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Combining aerobic training and resveratrol can improve hippocampal UPRmt genes expression better than either alone in Alzheimer's rats

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Abstract:

Background: Mitochondrial dysfunction are a key mechanism in the pathogenesis of Alzheimer's disease (AD). Both exercise and resveratrol (RSV) consumption have been identified as potential interventions against AD. The aim of this study was to evaluate the effects of aerobic exercise and RSV on hippocampal UPRmt in rats with AD.

Materials and Methods: In this experimental study, 35 male Wistar rats were divided into five groups: Normal (NO), Alzheimer's (AD), Alzheimer's-Training (ADT), Alzheimer's-Resveratrol (ADRSV), and Alzheimer's-Training-Resveratrol (ADTRSV). The supplement groups received 20 mg of RSV per kg of body weight orally during the intervention period. The aerobic exercise program involved running on a treadmill at speeds ranging from 6 to 18 meters per minute, performed 5 days a week for eight weeks.

Results: AD induction significantly decreased the expression of HSP10, HSP60, and HSP70 (p=0.0001). The expression of HSP60 and HSP70 was significantly increased in the ADT (p=0.024, p=0.041), ADRSV (p=0.029, p=0.046), and ADTRSV (p=0.0001, p=0.0001) groups compared to the AD group. Additionally, ADTRSV showed a greater increase in HSP60 and HSP70 expression compared to ADT (p=0.038, p=0.045) and ADRSV (p=0.032, p=0.040). A significant increase in HSP10 expression was observed in the ADT (p=0.032) and ADTRSV (p=0.0001) groups compared to the AD group, with ADTRSV showing higher levels of HSP10 expression compared to ADRSV (p=0.049).

Conclusion: Aerobic exercise and RSV can reduce neurodegeneration in AD rats by enhancing hippocampal UPRmt gene expression. The combination of exercise and RSV had a greater effect on UPRmt than either intervention alone.

Keywords: Alzheimer's Disease, Exercise, Resveratrol, Mitochondrial Unfolded Protein Response

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Introduction

Alzheimer's disease (AD) is a progressive neurological disorder that affects over 47.5 million people worldwide, a number expected to rise in the coming years (1). AD is characterized by memory loss followed by a decline in cognitive functions such as speech, problem-solving, and visuospatial perception (2). Histopathologically, AD is marked by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs), which result from the abnormal hyperphosphorylation of tau in the brain. Mutations in amyloid precursor protein (APP), the main component of Aβ plaques, have been linked to AD (3). Metabolic disorders and mitochondrial dysfunction are central mechanisms in Aβ-induced neurodegeneration (4).

Mitochondria are the energy factories of cells, but their roles extend beyond energy metabolism. They are critical for the production of metabolic intermediates, calcium homeostasis, immune responses, cell differentiation, apoptosis, and the maintenance of proteostasis (5). Mitochondrial function relies on mitochondrial homeostasis, which can be disrupted by various endogenous and exogenous factors. To protect against this damage, a cellular defense mechanism known as the mitochondrial unfolded protein response (UPRmt) is activated. UPRmt improves mitochondrial function by initiating a transcriptional program involving multiple genes through retrograde mitochondrial-to-nucleus signaling (6). This response helps stabilize the mitochondrial environment by refolding misfolded proteins, degrading damaged proteins through mitophagy, regulating mitochondrial biogenesis, and alleviating oxidative stress (7-9). UPRmt is essential for maintaining mitochondrial proteostasis and is implicated in many neurodegenerative disorders, including AD, which are often characterized by an accumulation of misfolded/unfolded proteins leading to UPR activation. Similar to the endoplasmic reticulum stress response, UPRmt upregulates genes that control cell fate (10).

Appropriate exercise has been shown to delay and improve symptoms of neurodegenerative diseases, particularly AD. For example, a study by Cui et al. (2023) demonstrated that twelve weeks of aerobic exercise significantly increased autophagy and UPRmt levels in the hippocampus and cerebral cortex of rats (11). Similarly, research by Deng et al. (2024) showed that aerobic exercise reduced cognitive impairment in AD rats by inhibiting endoplasmic reticulum stress and neuroinflammation in hippocampal tissue (12).

In addition to physical activity, nutrition and supplementation are critical for managing cognitive decline, especially in AD patients (13). Resveratrol (RSV), a polyphenol found in foods like grapes, berries, peanuts, red wine, and certain herbal supplements (14), has demonstrated a broad spectrum of therapeutic potential in animals, including antioxidant, anti-inflammatory, neuroprotective, and life-prolonging effects (14, 15). Experimental studies suggest that RSV plays a significant role in mitigating the pathogenesis of AD (16). Clinical studies have shown that RSV can reduce Aβ levels (17), lower proinflammatory markers, and improve cognitive function and overall outcomes in AD patients (17). In animal models, RSV has been found to improve memory and cognitive performance, reduce levels of amyloidogenic BACE1, Aβ, and tau proteins, and increase proteasomal activity (18).

Given the critical role of UPRmt in mitochondrial function and its involvement in AD, non-pharmacological treatments like aerobic exercise and RSV supplementation—both of which improve mitochondrial function—could offer effective strategies for mitigating and delaying AD progression. However, few studies have investigated the combined effects of aerobic exercise and RSV supplementation on hippocampal UPRmt in AD rats. Therefore, the hypothesis of this study is that concurrent aerobic training and RSV supplementation have synergistic effects, improving mitochondrial function through the modulation of UPRmt in AD rats.

Materials and Methods

This study was conducted as laboratory-based experimental research. All animal experiments were performed in accordance with animal protection policies, as outlined by the Helsinki Convention, and the guidelines provided by the National Institutes of Health (NIH) for the care and use of laboratory animals. Thirty-five 8-week-old male Wistar rats, with an average weight of 223.17 ± 9.08 grams, were obtained from the Pasteur Institute and housed in the animal laboratory. The ambient temperature was maintained at 22 ± 3°C with a 12:12-hour light-dark cycle. All animals had ad libitum access to water and a specialized rodent diet. After a one-week acclimatization period to the new environment, the rats were randomly divided into five groups of seven rats each: 1) Normal (NO), 2) Alzheimer's (AD), 3) Alzheimer's-Training (ADT), 4) Alzheimer's-Resveratrol (ADRSV), and 5) Alzheimer's-Training-Resveratrol (ADTRSV).

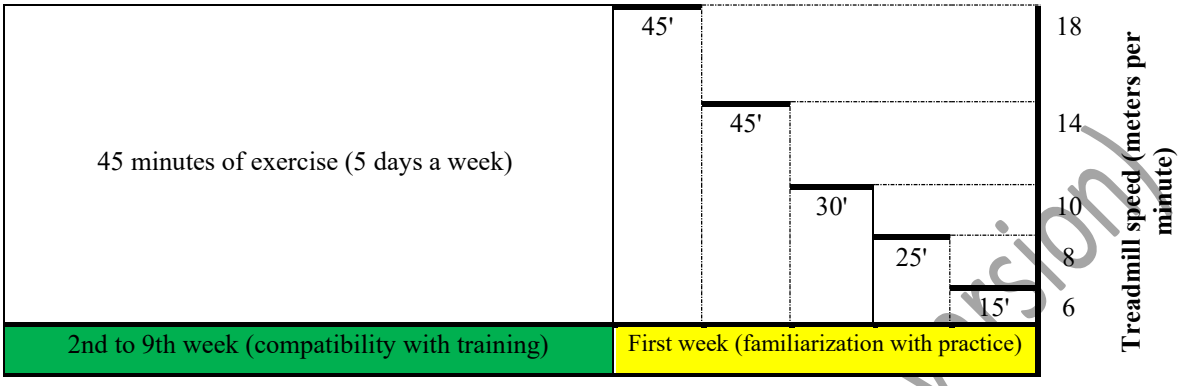
Alzheimer's Induction

Amyloid-β 1-42 (Sigma-Aldrich) was dissolved in double-distilled sterilized water and incubated at 37°C for one week. The rats were anesthetized using ketamine (50 mg/kg) and xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The scalp was shaved, and the bregma and lambda sutures were identified via a sagittal incision. The CA1 region of the hippocampus was marked, and a small hole was gently drilled in the skull. Using a Hamilton syringe, 2 μL of amyloid-β solution was slowly injected into the hippocampus over a period of approximately one minute (15).

Exercise Protocol

The exercise regimen for the AD rats is shown in Figure 1. The training commenced at 2 months of age and was divided into two stages: familiarization with the exercise (2 weeks) and adaptation to the full training protocol (8 weeks). In the familiarization phase, rats performed treadmill exercises at a speed of 6-18 meters per minute for 45-15 minutes over five sessions in the first week. During the following 8-week period, rats engaged in the main exercise protocol, running at a constant speed of 18 meters per minute for 45 minutes, five days a week.

Figure 1. Exercise protocol



Resveratrol Consumption

Resveratrol (20 mg/kg from Sigma-Aldrich) or an equivalent volume of saline (saline solution) was administered orally by gavage every morning (between 8:00 AM and 10:00 AM) for 8 weeks (16, 17).

Data Analysis Procedure

Data distribution was first checked for normality using the Shapiro-Wilk test and for homogeneity of variances using Levene's test. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. The data were analyzed with SPSS version 26, and statistical significance was set at $p \leq 0.05$.

Results

The average weight of the groups is presented in Tables 2.

Table 2. Average weight of groups

Groups		NO (n=7)	AD (n=7)	ADT (n=7)	ADRSV (n=7)	ADTRSV (n=7)
weight (grams)	First week	219.71±10.61	225.57±11.28	224.71±9.41	222±6.42	223.86±8.49
	8th week	240.14±11.46*	239.14±11.21*	240.43±7.61*	236.71±8.46*	237.29±10.09*c

NO: normal, AD: Alzheimer, ADT: Alzheimer-training, ADRSV: Alzheimer-resveratrol, ADTRSV: Alzheimer-training-resveratrol. * Difference from First week, c Difference from ADTRSV.

Data analysis revealed a significant difference in the expression of HSP10 in hippocampal tissue between the different groups ($p = 0.0001$, $F = 9.499$). Post-hoc tests indicated a

significant decrease in HSP10 levels in the AD group (p = 0.0001) and the ADRSV group (p = 0.038) compared to the NO group. Furthermore, significant increases in HSP10 expression were observed in the ADT (p = 0.032) and ADTRSV (p = 0.0001) groups compared to AD. Additionally, ADTRSV exhibited significantly higher levels of HSP10 expression compared to both ADRSV (p = 0.049) and ADT (p = 0.038) (Figure 1).

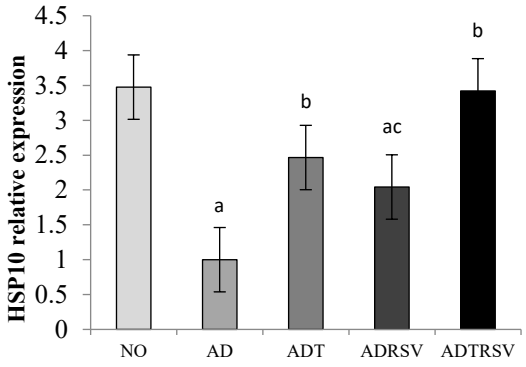


Figure 1. Hippocampus HSP10 expression by one-way ANOVA test (p<0.05).
a Difference from NO, b Difference from AD, c Difference from ADTRSV.
NO: Normal, AD: Alzheimer, ADT: Alzheimer-training, ADRSV: Alzheimer-resveratrol, ADTRSV: Alzheimer-training-resveratrol.

Analysis also showed a significant difference in the expression of HSP60 in hippocampal tissue across the groups (p = 0.0001, F = 13.917). Post-hoc tests revealed a significant decrease in HSP60 expression in the AD group (p = 0.0001), the ADT group (p = 0.026), and the ADRSV group (p = 0.022) compared to the NO group. A significant increase in HSP60 expression was observed in the ADT (p = 0.024), ADRSV (p = 0.029), and ADTRSV (p = 0.0001) groups compared to the AD group. Furthermore, the ADTRSV group had significantly higher levels of HSP60 expression compared to both ADT (p = 0.038) and ADRSV (p = 0.032) (Figure 2).

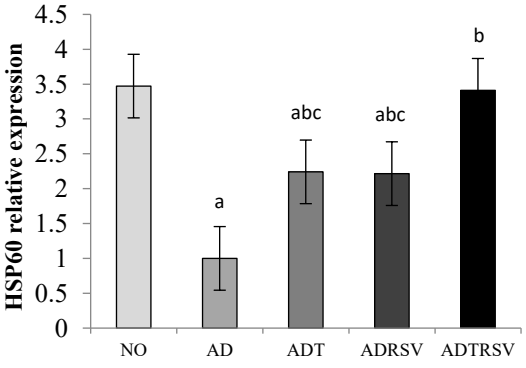


Figure 2. Hippocampus HSP60 expression by one-way ANOVA test (p<0.05).
a Difference from NO, b Difference from AD, c Difference from ADTRSV.

NO: Normal, AD: Alzheimer, ADT: Alzheimer-training, ADRSV: Alzheimer-resveratrol, ADTRSV: Alzheimer-training-resveratrol.

Lastly, data analysis showed a significant difference in the expression of HSP70 in hippocampal tissue among the groups ($p = 0.0001$, $F = 12.897$). Post-hoc tests demonstrated a significant decrease in HSP70 expression in the AD group ($p = 0.0001$), ADT group ($p = 0.027$), and ADRSV group ($p = 0.023$) compared to the NO group. A significant increase in HSP70 expression was observed in the ADT ($p = 0.041$), ADRSV ($p = 0.046$), and ADTRSV ($p = 0.0001$) groups compared to the AD group. Moreover, the ADTRSV group showed significantly higher levels of HSP70 expression compared to both ADT ($p = 0.045$) and ADRSV ($p = 0.040$) (Figure 3).

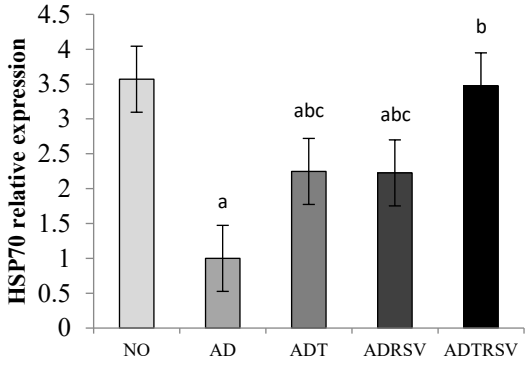


Figure 3. Hippocampus HSP70 expression by one-way ANOVA test ($p<0.05$).
a Difference from NO, b Difference from AD, c Difference from ADTRSV.
NO: Normal, AD: Alzheimer, ADT: Alzheimer-training, ADRSV: Alzheimer-resveratrol, ADTRSV: Alzheimer-training-resveratrol.

Discussion

The results of the present study showed that the induction of Alzheimer's disease (AD) decreased the expression of HSP10, HSP60, and HSP70 in mice. As AD is a proteinopathy, molecular chaperones play a crucial role in maintaining protein homeostasis (24). The primary components of the chaperone system are heat shock proteins (HSPs), which, in addition to maintaining protein homeostasis, also regulate tissue regeneration (25). The most important molecular chaperones in brain tissue include HSP60, HSP70, and HSP90 (26). AD, as a neurodegenerative disease, is associated with an increase in amyloid-β (Aβ) accumulation (3), and HSPs have been shown to inhibit Aβ aggregation (27).

In agreement with the present study, Gammazza et al. (2023) demonstrated that plasma levels of HSP60 and HSP70 are significantly lower in individuals with AD compared to healthy individuals (24). Similarly, Nuzzo et al. (2015) reported a reduction in HSP60 levels in the hippocampus of mice fed a high-fat diet, which was linked to the pathogenesis of AD (28).

Furthermore, a separate study observed significant decreases in HSP90 levels in AD, and the reduction of HSP90 in the blood was found to be an indicator of increased Aβ accumulation (29). Depletion of these chaperones through Aβ1-42 exposure led to increased protein misfolding, while enhanced expression of HSP60 in the cerebellum of AD mice reversed this process (30).

In the present study, it was demonstrated that following aerobic exercise, the expression of HSP10, HSP60, and HSP70 increased significantly. Additionally, resveratrol (RSV) consumption also enhanced the expression of HSP60 and HSP70 in AD mice. Regular aerobic exercise is an effective approach for mitochondrial regeneration, as it stimulates mitochondrial biogenesis, activates the mitochondrial unfolded protein response (UPRmt), and improves the organism's internal dynamic balance (30). Previous studies have shown that UPRmt levels decrease during the intermediate stages of AD, and the activation of UPRmt can delay the deposition of amyloid-β (Aβ) protein in AD mice (31). Nouri et al. (2020) observed that three months of aerobic exercise could regulate UPRmt and reduce Aβ deposition (33). Upregulation of UPRmt following aerobic exercise in AD patients was also demonstrated by Kang et al. (2018) (34). Another study confirmed the increase in UPRmt and the regulation of mitochondrial proteostasis after exercise in the brains of AD mice (11). The increased expression of HSPs in AD could be part of a mechanism aimed at restoring mitochondrial homeostasis. Physical activity alters mitochondrial proteostasis, increases UPRmt markers in the mouse hypothalamus, and stimulates oxidative phosphorylation (OXPHOS) production in neuronal mitochondrial DNA (35).

In vivo studies have shown that HSP60 plays a role in mitochondrial biogenesis through the PGC-1α pathway (36). Slavin et al. (2022) stated that PGC-1α is a key regulator of UPRmt gene expression (37). Thus, UPRmt appears to mediate the effects of exercise on mitochondria via PGC-1α. RSV seems to follow a similar pathway as exercise in improving AD. RSV increases AMPK protein levels and enhances the SIRT1 pathway activity. Furthermore, by activating PGC-1α and CREB in AD mice, RSV strengthens cognitive function and provides neuroprotection against damage caused by Aβ and tau proteins (18).

Improvement of proteostasis by resveratrol (RSV) has also been observed in healthy mice. RSV has been shown to enhance ubiquitin-proteasome system (UPS) levels, indicating improved UPS function (18). The UPS is the primary proteolytic mechanism responsible for the clearance of amyloid-β (Aβ) and tau proteins (38). In another study, RSV was found to regulate HSP70 and ubiquitin proteins, subsequently affecting SIRT1 (41). Lee et al. (2019) demonstrated that RSV protects against endoplasmic reticulum (ER) stress-related degradation pathways by inducing the expression of HSP proteins (40). Additionally, RSV has been reported to reduce the expression of UPR-related proteins and inflammatory mediators in the hippocampus, as well as alleviate learning and memory impairments in aged mice (42).

Arslan et al. (2012) observed that increased expression of HSP70 protects neurons from misfolded proteins (43). One of the key targets of RSV is the antioxidant Nrf2, which plays a critical role in regulating the proteostasis of the endoplasmic reticulum, proteasome, and autophagy (44). RSV also impacts the UBL-5 and XBP-1 pathways. It has been shown that

RSV regulates UPR in mitochondria by modulating UBL-5 and XBP-1 pathways, helping prevent Aβ toxicity in AD (45).

The results of the present study demonstrated that the effects of combining exercise and resveratrol (RSV) on the mitochondrial unfolded protein response (UPRmt) were greater than the effects of each intervention alone. Previous studies have shown the combined impact of exercise and RSV on improving hippocampal function (46). Liao et al. (2017) reported that both exercise and RSV, as well as their combination, increased SIRT1 expression and decreased P53 expression in aged mice (47). However, the simultaneous effect of exercise and RSV on UPRmt has not been extensively studied.

In a study by Broderick et al. (2020), it was shown that RSV combined with exercise reduced the toxicity of Aβ oligomers, suppressed neuronal autophagy, and decreased apoptosis in the brains of AD mice (48). In Broderick's research, RSV was found to reduce neuroinflammation, as well as the accumulation of Aβ oligomers, markers of apoptosis, autophagy, and UPS degradation in the brain. Furthermore, exercise training improved several neuroprotection-related markers, but the benefits were even greater when combined with RSV.

It appears that exercise and RSV share similar cellular pathways, such as the SIRT1 and PGC-1α pathways, which play crucial roles in improving AD. This synergy may explain why the combination of exercise and RSV supplementation produced enhanced effects. One limitation of the present study is the lack of measurement of SIRT1 and PGC-1α, which would provide a deeper understanding of how exercise and RSV together influence the improvement of UPRmt. Additionally, the induction of AD in this study may not have fully captured all the signs and symptoms of AD, which typically develop over a longer period.

Conclusion

The results of the present study indicate that the induction of Alzheimer's disease (AD) led to a decrease in the expression of HSP10, HSP60, and HSP70. Both aerobic exercise and resveratrol (RSV) improved the expression of UPRmt indices in the hippocampus of AD rats, with the combination of exercise and RSV supplementation having a greater effect. These findings suggest that aerobic exercise combined with RSV can regulate UPRmt levels to maintain mitochondrial proteostasis, potentially ameliorating or delaying the progression of AD. Our results highlight the importance of non-pharmacological approaches, such as physical activity and the use of natural substances, as strategies to promote brain health and delay age-related diseases.

Declarations

Ethical Considerations
Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch, with the code IR.IAU.MAMOL.REC.1403.174.

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Authors' contributions

Concept/Design- K. Azizbeigi/ E. Heydarzadeh. Acquisition of Data- Kh. Mohamadzadeh Salamat/ E. Heydarzadeh. Data Analysis/Interpretation- K. Azizbeigi. Drafting of the manuscript- K. Azizbeigi/ E. Heydarzadeh/ Kh. Mohamadzadeh Salamat. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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