese rats. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

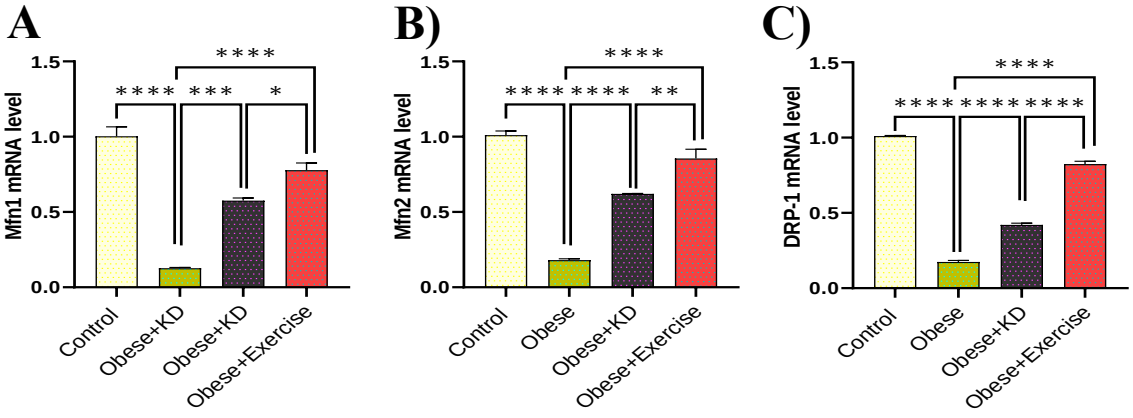

Fig. 6. Impact of KD supplementation and swimming exercise on the expression of genes involved in mitochondrial dynamics. A) Mfn1: B) Mfn2: C) DRP-1. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

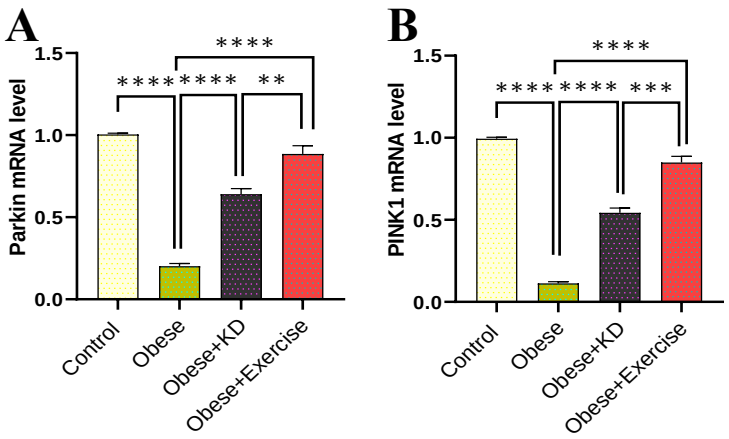

Fig.7. Impact of KD supplementation and swimming exercise on the relative expression of mitophagy-related Genes in the brain of obese rats. A) Parkin B) PINK1. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

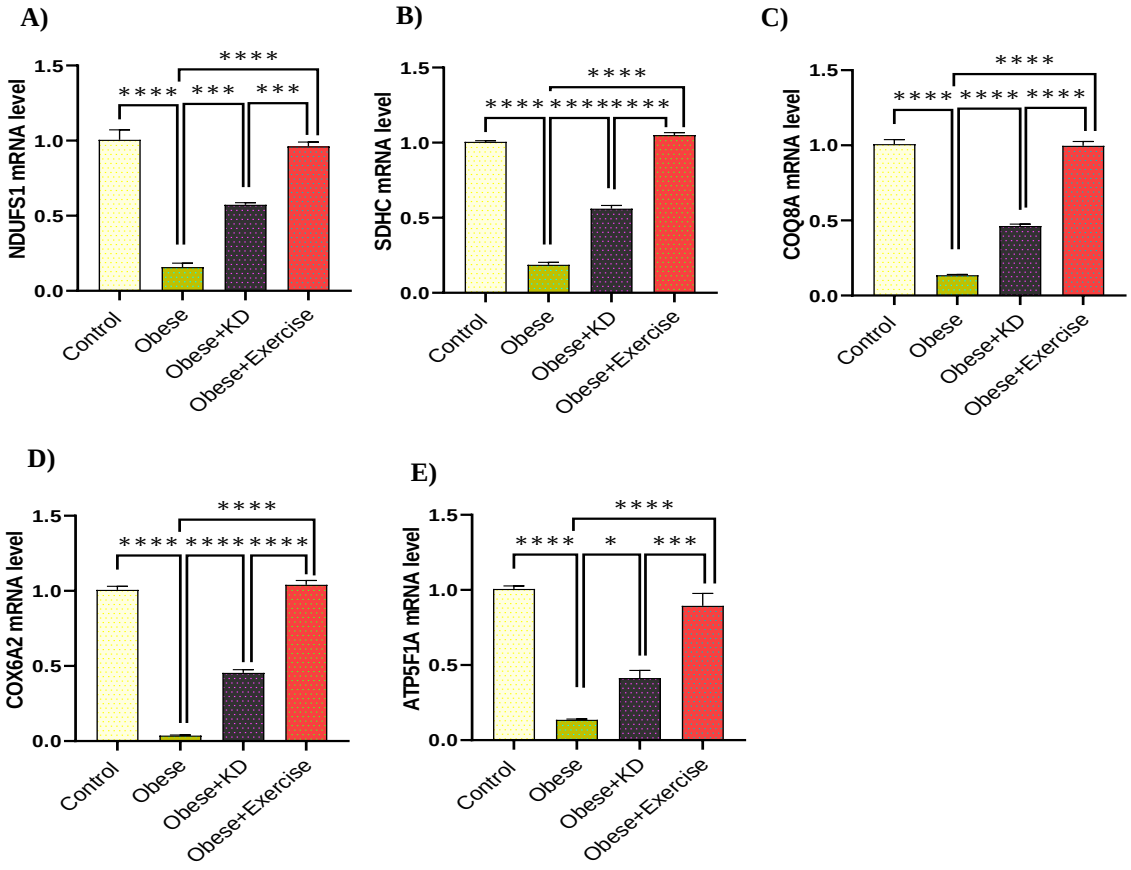

Fig. 8. Effect of KD supplementation and swimming exercise on mitochondrial respiratory chain complexes in brain tissues of obese rats. A) NDUFS1, B) SDHC, C) COQ8A, D) COX6A2, AND E) ATP5F1A. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates non-significant. Data are presented as the mean ± SEM (n = 7).

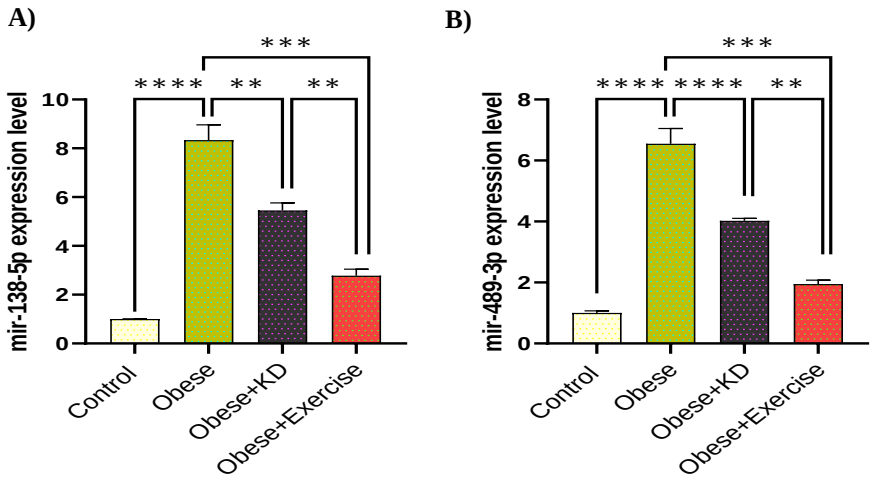

Fig. 9. KD supplementation and swimming exercise modulate miRNA expression levels of mir-138-5p and mir-489-3p in the brain in HFD-induced obese rats. ***P < 0.001, *P < 0.05 vs. control group. ##P < 0.01, #P < 0.05 vs. obese group, ns indicates nonsignificant. Data are presented as the mean ± SEM (n = 7).

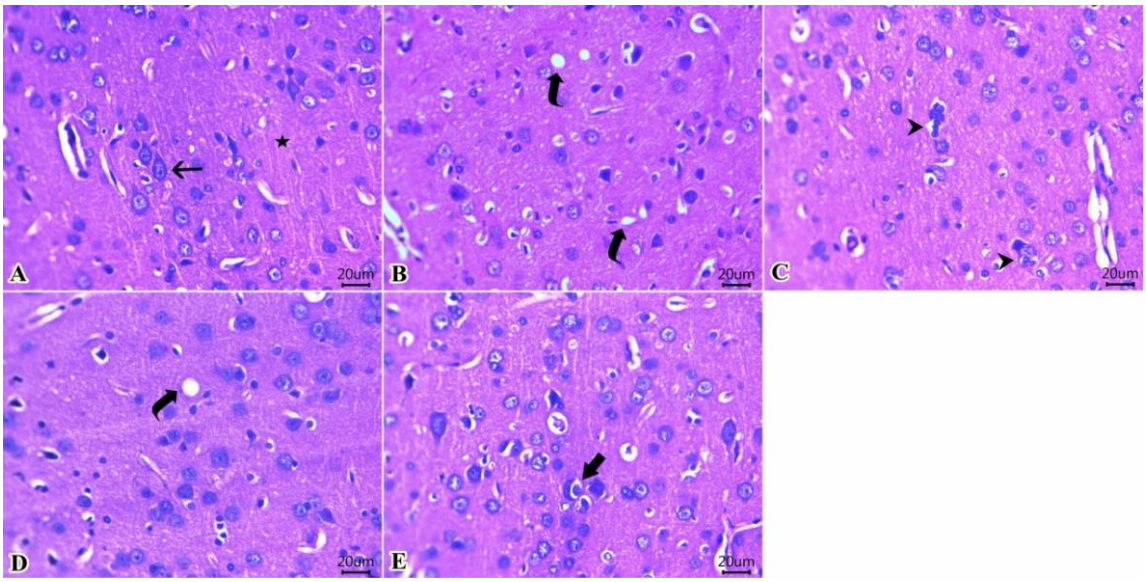

Fig. 10. Representative photomicrograph of H&E stained sections from cerebral cortex "Scale bar 20 µm" showing: A: normal histological structures of neuronal cells (arrow), glial cells, neuropil (star), and cerebral blood vessels in the control group. B, C: vacuolated neuropil (curved arrow), numerous pyknotic neurons with dark basophilic nuclei, and satellitosis (arrowheads) in the obese group. D: A few areas of vacuolated neuropil (curved arrow) in the exercise group. E: The KD group has a few pyknotic neurons and neuronophagia (thick arrow).

References

1. Blüher, M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*, **15**, 288–298 (2019).
2. Morys, F., Dadar, M. and Dagher, A. Association between midlife obesity and its metabolic consequences, cerebrovascular disease, and cognitive decline. *J. Clin. Endocrinol. Metab.*, **106**, E4260–E4274 (2021).
3. Wang, Z., Ge, Q., Wu, Y., Zhang, J., Gu, Q. and Han, J. Impairment of long-term memory by a short-term high-fat diet via hippocampal oxidative stress and alterations in synaptic plasticity. *Neuroscience*, **424**, 24–33(2020).
4. Sies, H., Belousov, V.V., Chandel, N.S., Davies, M.J., Jones, D.P., Mann, G.E., Murphy, M.P., Yamamoto, M., Winterbourn, C.C. and Forman, H.J. Defining roles of specific reactive oxygen species in cell biology and physiology. *Nat. Rev. Mol. Cell Biol.*, **23**, 499–515(2022).

5. Williams, C. and Buttriss, J. Improving the fat content of foods. [Book chapter] (2006).
6. Roh, H.T., Cho, S.Y. and So, W.Y. Obesity promotes oxidative stress and exacerbates blood–brain barrier disruption after high-intensity exercise. *J. Sport .Health Sci.*, **6**, 225–230(2017).
7. Nguyen, J.C.D., Killcross, A.S. and Jenkins, T.A. Obesity and cognitive decline: role of inflammation and vascular changes. *Front. Neurosci.*, **8**, 375 (2014).
8. Morrison, C.D., Pistell, P.J., Ingram, D.K., Johnson, W.D., Liu, Y., Fernandez-Kim, S.O. and White, C.L. High-fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. *J. Neurochem.*, **114**, 1581–1589(2010).
9. Otera, H. and Mihara, K. Molecular mechanisms and physiologic functions of mitochondrial dynamics. *J. Biochem.*, **149**, 241–251(2011).
10. Hebert, A.S., Dittenhafer-Reed, K.E., Yu, W., Bailey, D.J., Selen, E.S., Boersma, M.D., Carson, J.J., Tonelli, M., Balloon, A.J., Higbee, A.J., Westphall, M.S., Pagliarini, D.J., Prolla, T.A., Assadi-Porter, F.M., Roy, S., Denu, J.M. and Coon, J.J. Calorie restriction and SIRT3 trigger global reprogramming of the mitochondrial protein acetylome. *Mol. Cell*, **49**, 186–199(2013).
11. Liu, T., Ma, X., Ouyang, T., Chen, H., Xiao, Y., Huang, Y., Liu, J. and Xu, M. Efficacy of 5-aminolevulinic acid-based photodynamic therapy against keloid compromised by downregulation of SIRT1-SIRT3-SOD2-mROS dependent autophagy pathway. *Redox Biol.*, **20**, 195–203(2019).
12. Dent, R., McPherson, R., and Harper, M.E. Factors affecting weight loss variability in obesity. *Metabolism*, **113**, 154330(2020).
13. Nokia, M.S., Lensu, S., Ahtiainen, J.P., Johansson, P.P., Koch, L.G., Britton, S.L. and Kainulainen, H. Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained. *J. Physiol.*, **594**, 1855–1873(2016).
14. Matinfar, P., Peeri, M., and Azarbayjani, M.A. Swimming exercise attenuates anxiety-like behavior by reducing brain oxidative stress in type 2 diabetic mice. *Physiol. Behav.*, **237**, 113449(2021).
15. Khabour, O.F., Alzoubi, K.H., Alomari, M.A., and Alzubi, M.A. Changes in spatial memory and BDNF expression to simultaneous dietary restriction and forced exercise. *Brain Res. Bull.*, **90**, 19–24(2013).
16. Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., and Yung, A.R. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. *Neuroimage*, **166**, 230–238(2018).
17. Wu, C.W., Chen, Y.C., Yu, L., Chen, H.I., Jen, C.J., Huang, A.M., Tsai, H.J., Chang, Y.T., and Kuo, Y.M. Treadmill exercise counteracts the suppressive effects of peripheral lipopolysaccharide on hippocampal neurogenesis and learning and memory. *J. Neurochem.*, **103**, 2471–2481(2007).
18. Drabińska, N., Wiczkowski, W., and Piskuła, M.K. Recent advances in the application of a ketogenic diet for obesity management. *Trends Food Sci. Technol.*, **110**, 28–38(2021).
19. Barzegar, M., Afghan, M., Tarmahi, V., Behtari, M., Rahimi Khamaneh, S., and Raeisi, S. Ketogenic diet: overview, types, and possible anti-seizure mechanisms. *Nutr. Neurosci.*, **24**, 307–316(2021).
20. Mohamed, H.E., El-Swefy, S.E., Rashed, L.A., and Abd El-Latif, S.K. Biochemical effect of a ketogenic diet on the brains of obese adult rats. *J. Clin. Neurosci.*, **17**, 899–904(2010).
21. Ułamek-Kozioł, M., Czuczwar, S.J., Pluta, R., and Januszewski, S. Ketogenic diet and epilepsy. *Nutrients*, **11**, 2510(2019).
22. Jensen, N.J., Wodschow, H.Z., Nilsson, M. and Rungby, J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. *Int. J. Mol. Sci.*, **21**, 8767(2020).
23. Koh, S., Dupuis, N., and Auvin, S. Ketogenic diet and neuroinflammation. *Epilepsy Res.*, **167**, 106454 (2020).
24. Hernandez, A.R., Hernandez, C.M., Campos, K., Truckenbrod, L., Federico, Q., Moon, B., McQuail, J.A., Maurer, A.P., Bizon, J.L. and Burke, S.N. A ketogenic diet improves cognition and has biochemical effects in prefrontal cortex that are dissociable from hippocampus. *Front. Aging Neurosci.*, **10**, 337(2018).
25. Arsyad, A., Idris, I., Rasyid, A.A., Usman, R.A., Faradillah, K.R., Latif, W.O.U., Lubis, Z.I., Aminuddin, A., Yustisia, I. and Djabir, Y.Y. Long-term ketogenic diet induces metabolic acidosis, anemia, and oxidative stress in healthy Wistar rats. *J. Nutr. Metab.*, **2020**, 3642035(2020).
26. Konda, P.Y., Poondla, V., Jaiswal, K.K., Dasari, S., Uyyala, R., Surtineni, V.P., Egi, J.Y., Masilamani, A.J.A., Bestha, L., Konanki, S. and Muthulingam, M. Pathophysiology of high-fat diet-induced obesity: impact of probiotic banana juice on obesity-associated complications and hepatosteatosis. *Sci. Rep.*, **10**, 16894(2020).
27. Abd El-Hakim, Y.M., Abdel-Rahman Mohamed, A., Khater, S.I., Hamed Arisha, A., Metwally, M.M., Nassan, M.A. and Hassan, M.E. Chitosan-stabilized selenium nanoparticles and metformin synergistically rescue testicular oxidative damage and steroidogenesis-related genes dysregulation in high-fat diet/streptozotocin-induced diabetic rats. *Antioxidants (Basel)*, **10**, 1625(2021).
28. Czimmerer, Z., Hulvely, J., Simandi, Z., Varallyay, E., Havelda, Z., Szabo, E., Varga, A., Dezso, B., Balogh, M., Horvath, A. and Domokos, B. A versatile method to design stem-loop primer-based quantitative PCR assays for detecting small regulatory RNA molecules. *PLoS One*, **8**, e55168 (2013).
29. Bancroft, J.D., and Layton, C. The hematoxylins and eosin. In: *Bancroft's Theory and Practice of Histological Techniques*. 6th ed. Churchill Livingstone Elsevier, pp. 173–186(2007).

30. Lu, Y., Li, H., Shen, S.W., Shen, Z.H., Xu, M., Yang, C.J., Li, F., Feng, Y.B., Yun, J.T., Wang, L. and Qi, H.J. *Lipids Health Dis.*, **15**, 93(2016).

31. Bueno, N.B., De Melo, I.S.V., De Oliveira, S.L. and da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet vs low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. *Br. J. Nutr.*, **110**, 1178–1187(2013).

32. Petridou, A., Siopi, A., and Mougios, V. Exercise in the management of obesity. *Metabolism*, **92**, 163–169(2019).

33. Arika, W.M., Kibiti, C.M., Njagi, J.M. and Ngugi, M.P. Anti-obesity effects of dichloromethane leaf extract of *Gnidia glauca* in high-fat diet-induced obese rats. *Heliyon*, **5**, e01126(2019).

34. DeLany, J.P., Windhauser, M.M., Champagne, C.M. and Bray, G.A. Differential oxidation of individual dietary fatty acids in humans. *Am. J. Clin. Nutr.*, 72, 905–911(2000).

35. Moghadam, B.H., Bagheri, R., Ashtary-Larky, D., Tinsley, G.M., Eskandari, M., Wong, A., Kreider, R.B. and Baker, J.S. The effects of concurrent training order on satellite cell-related markers, body composition, muscular and cardiorespiratory fitness in older men with sarcopenia. *J. Nutr. Health Aging*, **24**, 796–804(2020).

36. Bagheri, R., Moghadam, B.H., Church, D.D., Tinsley, G.M., Eskandari, M., Moghadam, B.H., Motevalli, M.S., Baker, J.S., Robergs, R.A. and Wong, A. The effects of concurrent training order on body composition and serum concentrations of follistatin, myostatin and GDF11 in sarcopenic elderly men. *Exp. Gerontol*, **133**, 110869(2020).

37. El-Shial, E.M., Kabbash, A., El-Aasr, M., El-Feky, O.A. and El-Sherbeni, S.A. Elucidation of natural components of *Gardenia thunbergia* Thunb. leaves: effect of methanol extract and rutin on non-alcoholic fatty liver disease. *Molecules*, **28**(2), 879 (2023).

38. Halverstadt, A., Phares, D.A., Wilund, K.R., Goldberg, A.P. and Hagberg, J.M. Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. *Metabolism*, **56**, 444–450(2007).

39. Keller, J.N., Dimayuga, E., Chen, Q., Thorpe, J., Gee, J. and Ding, Q. Autophagy, proteasomes, lipofuscin, and oxidative stress in the aging brain. *Int. J. Biochem. Cell Biol.*, **36**, 2376–2391(2004).

40. Charradi, K., Elkahoui, S., Karkouch, I., Limam, F., Hassine, F.B. and Aouani, E. Grape seed and skin extract prevents high-fat diet-induced brain lipotoxicity in rat. Neurochemical research, 37(9), pp.2004-2013.Grape seed and skin extract prevents high-fat diet-induced brain lipotoxicity in rat. *Neurochem. Res.*, **37**, 2004–2013(2012).

41. Freeman, L.R., Zhang, L., Nair, A., Dasuri, K., Francis, J., Fernandez-Kim, S.O., Bruce-Keller, A.J. and Keller, J.N. Obesity increases cerebrocortical reactive oxygen species and impairs brain function. *Free Radic. Biol. Med.*, **56**, 226–233(2013).

42. Albrahim, T., Alangry, R., Alotaibi, R., Almandil, L. and Alburikan, S. Effects of regular exercise and intermittent fasting on neurotransmitters, inflammation, oxidative stress, and brain-derived neurotrophic factor in cortex of ovariectomized rats. *Nutrients*, **15**(19), 4270 (2023).

43. Greco, T., Glenn, T.C., Hovda, D.A., and Prins, M.L. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. *J. Cereb. Blood Flow Metab.*, **36**,1603–1613(2016).

44. Feng, Y., Gao, J., Cui, Y., Li, M., Li, R., Cui, C., Moon, B., and Zhong, J. Neuroprotective effects of resatorvid against traumatic brain injury in rat: involvement of neuronal autophagy and TLR4 signaling pathway. *Cell Mol. Neurobiol.*, **37**, 155–168(2017).

45. Liu, Y. and Fassbender, K. Deficiency of TLR4 ameliorates hypoperfusion-induced brain pathology. *Theranostics*, **8**, 6355(2018).

46. Li, M., Liu, J., Bi, Y., Chen, J., and Zhao, L. Potential medications or compounds acting on toll-like receptors in cerebral ischemia. *Curr. Neuropharmacol.*, **16**, 160–176(2018).

47. Yamashita-Kawanishi, N., Tsuzuki, M., Kasuya, F., Chang, H.W., and Haga, T. Genomic characterization of a novel bovine papillomavirus type 28. *Virus Genes*, **56**, 594–599(2020).

48. Qi, J., Yu, X.J., Fu, L.Y., Liu, K.L., Gao, T.T., Tu, J.W., Chen, L.L., and Zhang, D.M. Exercise training attenuates hypertension through TLR4/MYD88/NF-κB signaling in the hypothalamic paraventricular nucleus. *Front. Neurosci.*, **13**, 938(2019).

49. Huang, K., Huang, J., Xie, X., Wang, S., Chen, C., Shen, X., Liu, P., Huang, H., and Zhang, Y. Sirt1 resists advanced glycation end products-induced expressions of fibronectin and TGF-β1 by activating the Nrf2/ARE pathway in glomerular mesangial cells. *Free Radic. Biol. Med.*, **65**, 528–540(2013).

50. Han, M.K., Song, E.K., Guo, Y., Ou, X., Mantel, C., and Broxmeyer, H.E. SIRT1 regulates apoptosis and Nanog expression in mouse embryonic stem cells by controlling p53 subcellular localization. *Cell Stem Cell*, **2**, 241–251(2008).

51. Yeung, F., Hoberg, J.E., Ramsey, C.S., Keller, M.D., Jones, D.R., Frye, R.A., and Mayo, M.W. Modulation of NF-κB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J.*, **23**, 2369–2380(2004).

52. Rajendran, R., Garva, R., Krstic-Demonacos, M., and Demonacos, C. Sirtuins: molecular traffic lights in the crossroad of oxidative stress, chromatin remodeling, and transcription. *J. Biomed. Biotechnol.*, **2011**, 368276(2011).

53. Nonato, L.F., Rocha-Vieira, E., Tossige-Gomes, R., Soares, A.A., Soares, B.A., Freitas, D.A., Mendonça, V.A., and Lacerda, A.C. Swimming training attenuates oxidative damage and increases enzymatic but not non-enzymatic antioxidant defenses in the rat brain. *Braz. J. Med. Biol. Res.*, **49**, e5310(2016).

54. Xiong, W., Ma, Z., An, D., Liu, Z., Cai, W., Bai, Y., Zhan, Q., and Zhou, Y. Mitofusin 2 participates in mitophagy and mitochondrial fusion against angiotensin II-induced cardiomyocyte injury. *Front. Physiol.*, **10**, 411(2019).

55. Kaur, P. and Sharma, S. Recent advances in pathophysiology of traumatic brain injury. *Curr. Neuropharmacol.*, **16**, 1224–1238(2018).

56. Schmitt, L. and Gaspar, J.M. Obesity-induced brain neuroinflammatory and mitochondrial changes. *Metabolites*, **13**, 484(2023).

57. Schmitt, L.O. and Gaspar, J.M. Obesity-induced brain neuroinflammatory and mitochondrial changes. *Metabolites*, **13**, 484(2023).

58. Tang, Y.C., Tian, H.X., Yi, T., and Chen, H.B. The critical roles of mitophagy in cerebral ischemia. *Protein Cell*, **7**, 699–713(2016).

59. Yuan, Y., Zhang, X., Zheng, Y., and Chen, Z. Regulation of mitophagy in ischemic brain injury. *Neurosci. Bull.*, **31**, 395–406(2015).

60. Narendra, D., Tanaka, A., Suen, D.F., and Youle, R.J. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J. Cell Biol.*, **183**, 795–803(2008).

61. Jaroslawska, J., Gospodarska, E., and Korytko, A. Increasing energy expenditure through exercise and low ambient temperature offers oxidative protection to the hypothalamus after high-fat feeding to mice. *J. Neuroendocrinol.*, **34**, e13098(2022).

62. de Sousa Fernandes, M.S., Aidar, F.J., da Silva Pedroza, A.A., de Andrade Silva, S.C., Santos, G.C.J., dos Santos Henrique, R., de Matos, D.G., de Sousa Júnior, J.G., de Almeida-Neto, P.F., Cabral, S.E.N., and Nunes-Silva, A. Effects of aerobic exercise training in oxidative metabolism and mitochondrial biogenesis markers on prefrontal cortex in obese mice. *BMC Sports Sci. Med. Rehabil.*, **14**, 31(2022).

63. Silva, L.A., Tromm, C.B, Doyenart, R., Thirupathi, A., Silveira, P.C.L., and Pinho, R.A. Effects of different frequencies of physical training on electron transport chain and oxidative damage in healthy mice. *Motriz. Rev. Educ. Fis.*, **24**, e101814(2018).

64. Sinaei, M., Alaei, H., Nazem, F., Kargarfard, M., Feizi, A., Talebi, A., Khodadadi, D., and Vafaei, A.A. Endurance exercise improves avoidance learning and spatial memory, through changes in genes of GABA and relaxin-3, in rats. *Biochem. Biophys. Res. Commun.*, **566**, 204–210(2021).

65. Powers, S.K., Radak, Z., and Ji, L.L. Exercise-induced oxidative stress: past, present and future. *J. Physiol.*, **594**, 5081–5092(2016).

التأثيرات الإيجابية الأكثر فعالية لتمارين السباحة مقارنة بالنظام الغذائي الكيتوني في مكافحة تلف الدماغ الناجم عن السمنة لدى الجرذان

حسناء بنيامين[1] ، مهران محمد عبد الامام[1]، يوسف م. شحاته[1]، طارق خميس[2] و محمد فؤاد منصور[1]*

[1] قسم الكيمياء الحيوية والبيولوجيا الجزيئية، جامعة الزقازيق، الزقازيق 44511، مصر

[2] قسم علم الأدوية، كلية الطب البيطري، جامعة الزقازيق، الزقازيق 44519، مصر

الملخص

السمنة هي تراكم غير طبيعي للدهون في الجسم، وهو ما يعتبر أحد أكثر المشاكل الصحية شيوعًا في جميع أنحاء العالم. تسبب السمنة حالة من الإجهاد التأكسدي والالتهاب، مما يؤثر على جميع أنسجة الجسم تقريبًا بما في ذلك الدماغ. تؤثر السمنة على التطور المعرفي وقدرات الوظائف التنفيذية وحجم الدماغ ويمكن أن تزيد من خطر الإصابة بالخرف ومرض الزهايمر. لذلك، قمنا بتقييم تأثير تمارين السباحة مقابل النظام الغذائي الكيتوني على تلف دماغ الجرذان البدينات. تم تقسيم اثنين وثلاثين فأرًا إلى 4 مجموعات (8 فئران لكل منها) تشمل: مجموعة التحكم: تلقت الفئران نظامًا غذائيًا قياسيًا للفئران، مجموعة السمنة: تلقت الفئران نظامًا غذائيًا عالي الدهون، مجموعة النظام الغذائي الكيتوني: تلقت الفئران البدينات نظامًا غذائيًا كيتونيًا / يوميًا لمدة شهرين وتمارين السباحة: خضعت الفئران البدينات للسباحة (ساعة واحدة / اليوم / شهرين). أشارت النتائج إلى أن النظام الغذائي الكيتوني وممارسة السباحة حسنت محيط الخصر والكوليسترول الكلي و الدهون الثلاثية وHDL مقارنة بمجموعة البدينات. أظهرت تمارين السباحة تأثيرًا أقوى في المعايير المذكورة أعلاه من النظام الغذائي الكيتوني. فيما يتعلق بالحالة التأكسدية في الدماغ، قلل كل من النظام الغذائي الكيتوني وتمارين السباحة بشكل كبير من مستوى MDA، بينما زاد من مستوى السعة الكلية المضادة للأكسدة TAC وSOD. قلل كلا العلاجين من مستويات التعبير عن mRNA لمستقبل TLR4 / NF-κBوmir-138-5p وmir-489-3p في أنسجة دماغ الفئران البدينات. ومع ذلك، رفع النظام الغذائي الكيتوني وتمارين السباحة مستويات التعبير عن mRNA للجينات المرتبطة بمضادات الأكسدة (Nrf-2 و SIRT1) والجينات المرتبطة بالانشطار (Mfn1 و Mfn2) والجين المرتبط بالاندماج (DRP-1) والجينات المرتبطة بالالتهام الذاتي للميتوكوندريا (PINK1 و Parkin) والجينات المرتبطة بسلسلة التنفس للميتوكوندريا (NDUFS1 و SDHC و COQ8A و COX6A2 و ATP5F1A). علاوة على ذلك، أظهر كلا العلاجين تحسنًا في الأنسجة المرضية لأنسجة المخ لدى الفئران البدينات. وفي الختام، يعمل النظام الغذائي الكيتوني وتمارين السباحة على استعادة وظائف المخ الطبيعية لدى الفئران البدينات. ومن المثير للاهتمام أن بيانات هذه الدراسة أثبتت أن تمارين السباحة أظهرت تأثيرًا أقوى من النظام الغذائي الكيتوني ضد تلف المخ لدى الفئران البدينات.

الكلمات الدالة: السمنة، تلف الدماغ، النظام الغذائي الكيتوني، تمارين السباحة، خلل الميتوكوندريا.