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The Effect of Eight Weeks of Taking a Combined Supplement with Aerobic Exercise on Hippocampal ARC and IGF-1 Gene Expression and Cognitive Performance in Rats with Alzheimer's Diseases: An Experimental Study

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Original Article

Abstract

Introduction: ARC and IGF-1 are important molecular markers for brain neurogenesis, which are significantly reduced in brain tissue in various conditions such as Alzheimer's. The aim of this study was to investigate the effect of eight weeks of consuming combined supplement in conjunction with aerobic exercise on hippocampal ARC and IGF-1 gene expression and cognitive function in elderly rats with Alzheimer's disease.

Materials and Methods: In this experimental study, 25 male c57 mice with Alzheimer's (age: 14-16 weeks, weight: 30-35 grams), were randomly divided into healthy control groups, Alzheimer's, Alzheimer's + aerobic exercise, Alzheimer's + combined supplement, Alzheimer's + aerobic exercise + combined supplement. Alzheimer's induction was performed by injecting amyloid beta-42 (Aβ1) into the hippocampus. The aerobic exercise protocol was five days per week for eight weeks before and after Alzheimer's induction. Kibi's supplement of resveratrol with a concentration of 25 mg/kg and fisetin with a concentration of 20 mg/kg was used for eight weeks. To analyze the data, one-way analysis of variance and Tukey's post hoc test were used at a significance level of 0.05.

Results: Alzheimer's induction caused a significant decrease in the expression of ARC and IGF-1 gene (P = 0.001), a significant increase in the expression of the APP gene in the hippocampus (P = 0.001) and a significant decrease in the cognitive function of the hippocampus (P = 0.001). Aerobic exercise and combined supplement use separately and simultaneously caused significant improvement of all the above changes (P = 0.001).

Conclusion: It seems that aerobic exercise and taking a combined supplement can probably help to increase brain neurogenesis and improve cognitive function in elderly people with Alzheimer's through increasing the expression of ARC and IGF-1 in the hippocampus.

Keywords: Aerobic exercise; APP; ARC; IGF-1; Alzheimer

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Introduction

As in other biological systems in the body, the brain's functional capacities gradually decline with aging. This deterioration manifests as deficits in learning and memory, attention, decision-making speed, sensory perception (visual, auditory, tactile, olfactory, and gustatory), and motor coordination (1). One of the most critical changes associated with advancing age is the decline in cognitive function (2). The progression of age-related cerebral decline accelerates significantly

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after age 50, mirroring the decline of other physiological systems (3).

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder. Global studies indicate a steadily increasing prevalence of this disease among elderly populations worldwide; it is estimated that 36 million people are currently affected by Alzheimer's globally. Projections suggest that, due to the growing global geriatric population, the number of cases will reach 115 million by 2050 (4). A primary pathogenic factor in the development of Alzheimer's is the formation of senile plaques composed of amyloid-beta (Aβ42) peptides. Aβ42is naturally present in the brain in minute quantities, consisting of 37–49 amino acids, and is produced through the proteolysis of the Amyloid Precursor Protein (APP) (5). The most abundant secreted form is Aβ42, while a smaller percentage consists of Aβ42. Furthermore, increased markers of oxidative stress in Alzheimer's disease correlate with the aggregation and deposition of Aβ in the brain. In vitro studies have shown that injecting Aβ42 into primary hippocampal neurons in culture increases oxidative stress markers and neurotoxicity (6).

Additionally, the APP gene is located on chromosome 21; consequently, mutations in this gene lead to the overproduction of amyloid-beta plaques, which are a primary cause of neuronal death (7). Although the precise physiological function of the APP gene remains elusive, several studies have reported its involvement in cell adhesion, neuronal migration, synapse formation, cell survival, and the natural distribution of neurons within the brain (8).

The ARC (Activity-Regulated Cytoskeleton-Associated Gene) is primarily expressed in the glutamatergic neurons of the cerebral cortex and the hippocampus, where it is essential for the maintenance of Long-Term Potentiation (LTP) and memory consolidation. Stimulated neurons rapidly increase the expression of ARC mRNA, which facilitates the detection of neural network activity (9). The stabilization of LTP is heavily influenced by signaling events that follow the induction of ARC mRNA. One of the key regulators of this process is Brain-Derived Neurotrophic Factor (BDNF). In essence, the role of ARC in LTP stabilization is a two-step process: ARC translation is activated, which subsequently drives ARC-dependent LTP stabilization. External stimuli may activate postsynaptic NMDA receptors (NMDAR) and Tropomyosin receptor kinase B (TrkB); subsequently, the binding of glutamate and BDNF to these receptors triggers the transcription and translation of ARC (10).

Insulin-like Growth Factor 1 (IGF-1) exhibits neuroprotective effects in models of central nervous system (CNS) injury. It promotes the proliferation of progenitor cells, neurons, oligodendrocytes, and new blood vessels within the dentate gyrus of the hippocampus. It appears that circulating IGF-1 is essential for exercise-induced neuroplasticity, as blocking its entry into the brain completely abolishes the neurogenic and neuroprotective effects of exercise (11). Physical exercise and activity serve as non-invasive supportive strategies for enhancing brain function. One study revealed that individuals with memory and learning impairments were less active during middle age, and this inactivity was associated with a 25% increase in the development of Alzheimer's disease (12).

Beyond pharmacological interventions, medicinal plants have been utilized or empirically investigated for the treatment of cognitive disorders. Resveratrol, a potent polyphenol and bioactive compound found in certain seeds, vegetables, and fruits (particularly grapes and berries), has been shown to increase cellular longevity. Other attributed properties of this compound include anti-cancer activity, neuroprotection, hypoglycemic effects, and the reduction of glycated hemoglobin (13). Research indicates that resveratrol is neurobiologically significant; for instance, it has attracted attention for its anti-aging effects via activation of the Sirtuin-1 (Sirt1) deacetylase. Resveratrol crosses the blood-brain barrier, where it acts as a neuroprotective agent and restores spatial memory deficits following a stroke (14).

Furthermore, fisetin, a natural flavonoid abundantly found in various fruits and vegetables—including strawberries, apples, persimmons, grapes, onions, and cucumbers—possesses neurotrophic, anti-carcinogenic, and anti-inflammatory properties. It also exhibits potent antioxidant effects against cognitive and neurological disorders, such as Alzheimer's disease (15). Moreover, it has been demonstrated that fisetin inhibits the formation of amyloid-beta Aβ protein fibrils in vitro, improves behavioral performance, and mitigates aluminum chloride-induced neuronal apoptosis in the murine brain (16).

Given the paucity of research regarding the concomitant administration of resveratrol and fisetin alongside aerobic exercise on the hippocampus of Alzheimer's model mice, the present study aimed to investigate the effects of an eight-week regimen of fisetin and resveratrol supplementation, combined with aerobic exercise, on the gene expression of ARC and IGF-1 in the hippocampus and the overall cognitive performance of aged mice with Alzheimer's disease.

Materials and Methods

Animal Husbandry: Twenty-five C57 mice were obtained from the Animal Breeding and Multiplication Center of the Royan Institute, Isfahan. After being transferred to the university's specialized sports physiology laboratory, the animals were acclimated for 1 week. Throughout the study, the animals were maintained under standard conditions, including a 12-hour light/dark cycle, an ambient temperature of 20–22°C, relative humidity of 55%, and ad libitum access to food and water. All ethical principles for animal research were conducted in accordance with the Declaration of Helsinki and under the supervision of the Ethics Committee of the Islamic Azad University, Khorasgan Campus (Ethics Code: IR.IAU.KHUISF.REC.1401.387).

Induction of Alzheimer's Disease: Aβ1-42 oligomers were purchased from Sigma-Aldrich. C57 mice were anesthetized via intraperitoneal administration of 0.2% sodium pentobarbital (50 mg/kg) and subsequently placed in a stereotaxic frame (Stoelting, Wood Dale, IL, USA). Aβ1-42 oligomers (50 µM or 1 mM in 0.9% sterile saline) were bilaterally injected into the dentate gyrus (DG) of the posterior hippocampus (1 µL per side, at a rate of 0.2 µL/min).

Twenty-five AD-induced mice were randomly assigned to the following groups: Alzheimer's (AD), AD + Aerobic Exercise, AD + Resveratrol and Fisetin, and AD + Aerobic Exercise + Resveratrol and Fisetin. Additionally, five healthy mice were included in a healthy control group to verify the effects of the Alzheimer's induction.

Aerobic Exercise Protocol: The aerobic exercise program was conducted 5 times per week for 8 weeks. The training commenced in the first week with 30-minute sessions at 10 m/min on a treadmill, progressively increasing to 40-minute sessions at 27 m/min by the eighth week (Table 1).

Administration of Resveratrol and Fisetin: Resveratrol and fisetin were purchased from Sigma-Aldrich (USA). The safe dosage for each compound was determined based on existing literature; resveratrol (25 mg/kg) and fisetin (20 mg/kg) were administered via oral gavage.

Dissection and Sampling: Forty-eight hours after the final exercise session and following a 12-hour fast, the mice were anesthetized using a combination of ketamine (50 mg/mL) and xylazine (20 mg/mL). Before proceeding, the laboratory specialists performed a pain response test to verify the depth of anesthesia. Once complete, anesthesia was confirmed, the brains were harvested, and the tissue was immediately snap-frozen in liquid nitrogen. For the measurement of APP, ARC, and IGF-1, brain tissue was stored at −80°C.

Table 1. Aerobic Exercise Program

Duration (Weeks)	Running Speed (m/min)	Session Duration (min)	Sessions per week (days)
1	10	30	5
2	18	35	5
3	18	35	5
4	22	35	5
5	22	40	5
6	27	40	5
7	27	40	5

Measurement of APP, ARC, and IGF-1 Gene Expression: Total RNA was extracted from the hippocampal brain tissue using Trizol reagent, following the manufacturer's protocol (Yekta Tahiz Azma). RNA purity and concentration were verified using absorbance ratios. Subsequently, cDNA synthesis was performed using the BIOFACT kit.

The target gene sequences were retrieved from the NCBI database, and nucleotide sequences for the forward and reverse primers of APP, ARC, and IGF-1 were designed using Oligo7 and Beacon Designer. Finally, quantitative real-time PCR (qPCR) was conducted using the SYBR Green kit and the Corbett Rotor-Gene 6000 system. The B2M gene was utilized as the internal housekeeping gene. Relative gene expression was calculated and evaluated using the 2-ΔΔCT method (Table 2).

Data Analysis Method: To assess the normality of the variables, the Shapiro–Wilk test was used. The homogeneity of variances was assessed using Levene's test. In addition, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was applied for data analysis.

Table 2. Primer sequences of the study variables

Genes	Primer sequences	Temperature (°c)
B2m	F: ACAGTTCCACCCGCCTCACATT R: TAGAAAGACCAGTCCTTGCTGAAG	60
IGF-1	F: TGTTCTGTCGCACCCAGTGGTA-3′ R: TTCCAACTGCCACGGTCCTGAT-3′	60
ARC	F: CTGCTGTAACGATGAAGCCCTG-3 R: GCTGTAGGAAGCTCATCTCTCC-3′	60

The significance level was set at $p \leq 0.05$ for all analyses. All statistical analyses were performed using SPSS software, version 23.

Results

The results of one-way ANOVA showed significant differences in the expression levels of ARC (P = 0.001), IGF-1 (P = 0.01), and APP (P = 0.01) genes in the brain tissue of aged rats with Alzheimer's disease across the study groups (Table 3).

The levels of ARC and IGF-1 in the Alzheimer's group were significantly lower than in the healthy control group (P = 0.01). However, in the Alzheimer's + aerobic exercise, Alzheimer's + herbal supplement, and Alzheimer's + aerobic exercise + herbal supplement groups, ARC and IGF-1 levels were significantly increased compared with the Alzheimer's group (P = 0.01).

APP levels in the Alzheimer's group were significantly higher than in the healthy control group (P = 0.01). However, in the Alzheimer's + aerobic exercise, Alzheimer's + herbal supplement, and Alzheimer's + aerobic exercise + herbal supplement groups, APP levels were significantly lower than in the Alzheimer's group (P = 0.01).

Cognitive function in the Alzheimer's group was significantly lower than in the healthy control group (P = 0.01). However, in the Alzheimer's + aerobic exercise, Alzheimer's + herbal supplement, and Alzheimer's + aerobic exercise + herbal supplement groups, cognitive function was significantly improved compared with the Alzheimer's group (P = 0.01).

Discussion

The results of the present study showed that the expression of the ARC and IGF-1 genes plays an important role in neurogenesis and cognitive impairment in AD rats. The expression levels of ARC and IGF-1 were significantly lower in the AD group than in the other groups. Furthermore, aerobic training (AT) and resveratrol and fisetin supplementation increased the expression of ARC and IGF-1 compared with the AD group. A significant synergistic effect of AT combined with resveratrol and fisetin on gene expression and behavioral patterns was observed in the AD + resveratrol–fisetin + aerobic training group compared with the other groups.

Our analysis indicated that effective plant-derived compounds, particularly the bioactive substances resveratrol and fisetin, may improve cognitive impairment in AD rats. In the present study, the simultaneous effects of aerobic exercise and oral bioactive compound supplementation, including resveratrol (25 mg/kg) and fisetin (20 mg/kg), were investigated in aged rats with AD.

Synaptic abnormalities are among the main features of AD and appear during disease progression. Numerous studies have demonstrated that pathological changes in neural circuits and synapses may provide a mechanistic link between tau pathology and amyloid-beta pathology (17). The findings of the present study are consistent with those of Palop et al. (18), Shamsipour et al. (19), and Ghari et al. (20). Palop et al. (2005) investigated the susceptibility of dentate granule cells to impaired ARC expression in transgenic mice expressing human amyloid precursor protein. Their results showed that reduced ARC expression led to decreased synaptic function and cognitive deficits in hAPP mice and possibly in humans with Alzheimer's disease (18). Similarly, Shamsipour et al. (2021) reported that the combined use of Lactobacillus plantarum and Bifidobacterium bifidum, along with HIIT aerobic exercise, may exert neuroprotective effects in AD (19).

One of the most important cellular mechanisms involved in neuronal growth and neurogenesis is the expression of the ARC gene. ARC is a neuron-specific postsynaptic protein that is selectively expressed in Ca^{2+}/calmodulin-dependent protein kinase II-positive neurons (CaMKII) (19). Following activation, ARC is transported to the postsynaptic density of synaptically active dendritic spines, where it binds to polysomes.

Table 3. Average expression of Activity-regulated cytoskeleton-associated protein (ARC), Insulin-like growth factor 1 (IGF-1), and Amyloid precursor protein (APP) genes in the studied groups

Group	APP gene expression	P-value	IGF1 gene expression	P-value	ARC gene expression	P-value
Normal	0.97 ± 0.03	< 0.01	1.02 ± 0.06	< 0.01	0.97 ± 0.018	< 0.01
Alzheimer's disease	8.40 ± 0.04	*< 0.01	0.29 ± 0.01	*< 0.01	0.34 ± 0.016	*< 0.01
Alzheimer's + Resveratrol–Fisetin	5.30 ± 0.36	*< 0.01	0.55 ± 0.14	*< 0.01	0.47 ± 0.01	*< 0.01
Alzheimer's + Aerobic Exercise	4.32 ± 0.32	*< 0.01	0.63 ± 0.016	*< 0.01	0.64 ± 0.016	*< 0.01
Alzheimer's + Resveratrol–Fisetin + Aerobic Exercise	2.73 ± 0.52	*< 0.01	0.83 ± 0.03	*< 0.01	0.83 ± 0.015	*< 0.01

Values are presented as mean ± standard deviation

APP: Amyloid precursor protein; IGF1: Insulin-like growth factor 1; ARC: Activity-regulated cytoskeleton-associated protein

Table 4. Mean and standard deviation of cognitive function in the study groups

Group	Familiar Object	Novel Object	P-value
Normal	5.50 ± 0.96	18.50 ± 1.13	< 0.0001
Alzheimer's disease	20.60 ± 1.84	19.36 ± 1.20	< 0.01
Alzheimer's + Resveratrol–Fisetin	16.63 ± 0.67	20.12 ± 1.10	< 0.01
Alzheimer's + Aerobic Exercise	14.31 ± 0.13	20.36 ± 1.16	< 0.01
Alzheimer's + Resveratrol–Fisetin + Aerobic Exercise	10.13 ± 0.25	17.43 ± 1.53	< 0.01

Values are presented as mean ± standard deviation.

ARC interacts with endophilin 2/3 and dynamin to help regulate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPA receptors) by increasing their endocytosis (20).

ARC-mediated endocytosis suppresses neural network activity and increases activity-dependent Aβ production. If ARC expression and subsequent activity-dependent Aβ production are not regulated, a positive feedback loop may form, leading to a substantial loss of dendritic spines and synaptic activity, and ultimately to synaptic damage similar to that observed in Alzheimer's disease. ARC is likely important for limiting neuronal excitability, as ARC-mediated endocytosis attenuates neural network activity (21).

Previous studies have shown that aerobic exercise exerts its beneficial effects through multiple pathways, including increased cerebral oxygen consumption, enhanced brain neurotransmitter activity, and upregulation of neurotrophic factors. Aerobic exercise increases ARC expression in the hippocampus by upregulating the MAPK signaling pathway (22).

IGF-1is a growth factor that acts as a potent survival factor for neurons and oligodendrocytes and is also involved in neuronal growth and differentiation in the brain (23). Moreover, IGF-1 may serve as an upstream mediator of BDNF gene expression, neurogenesis, and the protective effects of exercise on the injured brain. It has been shown that IGF-1 induces the formation of new blood vessels in the brain by regulating vascular endothelial growth factor (VEGF), which is primarily involved in angiogenesis and vascular development. Aerobic exercise increases IGF-1 production and release in rodents, leading to the formation of new blood vessels (24).

In the present study, IGF-1 expression decreased following AD induction; however, it increased after resveratrol and fisetin supplementation combined with aerobic training. It has been demonstrated that exercise enhances cerebral uptake of IGF-1, a factor that increases neuronal differentiation of progenitor cells and upregulates BDNF gene expression in the hippocampus (24). Animal studies have shown that exercise protects against brain injury by increasing the uptake of circulating IGF-1 by the brain. Aerobic training likely enhances hippocampal neurogenesis through peripheral IGF-1 production. Moreover, IGF-1 is essential for exercise-induced angiogenesis in the brain and may indirectly induce the formation of new blood vessels through VEGF (25). In addition, IGF-1 and VEGF levels increase following aerobic exercise, which may contribute to the formation of new blood vessels in older adults. Ultimately, IGF-1 may mediate BDNF's effects (26).

In the present study, supplementation with resveratrol and fisetin combined with aerobic exercise increased ARC and IGF-1 expression in the hippocampus of AD rats. The results showed that fisetin supplementation substantially improved cognitive function and memory in AD rats. The findings also indicated that fisetin activates this important neuronal survival pathway by upregulating ARC and IGF-1 in Aβ1–42-induced rat models. Fisetin supplementation has been reported to reduce aluminum-induced apoptosis and neurodegeneration in the hippocampus of adult rats (27). These findings suggest that polyphenolic flavonoids, such as fisetin, extracted from natural plant sources, play an important role in preventing age-related neurological disorders, such as AD.

In addition, resveratrol, a natural polyphenol extracted from red wine, possesses anti-inflammatory, antioxidant, and neuroprotective properties under experimental conditions (28-30). The results of the present study showed that supplementation with resveratrol and fisetin improved cognitive function and increased hippocampal ARC and IGF-1 expression in aged rats with AD.

Limitations

One limitation of the present study was the lack of measurement of other factors related to cognitive function and brain neurogenesis. Therefore, future studies should use multiple measurement methods, such as Western blotting and ELISA, to provide more comprehensive findings.

Recommendations

Future studies should use multiple measurement methods, such as Western blotting and ELISA, to provide more comprehensive findings.

Conclusion

Overall, this study's results indicate that aerobic training and supplementation with resveratrol and fisetin, both alone and in combination, may be effective in improving Alzheimer's disease-related outcomes. Therefore, the combined use of resveratrol and fisetin, along with aerobic exercise, is recommended in aged individuals with Alzheimer's disease. However, further complementary studies are necessary in this field.

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Authors' Contribution

The authors (Amir Jahanbakhsh, Khosro Jalali Dehkordi, and Farzaneh Taghian) contributed equally to the following:

- Project conceptualization and design.
- Acquisition of funding and resources.
- Scientific, executive, and technical support.
- Provision of equipment and experimental samples.
- Data collection and curation.
- Data analysis and interpretation of results.
- Statistical analysis.
- Manuscript drafting, critical revision, and scientific evaluation.
- Final approval of the manuscript for submission.
- Ensuring the integrity of the study from inception to publication and responding to reviewers' comments.

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Conflict of Interest

The authors did not have a conflict of interest.

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