

Simultaneous Effect of Interval Training and Octopamine Extract on NLRP-1 and NLRP-3 in Brain Tissue of Alzheimer's Rats

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Abstract

Background and Objective: Alzheimer's disease is a common cause of dementia and reduces progressive perception, memory, and tasks. This study aimed was to investigate the effects of interval training and octopamine extract on NLRP-1 and NLRP-3 in brain tissue of rats with Alzheimer's disease.

Material and Methods: The research method was experimental with a post-test design. A total of 42 male Wistar rats, all of which were eight weeks old, were obtained. Rats were randomly divided into 5 groups (healthy control, Alzheimer's sham, Alzheimer's+ interval training, Alzheimer's+ octopamine supplementation, Alzheimer's+ interval training+ octopamine supplementation). Alzheimer's induction was performed with beta-amyloid peptide 1-14. The training protocol was intense periodic. Octopamine was supplemented by intra-peritoneal injection. Morris's blue maze test was used for the spatial memory test. Seventy-two hours after the last training session, anesthetized rats and hippocampus were quickly extracted. A one-way ANOVA test was used to estimate intergroup differences after Alzheimer's induction.

Results: The results of one-way ANOVA showed a significant difference between the groups in NLRP-1 and NLRP-3 mRNA. Bonferroni test confirmed significant between the control group and Alzheimer's groups ($P \leq 0.05$).

Conclusion: The changes were considered to be synergistic of the beneficial effects of physical activity and octopamine in preventing or reducing the harmful effects of pathological conditions. Exercise and supplementation seem to be effective in the relationship between inflammatory and neurotrophic factors in neurological disorders.

Keywords: Exercise [[MeSH](#)], Inflammasomes [[MeSH](#)], Octopamine [[MeSH](#)], Alzheimer Disease [[MeSH](#)]

Highlights

Synergistic effects of exercise and supplementation reduce the levels of inflammasomes complex index indices and can have a regulatory effect on improving cognitive and cognitive function and delaying dementia-related disorders.

Introduction

Alzheimer's disease is the most common cause of dementia in the elderly and is characterized by atrophy of certain areas of the brain, reduced progressive perception, and loss of memory, and inability to perform daily tasks. The innate immune response plays an important role in post-Alzheimer's pathology. Inflammation systems are a key component of the innate immune response. Inflammasomes are a set of several proteins based on: NLRP-3 and NLRP-1 (NOD-, LRR- and pyrin domain-containing protein 3), responsible for activating caspase-1, injury, and autoimmune diseases (1). Studies show that NLRP-3 and NLRP-1 may play important roles in metabolic disorders, inflammatory responses, Alzheimer's, and ischemia (2). Physical activity can affect dementia and the perception and development of Alzheimer's disease (3) and mediate its anti-inflammatory effects by regulating the activity of inflammation. Mardar et al. (2016) showed that endurance training protocols increased glucose tolerance. Biomarkers of inflammation were also reduced by decreasing the expression of NLRP-3 and IL-18 (4). In this regard, moderate physical activity reduced the activity of NLRP-3, NLRP-1, and IL-1 β and IL-18 levels in the hippocampus of mice and improved depressive behavior (5). Oxidative stress and neurodegenerative diseases have been reported to increase NLRP-1 activity, leading to neuroinflammation and axonal degeneration (6). Liang et al. (2010) examined the levels of physical activity in older adults that were perceptually normal. It has also been noted that they had less exercise history due to high accumulations of A β , Tau protein, and phosphorylated tau, and active subjects had lower A β accumulations and higher A β 42 cerebrospinal fluid levels. Higher levels of cerebrospinal fluid

A β 42 indicate greater clearance from the brain (7).

Song et al. (2016) reported that exercise improves recovery from neurological disorders by modulating inflammatory biomarkers and inhibiting the NLRP complex (8). Wang et al. (2016) also showed that aerobic exercise reduced NLRP-3 in the rat hippocampus (5). It seems that the most important effect of physical activity is to reduce sediment and increase brain A β clearance. Brain mass protection may have functional benefits for AD patients who participate in regular exercise. Meng et al. (2020) showed that exercise has fewer side effects than drugs (9). Lin et al. (2015) reported that 10 weeks of treadmill training in transgenic mice increased memory and dendritic networks associated with hippocampal CA1 and CA3 neurons and decreased soluble A β levels in the hippocampus and amygdala. Exercise did not alter APP or RAGE levels but did increase LRP-1 levels in both areas of the brain (10). Wolf et al. (2006) showed that in transgenic mice under environmental enrichment, plaque A β , Morris water maze function improved, hippocampal neutrophils were upregulated, and hippocampal neurogenesis increased. However, transgenic mice did not show any change in the constant load of plaque A β , spatial learning, and hippocampal neurogenesis with running training, and in them, hippocampal growth factors and cerebral cortex were negatively regulated (11). Overall, the current study demonstrated that probiotic consumption for 12 weeks positively affects cognitive function and some metabolic statuses in AD patients (12). They found probiotics and selenium co-supplementation for 12 weeks to patients with AD improved cognitive function and some metabolic profiles (13).

Beneficial effects included decreased disease severity, improved mental health, metabolic parameters, mainly insulin sensitivity, dyslipidemia, inflammation, anti-oxidative capacity, and lower use of healthcare. Co-supplementation of vitamin D and probiotics generated greater health benefits than its comparators did. More studies in other diseases and various populations are needed to confirm

these findings and to elucidate the optimal form, composition, and frequency of this co-supplementation (14).

Although several drugs have been proposed to treat AD, they have failed due to limited efficacy, side effects, and no significant change in AD course. Some studies have shown that octopamine, as a biogenetic amine, plays an important role in memory formation (15). The effects of octopamine include antioxidant, anti-inflammatory, and anti-cancer effects. Its possible effects appear to be partly due to the release of glutamate by monoamine neurons (16). Examination of the inflammasome system, especially NLRP3 and NLRP1, provides new information for therapeutic interventions aimed at controlling inflammation in this area. Therefore, this study aimed was to investigate the effects of interval training with octopamine extract on NLRP1 and NLRP3 in the brain tissue of Alzheimer's rats.

Materials and Methods

• Animals

The research was conducted experimentally with a post-test design. The statistical population of this study was male Wistar rats (220-250 g). Thirty male Wistar rats at the age of eight weeks were obtained from the Pasteur Institute. All stages of the research were carried out under the rules of ethics in research, under the supervision and obtaining a code of ethics from the Medical School of the Islamic Azad University (IR.IAU.VARAMIN.REC.1399.042 ,1399/12/20). Rats were kept in the animal laboratory (12 hours of light and 12 hours of darkness), the temperature of 22 ± 2 °C and humidity of about 45% and they had free access to standard water and food. Three to five rats were kept in Plexiglas cages with mesh doors measuring 25 by 27 by 43 cm so that they had free access to standard water and food (17, 18).

• Grouping

After three days of familiarity with the environment, the rats were introduced to the

treadmill and how to run on it for 10 minutes, five times a week. After 48 hours of rest from the last familiarization session, the rats were tested for measurement of maximal exhaustion test and the maximum oxygen consumption was predicted (19). Rats were randomly divided into 5 groups (healthy control, Alzheimer sham, Alzheimer+ interval training, Alzheimer+ octopamine, interval training+ Alzheimer+ octopamine).

• Alzheimer induction

To prepare beta-amyloid peptide 1-42, we first dissolved beta-amyloid in DMSO buffer solution until its pH reached 7.4, and then the resulting solution was incubated at 37°C for three days to make the beta-amyloid dense. It was then stored at -70°C (20). After overnight rest, the animals were anesthetized by intraperitoneal injection of ketamine and xylazine. The heads of the animals were then fixed in the stereotaxic device and by creating a longitudinal incision in the posterior part of the skull, special injection cannulas were inserted into the lateral ventricles in the posterior position of 0.8 mm, 1.5 mm on both sides of the longitudinal incision and 2.5 mm below the surface of the skull. Beta-amyloid (one microliter on each side) was injected into the hippocampus with a Hamilton syringe. To ensure the correct injection site in the brain, the dye was injected into two heads of rats and the injection site was examined after euthanized. In the sham group, all laboratory steps were the same as in the beta-amyloid injection group, except that in the sham group, one microliter of DMSO buffer was injected into each of the hippocampi.

After the end of the study period, the rats were euthanized and the injection site was examined (21).

• Exercise protocol

The main exercise consisted of a combination of intense interval repetitions and active rest. Intense interval includes running, 80-110% maximum intensity in the first week-ten week (Table 1). Active rest includes two minutes of running, 40% maximum intensity from the first week to the end of the third week, and 30% maximum speed. The

number of high-intensity interval repetitions is determined according to the training week of the mice. So that in the first week 2 repetitions, in the second week 4 repetitions and from the beginning of the third week onwards it included 6 repetitions (22). Rats were monitored in all training sessions and encouraged to continue running by manipulating with a sponge (23).

Table 1. Exercise training protocol

| weeks | Time (min) | speed % |
|-----------------------|------------|---------|
| First week | 2 | 80 |
| Second week | 2 | 90 |
| Third week | 2 | 100 |
| Fourth week- ten week | 2 | 110 |

• Supplementation

Consumption of octopamine was injected as a supplement for 6 weeks, 5 days a week. Octopamine was a product of Sigma Aldrich Company, which was prepared in solution with 9% normal saline in a homogenase device. According to the instructions for use, rats were injected 81 micromoles per kilogram of body weight per 100 grams (24). The Morris water maze test was used to examine learning, which

has adaptation stages and learning stages. And with the probe test, the spatial memory of the animals was evaluated. The explicit platform test was also used to evaluate the sensory-motor coordination and motivation of the animal (25).

• Laboratory Measurements of NLRP-1 and NLRP-3 expression

Three days after the last training session, rats were rapidly extracted by intraperitoneal injection of ketamine (90mg/kg) and xylazine (10 mg/kg). The hippocampus was frozen and refrigerated. Hippocampus was powdered by the mortar method and homogenized to extract total RNA. In order to remove the protein components of the product, the pellet containing RNA was washed. For each reaction, the kit instructions were used to prepare and add ingredients. In the beginning, the optimal cDNA concentration, as well as the primers related to each gene, was determined separately for each using a serial concentration test so that the lowest dimer and the best Ct were observed. Real time-PCR was performed (26) (Table 2).

Table 2. Sequence of primers

| Gene | Forward primer 5'-3' | Reverse primer 5'-3' |
|--------|----------------------------|-----------------------|
| NLRP-1 | AAGCTGAAAGTCAACAAATGACAGTT | TGGACTGTCTGCCCATTTGG |
| NLRP-3 | ACTTGCATTGCTGATTGCTG | TTGAATAGGCCAGGGTTTTTG |
| 18S | GCAATTATCCCCATGAACG | GGCCTCACTAAACCATCCAA |

• Statistical analysis

Data analysis was collected and analyzed using SPSS and Excel software. Mean, Standard Deviation, graph drawing was used. Normality of data was assessed using the Shapiro-Wilks and using the Leven test, the homogeneity of variance was determined ($P \leq 0.05$). The one-way ANOVA and Bonferroni post hoc test were used to estimate inter-group differences after Alzheimer's induction ($P \leq 0.05$).

Result

• Response NLRP-1 to interval training and octopamine

Descriptive information was reviewed and recorded. Using the Leven test, the homogeneity of variances was investigated and confirmed. The results of the Shapiro-Wilks test also showed the normal distribution of data. The highest decrease in NLRP-1 mRNA was observed in the interval training + octopamine+ Alzheimer group. The largest increase is in the Alzheimer's group, followed by Alzheimer's and supplements. There was a significant difference in NLRP-1 mRNA

levels between the groups. Bonferroni post hoc test was used to examine the details in more detail and to compare the groups with each other. The results of the Bonferroni post hoc test showed that there was no significant difference only between the control group and the Alzheimer's group + interval training + octopamine supplementation. But there is a significant difference between the control group and other groups ($P \leq 0.05$). There was a significant difference between Alzheimer's group and all groups except Alzheimer's + octopamine supplement ($P \leq 0.05$) (Figure 1).

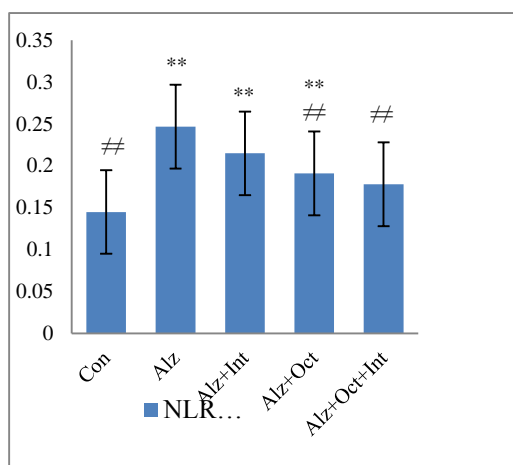


Figure 1. Comparison of gene expression and significant changes NLRP-1 between five Groups of male rats

** $: P \leq 0.05$, significant difference between control group and another group

$: P \leq 0.05$, significant difference between Alzheimer group and another group

• Response NLRP-3 to interval training and octopamine

The greatest decrease in NLRP-3 mRNA was observed in the interval training group. The largest increase is in the Alzheimer's group. There was a significant difference in NLRP-3 mRNA levels between the groups. Bonferroni post hoc test was used to examine the details in more detail and to compare the groups with each other. The results showed there was no significant difference only between the control group and the Alzheimer's group+ interval training+ octopamine. But there is a significant difference between the control group and other groups

($P \leq 0.05$). There was a significant difference between Alzheimer's group and all groups except Alzheimer's + octopamine supplement ($P \leq 0.05$) (Figure 2).

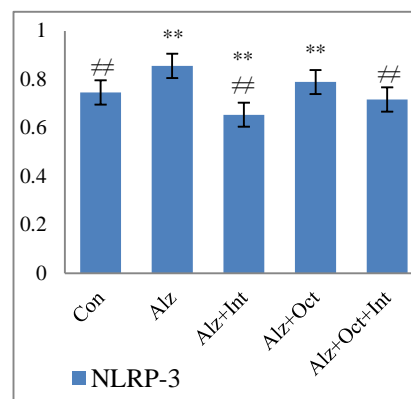


Figure 2. Comparison of gene expression and significant changes NLRP-3 between five Groups of male rats

** $: P \leq 0.05$, significant difference between control group and another group

$: P \leq 0.05$, significant difference between Alzheimer group and another group

Discussion

The results of the present study showed that there was a significant difference between the groups in the amount of NLRP-1 mRNA and NLRP-3 mRNA. Alzheimer's disease is associated with decreased cognitive function and the hippocampus appears to be more susceptible to aging and neurodegenerative diseases of the joints and synaptic plasticity (27). It has been suggested that interval training may be effective against inflammation and the factors involved in neurodegeneration. The effect of physical activity on improving brain function has been confirmed by ductile adaptations at the synaptic and mitochondrial levels (28). Thus, the interval training protocol has been implicated as a mediator in controlling cytokines, regulating receptor activity, and supporting the immune system. As a result, it has improved the cognitive status of Alzheimer's rats and the anti-inflammatory effects of exercise have been effective in regulating the activity of inflammation. Stranahan et al (2010) achieved these results using rodents and long periods of forced exercise on an ergometer (28). In line with

the results of this study, Cotman et al (2002) showed that long-term moderate-intensity exercise programs are suitable for improving cognitive function (29). Also, Parachikova et al (2008) showed, after three weeks of running an optional ergometer in Tg2576 transgenic Alzheimer's mice, cognitive function improved unchanged at insoluble levels of A β 1-40 and A β 1-42. This condition may be caused by changes in the inflammatory response (30).

Of course, these studies had different training protocols. Mardar et al. (2016) showed that endurance training increased glucose tolerance and decreased biomarkers of inflammation and body weight. This decrease is due to the increased expression of NLRP-3 and IL-18 in adipose tissue (4). Wang (2016) et al showed that moderate-intensity physical activity protocol reduces the activity of NLRP-3 in the hippocampus of mice (5). Decreased NLRP-3 in the hippocampus of obese mice with endurance training and increased BDNF expression has also been reported (31). The results of Darvishzadeh et al. (2021) also showed a decrease in NLRP-3. Their samples were poisoned mice (32).

The contradiction between the results of this study and other studies is due to the intensity, duration of training. Increasing the training period, the number of training sessions, and the mechanism involved in the beneficial effects of periodic training affect the structure and function of the brain. Reduction of oxidative stress, NLRP-1, NLRP-3, and secretion of neurotrophins also affect the structure of the hippocampus (5, 6, 19, 33).

Regarding the role of octopamine, it can be said that this supplement led to a decrease in NLRP-1 and NLRP-3 in the exercise and supplement groups. Octopamine has antioxidant, metabolic, and fat-burning effects. It also has anti-cancer effects and an adrenergic role. Therefore, it has been able to control the effects of Alzheimer's and cognitive limitations to some extent. The role of NLRP-1 in the production of inflammatory factors, axonal degradation, and increasing the positive immune response of neurons to NLRP-1

in Alzheimer's brain is 25-35 times compared to non-Alzheimer's brain (6).

Octopamine is an adrenoceptor due to its close association with norepinephrine, its effect on adrenergic and dopaminergic systems, and its mimicry of sympathetic function. Therefore, in the present study, the use of octopamine in combination with periodic exercise has led to a further reduction of inflammatory factors (NLRP-1 and NLRP-3) compared to exercise groups and increased antioxidant activity in Alzheimer's mice (16).

Kazemi et al. (2015) reported that octopamine use combined with aerobic exercise reduced the complexity of inflammation and apoptosis and improved the regenerative capacity of heart cells in obese mice (25), the results of which are similar to the present study. In this regard, long-term forced exercise increases memory and learning, and at the same time, affects the number of nerve cells and inflammatory factors such as NLRP-1 and NLRP-3.

Of course, better cognitive performance is due to increased exercise. Exercise also facilitates the repair of brain damage, facilitates nutritional factors in differentiating progenitor cell survival, changes in the synaptic system, long-term strengthening, and better memory function. Therefore, exercise activity of synaptic organization has increased learning and neurogenesis, and octopamine supplementation has synergized cognitive improvement in Alzheimer's mice.

Conclusion

Alzheimer's drug therapies have limited efficacy and side effects and have failed to treat and prevent AD. Octopamine as a biogenetic combination of amines, adrenergic, and antioxidants is effective in the formation of memory and with interval training led to a significant reduction of the inflammatory system (NLRP3 and NLRP1) compared to Alzheimer's and non-exercise groups. Therefore, a healthy lifestyle combined with exercise and complementary foods can help fight Alzheimer's.

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