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Aerobic Exercise Prevents Memory Deficits Induced by Electromagnetic Radiation by Altering Cholinergic Biomarkers and Amyloid Beta Levels

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Abstract

Background: As technology advances, concerns regarding neurobehavioral disorders, particularly memory deficits caused by electromagnetic radiation (EMR) from wireless devices such as Wi-Fi routers have increased dramatically.

Aim: This study aimed to investigate the impact of aerobic exercise on cholinergic biomarkers and amyloid beta (Aβ) levels in the hippocampus of male Wistar rats exposed to 2450MHz EMR emitted by Wi-Fi routers.

Materials and Methods: Eighteen rats were randomly divided into three groups: 'control', 'wave', and 'wave+aerobic exercise'. During four weeks, the 'wave' groups were exposed to 2450MHz EMR from Wi-Fi routers for four hours daily, seven days a week the 'wave+aerobic exercise' group also participated in a running program five days a week in addition to EMR exposure. Cognitive behavioral changes resulting from the interventions were evaluated using the Morris Water Maze (MWM) test.

Results: Exposure to EMR significantly decreased acetylcholine and acetylcholinesterase levels, and increased Aβ levels in the hippocampus ($P<0.05$). The MWM test also revealed a significant impairment in spatial memory among the exposed rats compared to the 'control' group. However, the 'wave+aerobic exercise' group exhibited a significant increase in acetylcholine and acetylcholinesterase levels, a significant reduction in Aβ levels, and demonstrated considerably better performance in the MWM test compared to the 'wave' group ($P<0.05$).

Conclusion: The findings of this study demonstrate the beneficial effects of aerobic exercise in preventing pathophysiological alterations and cognitive impairments caused by electromagnetic radiation.

Keywords: electromagnetic radiation; acetylcholine; acetylcholinesterase; amyloid beta; aerobic exercise; Morris water maze

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1. Introduction

Electromagnetic radiation (EMR) wireless devices like Wi-Fi routers have increased as the global telecommunication industry has grown. Wi-Fi routers use the 2450MHz band of Non-Ionizing Electromagnetic Radiation (NI-EMR), which has insufficient energy to produce ionization, yet studies have shown that they may affect human organs, particularly the brain [25,66]. Previous research has demonstrated that EMR-induced oxidative stress can generate reactive oxygen species (ROS), leading to cell and tissue damage [20,39,40,68] and can affect the central nervous system (CNS) with cellular damage, apoptosis, DNA damage, neurotransmitters dysregulation, protein synthesis, enzyme activity, and energy metabolism; it may influence the brain's function particularly learning and memory, and increase the risk of neurobehavioral disorders and Alzheimer's disease (AD) [8,9,12,15,73,75].

Memory and cognition depend on the cholinergic hippocampus. The cholinergic theory of AD states that cholinergic neurons loss and dysfunction can affect memory and cognition. Conversely, enhancing cholinergic synapses can improve cognitive function. Acetylcholine (Ach), a neurotransmitter, and Acetylcholinesterase (AChE) which hydrolyzes Ach in synaptic clefts, are the most important cholinergic biomarkers for memory formation [13,32,49,57]. Previous studies have reported that oxidative stress caused by EMR may disrupt the cholinergic system and can lead to memory and cognitive dysfunction [35]. The Aβ theory also links oxidative stress, mitochondrial malfunction, Aβ overproduction and neuronal cell death. Aβ, which is important in hemostasis and neuroprotection, formed from Amyloid Precursor Protein (APP) and found in the mitochondrial membrane, is linked to neurobehavioral disease [37,56]. Several studies have demonstrated a negative correlation between Aβ accumulation in the hippocampus and spatial memory, evidenced by the Morris Water Maze (MWM) test, a common assessment of spatial "reference" memory task in rodents [70]. While the exact relationship between Aβ and the cholinergic system remains unclear, Aβ overproduction may disrupt mitochondria, leading to cholinergic impairment. Conversely, dysregulation of the cholinergic system can promote alterations in APP metabolism, resulting in Aβ accumulation and subsequent neurotoxicity, neuroinflammation, and neuronal cell death [58]. Despite limited research on the effects of EMR on the cholinergic system, Aβ aggregation, and memory impairment, it is crucial to further investigate these areas [30].

On the other hand, aerobic exercise may reduce brain oxidative damage and prevent cognitive decline. It boosts neurotransmitters production, mitochondrial function, antioxidant defense, and Aβ reduction. Aerobic exercise has also been associated with increased neurotrophic and growth factors, such as Brain-derived neurotrophic factor (BDNF), Nerve growth factor (NGF), and Vascular endothelial growth factor (VEGF), which promote neurogenesis, neuroprotection, angiogenesis, synaptogenesis, and cell survival in the hippocampus [50]. Given the hippocampus's central role in cognitive function and memory, these effects of aerobic exercise have been demonstrated through improved performance in spatial memory tasks, such as the MWM test, and have been observed at the behavioral level [1,6,28,29,34,41,51,53,63,65,67,69,76,79,87]. Therefore, the present study aims to assess the effect of aerobic exercise on acetylcholine, acetylcholinesterase, and amyloid beta levels in male Wistar rats, thus potentially preventing alterations caused by exposure to 2450MHz EMR emitted by Wi-Fi routers.

2. Methods and Materials

2.1. Participation

In this research, eighteen 8-week-old male Wistar rats (180±20 gr) were purchased from the Pasteur Institute of Iran and housed in the animal laboratory of the University of Tehran. They were maintained under a sleep-wake cycle of 12 hours of light and 12 hours of darkness, with a temperature of 22±3 degrees Celsius and a relative humidity of 40-60%. The rats had free access to standard rodent pellets and water. After a two-week acclimatization period, the rats were randomly divided into three groups: 'control', 'wave', and 'wave+aerobic exercise', with 6 rats in each group. This study received ethical approval from the Research Ethics Committee of the University of Tehran (Ethical number: IR.UT.SPORT.REC.1401.028).

2.2. Electromagnetic Exposure Design

In the 'wave' groups, male rats were exposed to electromagnetic radiation (EMR) at a frequency of 2450MHz using a Wi-Fi router (D-Link Corporation, DWR-M920, Taiwan) for 4 hours every morning for 28 consecutive days. The rats in the 'wave' groups were placed in rectangular polycarbonate cages measuring 26.5 × 42 × 15 cm. The Wi-Fi router was positioned at the center of a circular area with a radius of 30 cm, and the cages were placed around it so that each rat received an equal amount of radiation (Figure 1) [86]. Throughout the exposure period, there was continuous data exchange between the router and a laptop. The specific absorption rate (SAR) value for the whole body was calculated as 0.03 W/kg using the formula: SAR = $(\sigma.\ E^2)/\rho$, where σ represents the electrical conductivity of the tissue, ρ represents the mass density of the tissue, and E represents the value of the electric field, which was measured as 4.53 V/m using an electromagnetic radiation tester (ERT2000, Taiwan). The 'wave' and 'wave + aerobic exercise' groups were studied under the same laboratory conditions.

2.3. Aerobic Exercise Program

The 'wave+aerobic exercise' group underwent a 4-week aerobic exercise program on a rodent treadmill, five days a week from 12-3 pm. During this training period, the rats were exposed to EMR for one hour every morning. Each exercise session started and ended with a 3-5 minute warm-up and cool-down period, respectively, at a speed of 5-7 meters per minute. To familiarize the rats with the aerobic exercise program, they were introduced to the running protocol on the rodent treadmill for two weeks, starting at a very low speed. Over the two weeks, the duration of exercise increased gradually to 20 minutes, and the speed increased until it reached 15 meters per minute.

During the first week of the aerobic exercise program, the rats exercised at a speed of 20 m/min for 25 minutes. In the following two weeks, the duration of exercise was increased by 5 minutes, and the speed was increased by 5 m/min (2nd week: 25 m/min for 30 min, 3rd week: 30 m/min for 35 min). The speed for the final week (4th week) was kept the same as the third week, at 30 m/min for 35 minutes. It's important to note that during the exercise sessions, the Wi-Fi router was turned off to prevent any interference (Note: During the exercise, the Wi-Fi router was turned off) [72]. After completing the exercise program, changes in cognitive behavior were assessed using the Morris water maze test, 48 hours following the final exercise session.

2.4. The Morris Water Maze (MWM)

The Morris water maze (MWM) is a widely used task in behavioral neuroscience to evaluate spatial ability and memory in animals. The MWM is a swimming-based model in which animals learn to locate hidden platforms. The test apparatus consisted of an indirect plastic basin with a circumference of 150 cm and a height of 50 cm, filled with clear water to a depth of 30 cm at a temperature of 25 ± 2 °C. A platform with a circumference of 10 cm was placed in the center of the water tank, positioned 1 cm above the water surface.

The test was conducted over a period of 5 days and divided into two phases: The Training Phase and the Test Phase. During the Training Phase (Spatial Access Phase), the rats were trained to swim freely in the water pool for four sessions per day over four days. Each trial started from a different position, and the rats learned to swim and find the hidden platform within 60 seconds.

After the Training Phase, the Test Phase (memory retention phase) began. In this phase, the platform was removed, and the rats underwent a 1-minute trial similar to the training sessions to find the platform. The average time spent (in seconds) and the distance traveled (in centimeters) in the quadrant where the platform was previously located during the training sessions were measured to assess the rats' ability to retain spatial information. The software program 'Neurovision' was used for the analysis of the task [2].

2.5. *Biochemical Assessment*

2.5.1. Tissue Sample Preparation

After 48 hours of the last exercise session, the rats were anesthetized using a mixture of

Ketamine and Xylazine. The brain tissue, specifically the hippocampus, was dissected out and immediately frozen in liquid nitrogen. The frozen tissue samples were then stored at -80°C until further laboratory processing and biochemical estimation.

2.5.2. Assessment of Acetylcholine (Ach)

The concentration of acetylcholine (Ach) in the hippocampus tissue was measured using a specific kit (Ach: MBS282680, USA). The results were reported as pg/mL and were read using an ELISA reader (Biotek-refelx800, USA).

2.5.3. Assessment of Acetylcholinesterase Activity

The activity of acetylcholinesterase in the hippocampus tissue was evaluated by Acetylcholinesterase Activity Assay Kit and the results were reported as Unit/ml [AChE activity: Cat No.MAK119, Germany] and was read by an ELISA reader (Biotek-refelx800, USA).

2.5.4. *Assessment of Acetylcholinesterase and Amyloid beta: Western Blotting Analysis*

For Western blotting analysis, the hippocampus tissue was lysed in a buffer containing a complete protease inhibitor cocktail. The protein concentrations in the lysates were determined using Lowry's method [52]. Electrophoresis was performed on SDS-PAGE gels to separate the amyloid beta (Aβ) and acetylcholinesterase (AChE) proteins (BIO-RAD, USA). Then the membrane was incubated overnight with primary antibodies specific to mouse Amyloid beta antibody (72kDa; GTX37467, USA) and rabbit acetylcholinesterase antibody (60kDa; orb13233, USA). In this study, the GAPDH antibody (35kDa; GTX100118, USA) was used as a loading control antibody to normalize the protein levels detected. The next day, the membrane was probed with secondary antibodies (Secondary (rabbit): BA1054-2, Secondary (mouse): SC-516102). Immunoreactive protein bands were detected using enhanced chemiluminescence (ECL) reagents (REF B111420, Parstous, IRAN), and the appearance of the bands was visualized using an X-Ray film. The software program 'ImageJ' was used for the visualization and analysis of the proteins of interest.

2.6. Statistic

The statistical analysis of the data was conducted using SPSS version 26 software. Before conducting the statistical tests, the normal distribution of the data and the homogeneity of variances were checked. To compare the average variables between different groups (in cases where there were three or more groups), one-way ANOVA followed by Tukey's post hoc test was used. A significance level of 0.05 ($P < 0.05$) was used to determine statistical significance. The result was considered statistically significant if the calculated P-value was less than 0.05. The results were presented as Mean ± SEM.

3. Results

Figure 2A: Rats exposed to 2450MHz EMR spent significantly less time in the target quadrant compared to the control group [F=9.54; P=0.01]. Figure 2B: Rats exposed to 2450MHz EMR traveled a shorter distance in the target quadrant compared to the control group [F=17.29; P=0.003]. After aerobic exercise intervention, rats performed significantly better by spending more time and traveling a longer distance in the target quadrant compared to the wave group [P=0.0166, P<0.0001].

Figure 3: Rats exposed to 2450MHz EMR showed significantly decreased levels of Ach compared to the control group [F=51.33; P=0.001]. After aerobic exercise intervention, Ach levels increased significantly in 'wave+aerobic exercise' group compared to the wave group [P=0.0001].

Figure 4A: Rats exposed to 2450MHz EMR exhibited a significant decrease in AChE concentration compared to the control group [F=48.92; P=0.001]. After the aerobic exercise intervention, AChE concentration significantly increased notably compared to the wave group [P=0.004].

Figure 4B: Rats exposed to 2450MHz EMR showed a significant decrease in AChE activity compared to the control group [F=24.26; P=0.0001]. After aerobic exercise intervention, AChE activity increased markedly compared to the wave group [P=0.028].

Figure 5: Rats exposed to 2450MHz EMR exhibited significantly increased levels of Aβ compared to the control group [F=62.24; P=0.0001]. After aerobic exercise intervention, Aβ levels significantly decreased compared to the wave group [P=0.003].

Additionally, western blotting bands of Acetylcholinesterase and Amyloid beta proteins compared to GAPDH protein in 'control', 'wave', and 'wave + aerobic exercise' groups in rat hippocampus of male Wistar rats are represented on Supplementary Figure file. The wave group displayed higher levels of Aβ proteins and lower levels of AChE compared to the control group. However, after exercise intervention, significant changes in both proteins were observed.

3.1. Figures, Tables and Schemes

Figure 1. Setup of the electromagnetic exposure; wave: 2450MHz EMR by Wi-Fi router.

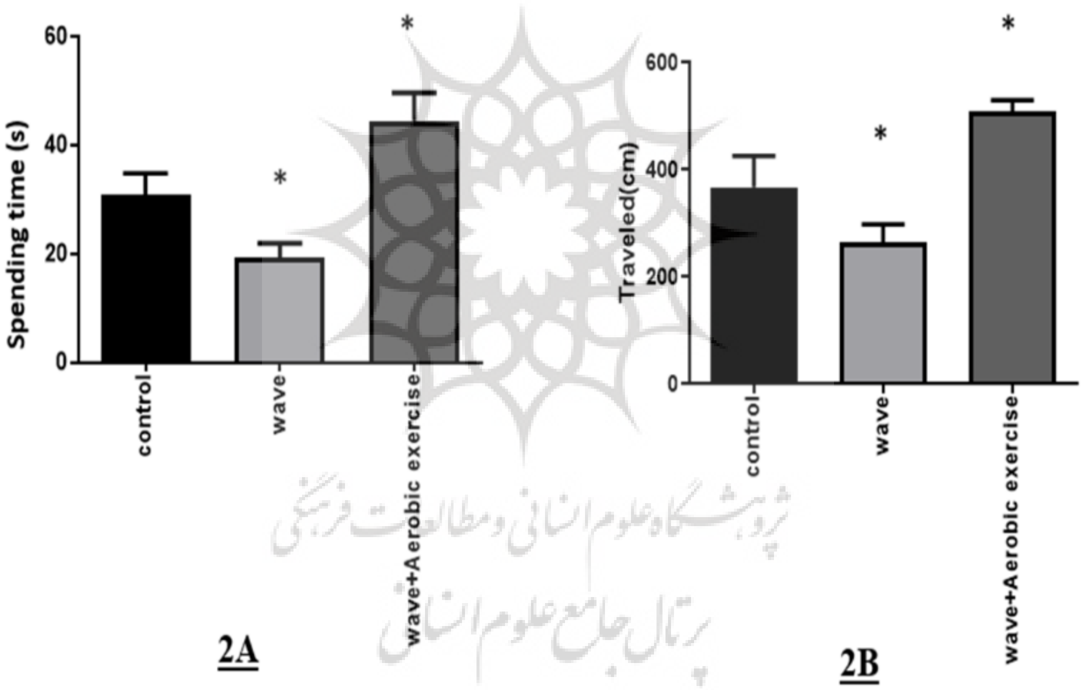

Figure 2. The results of the memory retention phase of Morris Water Maze test including spent time (2A) and traveled distance (2B) in the target quadrant in 'control', 'wave' and 'wave + aerobic exercise' groups in male Wistar rats (*p<0.05). s: second; cm: centimeter; wave: 2450MHz EMR by Wi-Fi router

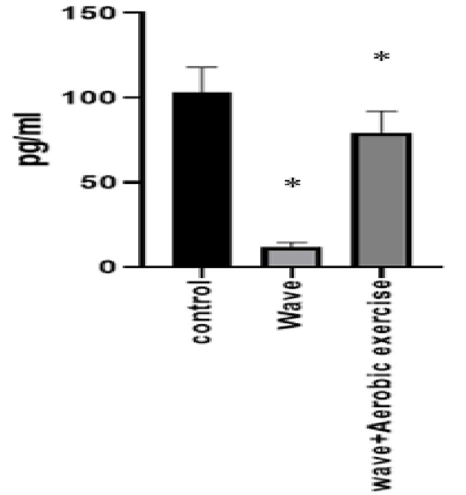

Figure 3. Alterations in the concentration of Acetylcholine by 'wave' and 'wave + aerobic exercise' in comparison with control group in the hippocampus of male Wistar rats (*p<0.05). Ach: Acetylcholine; pg/ml: picogram per milliliter; wave: 2450MHz EMR by Wi-Fi router.

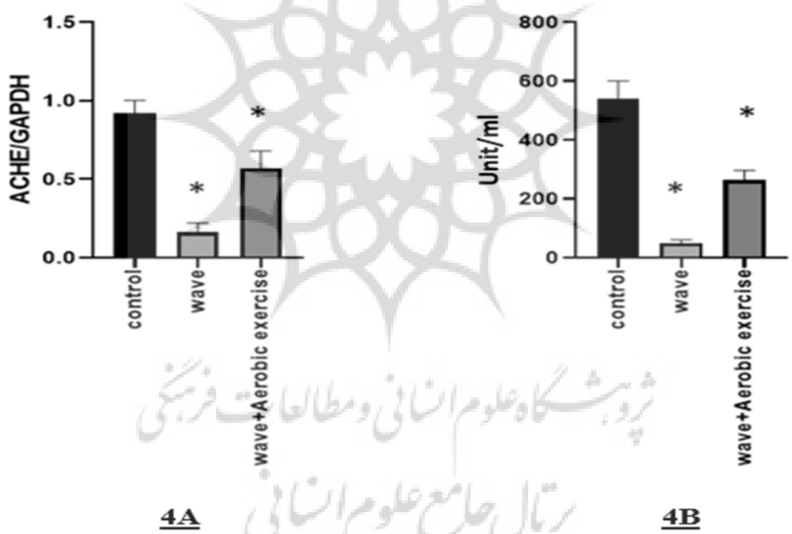

Figure 4. Changes in the level of Acetylcholinesterase concentration compare to GAPDH protein (4A) and Acetylcholinesterase activity (4B) in 'control', 'waves' and 'wave + aerobic exercise' in the hippocampus of male Wistar rats (*p<0.05). AChE: Acetylcholinesterase; Unit/ml: unit per milliliter; wave: 2450MHz EMR by Wi-Fi router.

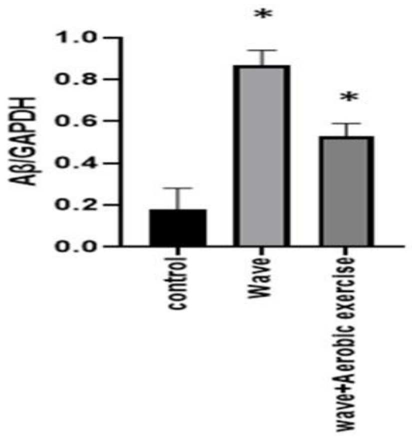

Figure 5: Alterations in Amyloid beta levels compare to GAPDH protein between (a) 'control', 'wave', and 'wave + aerobic exercise' groups in the hippocampus of male Wistar rats (*p<0.05). Aβ: Amyloid beta; wave: 2450MHz EMR by Wi-Fi router.

4. Discussion

The study investigated on the effects of exposure to electromagnetic radiation (EMR) from a Wi-Fi router on memory and cognitive function in male Wistar rats. The researchers found that rats exposed to 2450MHz EMR showed cognitive deficits, dysregulation of cholinergic biomarkers, and increased levels of amyloid beta (Aβ) protein, which is associated with memory impairment and Alzheimer's disease which was considerably reversed by an aerobic exercise intervention.

The relationship between EMR exposure and cognitive function has been explored in previous studies, but the findings have been inconsistent. Some studies have reported decreased learning and memory abilities in animals exposed to EMR, while others have found no significant effects. For instance, similar to our result, a previous study by Wang and Lai (2000) found that rats exposed to 2450MHz EMR had decreased learning and memory abilities as measured by the Morris Water Maze test [88]. In addition, Deshmukh and colleagues (2015) showed that rats exposed to 2450MHz EMR experienced a deterioration in cognitive performance [22]. Also, Varghese and colleagues (2018) showed lower antioxidant capacity and elevated apoptotic factors in 2450MHz irradiated rats, which led to a reduction in memory and learning as measured by the MWM test [86]. Additionally, Tang and colleagues (2015) reported even exposure to lower-frequency EMR can result in substantial impairment in spatial memory [80]. However, some studies asserted that EMR has no substantial influence on learning and memory [7,11,14,16,23,77]. The variations in outcomes could be attributed to factors such as different experimental conditions, including the type of

EMR, frequency, power density, duration of exposure, and performance tasks used.

According to the cholinergic hypothesis, memory formation depends on the cholinergic system including Ach, receptors, and enzymes which play a crucial role in learning, paying attention, and other higher-level cognitive processes [31,32]. This study found a significant decrease in ACh levels, acetylcholinesterase (AChE) activity, and dysregulation of AChE in rats exposed to EMR.

These findings suggest that exposure to 2450MHz EMR negatively impacts spatial memory, acetylcholine levels, acetylcholinesterase concentration and activity, as well as increases amyloid beta levels in the hippocampus. Aerobic exercise intervention appears to mitigate these effects by improving memory performance, increasing acetylcholine levels, restoring acetylcholinesterase concentration and activity, and reducing amyloid beta levels.

Although the underlying mechanisms of the relationship between exposure to EMR, decrease in cholinergic neurotransmission, memory deficit and even AD are not fully understood, several studies have reported changes in cholinergic biomarkers including a reduction in the production and recharge of Ach and dysregulation in activity and concentration of AChE in AD cases as our results have shown [58,81]. To support our findings, Gökçek and colleagues (2020) exposed male Wistar rats to 2.1GHz electromagnetic radiation for one week to show the effects of different doses of radiation on learning, and hippocampal levels of cholinergic biomarkers and they found that closer positioning to the antenna (higher dose) resulted in significantly lower hippocampal protein levels and expression of AChE, ChAT, and VAChT, as well as impaired memory by hippocampal-dependent tasks [27]. Furthermore, Obajuluwa and colleagues (2017) studied on exploratory and motor coordination-linked behavior in male rats exposed to 2.5GHz EMR by Wi-Fi device (8 weeks); they reported a significant rise in anxiety level and affect locomotor function, a significant decrease in AChE activity, and a concurrent rise in AChE gene expression [64]. Even in earlier studies, acute exposure to 2450MHz EMR showed a 40%-60% decrease in mean Ach release from the hippocampus [44,83]. Moreover, a decrease in the level of Ach, choline uptake, cholinergic activity, and increase in AChE activity in the hippocampus with a significant decline in performance by 2450MHz EMR were observed by Lai and colleagues (1987, 1988, 1992) [46-48]. These findings suggest a link between EMR exposure, impairment in the cholinergic system, and memory deficits. However, some studies have shown no significant changes in the concentration of Ach have been reported and radial-arm maze performance remained unchanged [17].

Additionally, the study observed an increase in Aβ levels in rats exposed to EMR, which is associated with the pathophysiology of

Alzheimer's disease. According to the amyloid hypothesis, accumulation and deposition of Aβ can lead to cognitive deficits and the development of AD. Although the relationship between AD and EMR is still contradictory, some studies suggest that EMR exposure may increase the risk of memory deficits and AD by promoting Aβ production and decreasing melatonin production. Therefore exposure to EMR may prepare the ground for memory deficit and the possibility of AD in the future [18,21,26]. For example, Gupta and colleagues (2018) reported significant cognitive deficits in animals exposed to EMR-2450MHz for 1 h/28 days by Y-maze test. They found a significant increase in Aβ expression along with memory impairment, a significantly decreased level of Ach, and an increase in the enzymatic activity of AChE in irradiated rats; they claimed that these alterations might be related to mitochondrial dysfunction and activation of the intrinsic pathway of apoptosis [30]. Furthermore, Dasdag and colleagues (2012) claimed that induced expression of Aβ by EMR may cause a cognitive deficit in rats [19]. In addition, Stefi and colleagues (2019) announced alterations in APP and cellular topology, following 3 times EMR exposure [78]. However, some studies found no effect on Aβ-related memory impairment or Aβ accumulation following EMR exposure in animal models [4,5,77]. These conflicting results might be related to different experimental models and details of the exposure setup of EMR.

On the other hand, aerobic exercise has been shown to have positive effects on cognitive function. Exercise improves blood flow, brain metabolism, neurotrophic factors such as BDNF, and synaptic plasticity. It also reduces oxidative stress and enhances antioxidant capacity which can offer beneficial effects on cognitive function and could be a significant alternative or supplemental treatment for neurocognitive disorders such as memory and learning deficiency [10]. Although the exact neuroprotective pathways of exercise are not fully understood, various known physiological pathways such as BDNF/TrkB signaling, PGC1α/Irisin/BDNF signaling, and anti-apoptotic pathways including MnSOD, IGF-1/PI3K/Akt, and ERK mediated by exercise, can cause the upregulation of molecules associated with learning and memory functions and can be shown in improved performance [54] which can be a preventive strategy to enhance the cognitive function and might be beneficial for whom are at risk of memory and learning disorders or AD patients [89].

Previous studies have demonstrated the neuroprotective effects of exercise on cognitive function in animal models [43,59,60,85]. Exercise can increase Ach concentration, promote angiogenesis, suppress AChE expression, reduce Aβ plaques, enhance neuronal survival, and improve cognition [42,45,61,62,84]. For example, Heo and colleagues (2014) reported suppressed AChE expression, enhanced angiogenesis, and improvement in short-term memory impairment in scopolamine-treated mice after treadmill exercise [33]. Moreover, Jiangbo and colleagues (2018) reported a significant decrease in AChE and an increase in AChT Aβ1-40 induced rats following 4 weeks of swimming program; they also showed a reduction in neuronal loss and improvement in cognition [36]. Similarly, Farzi and colleagues (2019) reported significant improvement in cognition and a decrease in AChE by 8 weeks progressive treadmill running program in Aβ25-35 induced rats [24]. In addition, Shamsipour and colleagues (2021) investigated the effects of 8-week treadmill running (and/or Probiotics) on Aβ1-42 induced rats and they observed a significant increase in Ach, a reduction in Aβ plaques and neuronal death, and an improvement in cognitive function [74]. Another study by Ke and colleagues (2011) 4-week treadmill running program by aged APP/PS1 mice can cause an increase in cholinergic neurons, a significant decrease in Aβ1-40, Aβ1-42 along with improvement in cognition [38].

Aerobic exercise appears to promote antioxidant capacity in the brain (to protect against oxidative stress) and also can cause improvement in blood flow and tissue content of neurotransmitters such as Ach in the central nervous system which is associated with memory and learning; increasing the neurotransmitter content in corporation with increasing neurotrophic factors (BDNF signaling) can enhance neuronal survival and synaptic plasticity. It means that increasing physical activity can promote the neurotrophic pathways, hippocampal neurogenesis, and synaptic plasticity in the brain which neuronal adaptations and cognitive improvements associated with exercise have been shown in studies. Also, protecting against Aβ accumulation and toxicity might be facilitated by decreasing the oxidative stress and increasing the BDNF levels driven by regular, aerobic physical activity [71,87,89]. Suprisingly, Tahmasebi and colleagues (2020) studied the effects of EMR and physical activity on the levels of BDNF, learning, and spatial memory in the offspring of pregnant rats and they claimed that rat offspring's memory and learning are severely harmed by EMR during pregnancy; they reported that swimming and other forms of exercise can lessen the damaging effects of these waves during pregnancy. Also, recently Amiri and colleagues (2023) reported a significant improvement in antioxidant levels and enzyme activity in the liver following swimming exercise in male rats exposed to Wi-Fi radiations which can be explained by the protective role of exercise against negative health effects of irradiadtions [3]. Also, this study found that an aerobic exercise intervention considerably reversed the cognitive deficits, cholinergic dysregulation, and Aβ accumulation induced by EMR exposure in rats.

5. Conclusions

In conclusion, numerous studies have demonstrated the importance of exercise for maintaining a healthy body and brain across all age groups which is supported by current study. Aerobic exercise offers substantial benefits to the cholinergic system (increase in Ach concentration, modifications in AChE concentration and activity), along with a notable reduction in Aβ concentration in the hippocampus. These changes were associated with improved memory and cognitive function, as evidenced by better performance in the MWM task among male Wistar rats exposed to 2450MHz-EMR.

The study suggests that aerobic exercise can serve as a preventive strategy against potential memory decline due to electromagnetic radiation. However, it is important to note that due to variations in research methods, parameters, conditions, and a better understanding of the mechanisms underlying the relationship between EMR exposure, cognitive function, and the potential benefits of exercise, further detailed research is needed.

Conflict of interest

The authors declared no conflicts of interest.

Authors' contributions

All authors contributed to the original idea, study design.

Acknowledgment

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Ethical considerations

The author has completely considered ethical issues, including informed consent, plagiarism, data fabrication, misconduct, and/or falsification, double publication and/or redundancy, submission, etc.

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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