

## ⇒ Research Article



# Simultaneous Effect of Resistance Training and Folate Nano-liposome on Dopamine Receptors in the Brain Hippocampus of Alzheimer's Rats

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**Background:** Alzheimer's is progressive dementia with loss of nerve cells. Physical activity and the use of nano-pharmaceutical supplements may prevent the progression of Alzheimer's. The aim of this study was to investigate the effects of resistance training and Folate nano-liposome on the expression of D1 and D2 receptors in the hippocampal tissue of Alzheimer's rats.

**Methods:** Thirty-three male Wistar rats at the age of eight weeks were prepared from Pasteur Institute and randomly divided into 5 groups (healthy control, Alzheimer's control, Alzheimer+resistance training, Alzheimer+Folate nano-liposomes, and Alzheimer+resistance training+Folate nano-liposomes). Alzheimer's was induced, and Folate nano-liposomes were injected as a supplement. The animals were anesthetized, and the hippocampus was analyzed after the last training session. Eventually, a one-way ANOVA test was used to estimate the differences between groups ( $P \leq 0.05$ ).

**Results:** The results of one-way ANOVA showed a significant difference between the groups in terms of D1 mRNA and D2 mRNA ( $P \leq 0.000$ ). Based on the results of the Bonferroni post hoc test, there was a significant difference between the control group and the Alzheimer's, Alzheimer's+resistance training, and Alzheimer's+Folate nano-liposomes. Similarly, a significant difference was found between the Alzheimer's group and Alzheimer's+resistance training and Alzheimer's+resistance training+Folate nano-liposomes ( $P \leq 0.05$ ).

**Conclusion:** Resistance training and Folate nano-liposomes changed the content of D1 and D2 in the brain after Alzheimer's induction. These changes may be partly due to the synergistic effect of physical activity and nano-pharmaceuticals on preventing or reducing the detrimental effects of pathological conditions. Inflammatory factors appear to be associated with neurotrophic factors during activity and exercise in neurodegenerative diseases.

**Keywords:** Exercise training, Dopamine receptors, Supplement, Immune system

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**Background**

Alzheimer's disease (AD) is classically defined as a dual pathological clinical process and a progressive disorder that causes the death of the brain cells (1), thus it is the most common cause of dementia and persistent decline in thinking, as well as behavioral and social skills that destroy a person's ability to stand on their own (2). Mild cognitive impairment (MCI) is recently known as the pre-production stage of AD and a transition period from normal aging. Therefore, it is often used as a primary clinical tool to assess AD, especially amnesia-associated MCI (3). Alzheimer's is progressive dementia with loss of nerve cells and has two main microscopic neuropathological symptoms, including extracellular amyloid plaques and intracellular fiber nerve nodes (4). Plaques are formed in the hippocampus, which is a structure deep in the brain that helps encode memories

and is involved in thinking and decision-making in the other areas of the cerebral cortex (5).

Regular exercise is one of the lifestyle factors that not only fights obesity and related metabolic diseases but also reduces the risk of AD. Epidemiological studies have demonstrated a positive relationship between inactivity and AD mortality (3). Exercise is also effective in preventing neuritis. Researchers believe that treadmills in neurons with the AD phenotype of inflammatory neurotransmitters reduce the death of neurons and inflammatory cytokines. Exercise and physical activities have been introduced for biological health (5, 6). Exercise increases blood flow throughout the body and increases blood flow to the brain (6).

In addition, exercise causes more synapses in neurons and changes in blood flow and capillary density, which have positive effects on Alzheimer's (7).

Likewise, exercise increases dopamine, along with the stimulation and sensitivity of the brain to dopaminergic receptors. Further, it is a strong stimulant for the H-P-A system (8), and the sensitivity of neurotransmitter receptors in the synaptic space and dopamine carriers by increasing brain-derived neurotrophic factor (BDNF) levels. Modulation of tyrosine hydroxylase receptor activity also induces dopamine receptor expression (7).

As ferritin decreases, fat peroxidation occurs in the hippocampus, which may be accompanied by a weakened immune system and reduced cognitive perception. However, neurological disorders may be associated with the abnormal accumulation of ferritin in the striatum, Parkinson's disease, Huntington's disease, depression, hyperlipidemia, Alzheimer's, and peroxidation in the hippocampus (9).

Some treatments have failed due to limited efficacy, side effects, and generally no significant change in the AD course (10). Nano-liposomes may have beneficial effects. They are self-forming nanostructures that result from the juxtaposition of lipid molecules in the aqueous solution. Phospholipid lipid-friendly molecules are grouped so that their hydrophobic and hydrophilic groups are directed inward and outward, respectively. In this way, a bilayer spherical membrane is formed, and loading hydrophilic drugs in the nucleus and hydrophobic drugs in the shell of liposomes is possible (11). Dietary folate deficiency is common in the elderly (12). Plant and fish diets are the most protective diet against AD and are therefore rich in the B vitamin group (B12 and B6) and folate (13). The deficiency of these vitamins leads to increased levels of homocysteine and an increased risk of cardiovascular disease, cognitive impairment, and Alzheimer's (14). Folate deficiency can increase or decrease gene expression with changes in DNA methylation. It also alters protein synthesis and affects metabolic pathways, signal transduction, and cellular processes. These changes will play a role in the etiology and pathology of the disease if they occur in the genes involved in AD (15).

Dopamine is an organic compound in the family of catechol-amines and phenyl-amines that plays a vital role in the body and brain. It is stored as a precursor in the brain, secretions, the vesicles of dopaminergic neurons, and adrenal glands. Furthermore, it acts as a neurotransmitter and a hormonal factor in the brain (16). An increase in this substance in certain areas of the brain, known as the reward center, causes a feeling of euphoria, which is why dopaminergic drugs are widely misused. It is also involved in controlling the loco-motor system and reducing the symptoms of Parkinson's and schizophrenia by destroying dopaminergic neurons or dopamine dysfunction (17).

### Objectives

Considering that nano-liposomes and exercise activities

contribute to the treatment of diseases and may be effective in the treatment of neurological diseases, The current study aimed to evaluate the effects of periodic exercise and Folate nano-liposomes on dopamine receptors in the brain tissue of rats with AD.

### Methods

#### Subjects

The research was experimentally conducted with a post-test design. The statistical population of this study included 30 male Wistar rats with an average age of eight weeks and a mean weight of  $250 \pm 20$  g which were obtained from the Pasteur Institute of Iran. All the living, feeding, and sleeping facilities of the rats were provided, and the experimental steps were performed, without the use of a shocker, in a standard laboratory by a technician and an animal specialist. The rats were kept in the animal laboratory of the Physiology and Pharmacology under controlled light conditions (12 hours of light and 12 hours of darkness), a temperature of  $22^{\circ}\text{C}$ , and humidity of about 45%. Three-five rats were kept in Plexiglas cages with netting and dimensions of  $25 \times 27 \times 43$  cm in storage so that they had free access to standard water and food.

#### 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 animals were tested for the measurement of the maximal exhaustion test, and the maximum oxygen consumption was predicted using the maximum velocity during exhaustion (18). The rats were randomly divided into 5 groups (healthy control, Alzheimer control, Alzheimer + resistance training, Alzheimer + Folate nano-liposomes, and resistance training + Alzheimer Folate nano-liposomes) each containing 6 rats.

#### Alzheimer Induction

To prepare the peptide, first, beta-amyloid was dissolved in the buffer solution until its pH reached 7.4, then the resulting solution was incubated at  $37^{\circ}\text{C}$  for three days to form a dense beta-amyloid and then at  $-70^{\circ}\text{C}$ . Next, animal physicians and technicians anesthetized the rats by the intra-peritoneal injection of ketamine and xylazine. The animals' heads were then fixed in a stereotaxic device, and by creating a longitudinal incision in the posterior part of the skull, the injection cannulas were inserted into the lateral ventricles in the posterior position of the Bergman 0.8, 1.5 mm on either side of the longitudinal incision and 2.5 mm lower. The surface of the skull was placed, and the injection into the beta-amyloid hippocampus (one microliter on each side) was performed with a Hamilton syringe. To ensure the correct injection site in the brain, the dye was injected into two heads of rats. After the

end of the study period, the rats were slaughtered, and the injection site underwent examination. 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 the DMSO buffer was injected into each of the hippocampi (19).

### Exercise Protocol

The exercise protocol was resistance training and consisted of a warm-up, resistance training, and cooling parts. Rats performed the warm-up phase with an intensity of 40-50% maximum for 5 minutes on the turntable, resistance training, and then the cooling phase with an intensity of 40-50% of the maximum rate (20). They performed the exercise protocol 5 sessions per week for six weeks. In this protocol, the weight was attached to the rats' tails, which had to be lifted up a 26-step ladder. Each time they climbed, the animals lifted the bar 13 times with their left hand and foot and 13 times with their right hand and foot (Figure 1). The training groups were accurately weighed each week, and the training weight of each rat was selected based on its weight. Weight training started with 30% of their body weight and gradually increased to 140% of their body weight over 6 weeks. The weight increased from the first to the last week (21).

### Supplementation

Folate nano-liposomes were injected intra-peritoneal as



Figure 1. Demonstration of Resistance Training Protocol.

a supplement for 6 weeks and 5 days a week using a dose of 80  $\mu\text{mol/kg}$ . Maurice Blue Maze memory and spatial learning tests, as well as Probe and visible platform tests, were used to determine the status of Alzheimer's.

### Laboratory Measurements of D1 and D2 Expression

Laboratory tests were performed using the real-time polymerase chain reaction (RT-PCR). Three days after the last training session, rats were rapidly extracted by intra-peritoneal injection of ketamine (90 mg/kg) and xylazine (10 mg/kg). The hippocampus was frozen and refrigerated at  $-80^{\circ}\text{C}$  for analysis. Approximately 100 mg of hippocampus was powdered by the mortar method and homogenized to extract total RNA in 1 mL of the Isol RNA-Lysis reagent. To remove the protein components of the product at  $12^{\circ}\text{C}$ , 12000 g were centrifuged for 10 minutes. The supernatant was removed and kept at room temperature ( $15-25^{\circ}\text{C}$ ) for 5 minutes. The chloroform was then mixed with the initial Isol in a ratio of 1:5 and vigorously shaken for 15 seconds. The product was kept at room temperature for 2-3 minutes. The microtubes were then separated at  $4^{\circ}\text{C}$  for 15 minutes and centrifuged, and the mineral and aqueous portions were separated. The RNA portion was removed and mixed with isopropanol in a ratio of 1:0.5 and left for 10 minutes at room temperature and then centrifuged for 10 minutes at  $4^{\circ}\text{C}$ . The pellet containing RNA was washed in ethanol and dissolved in RNase-free. The RNA concentration was measured using a nano-prop device, and a ratio of 260:280 between 1.2 and 1.8 was defined as the optimal purification. C-DNA was synthesized by PrimeScript<sup>TM</sup> RT reagent Kit (catalog number #RR037A) according to the kit instructions. For each reaction, the instructions were used to prepare and add ingredients. The mixture was incubated at  $37^{\circ}\text{C}$  for 15 minutes, and then the tubes were heated at  $85^{\circ}\text{C}$  for 5 seconds to stop the reaction. In the beginning, the optimal cDNA concentration, as well as the primers related to each gene was separately determined for each using a serial concentration test so that the lowest dimer and the best Ct were observed (22). The RT-PCR was performed using RealQ Plus 2x Master Mix Green from AMPLIQON Company (Table 1).

### Data Analysis

Data were collected and analyzed by SPSS and Excel software using the mean and standard deviation (SD) and graph drawing. One-way ANOVA was applied to estimate inter-group differences after Alzheimer's induction. The results were analyzed by the Bonferroni post hoc test, and  $P \leq 0.05$  was considered statistically significant.

### Results

#### Effects of Folate Nano-liposomes and Resistance Training on D1 Expression

Descriptive information was reviewed and recorded,

**Table 1.** Sequence of Primers

Gene	Forward Primer 5'-3'	Reverse Primer 5'-3'
D1	AAGCTGAAAGTCAACAAATGACAGTT	TGGACTGTCTGCCCATTTGG
D2	ACTTGCAATTGCTGATTGCTG	TTGAATAGGCCAGGGTTTTG
18S	GCAATTATTCCCATGAACG	GGCCTACTAAACCATCCAA

and the homogeneity of variances was investigated and confirmed using the Leven test. The results of the Shapiro–Wilk test also showed the normal distribution of data. The comparison of D1 expression demonstrated a significant difference between the control and Alzheimer’s groups ( $P < 0.001$ ,  $P \leq 0.05$  was considered significant). Based on the results of Bonferroni post hoc test, a significant difference was observed between the control group and the Alzheimer’s and Alzheimer’s+Folate nano-liposomes groups ( $P < 0.001$ ,  $P \leq 0.05$  was considered significant). There was a significant difference between the Alzheimer’s group and Alzheimer’s+resistance training, and Alzheimer’s+resistance training+Folate nano-liposomes supplement groups ( $P < 0.001$ ,  $P \leq 0.05$  was considered significant, Figure 2).

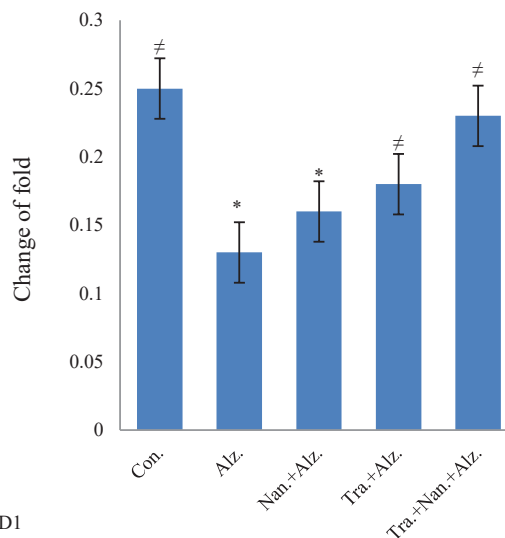
**Effects of Folate Nano-liposomes and Resistance Training on D2 Expression**

The comparison of D2 expression represented a significant difference between the control groups and the Alzheimer group ( $P < 0.001$ ,  $P \leq 0.05$  was considered significant). The results of Bonferroni post hoc test revealed a significant difference between the control group and Alzheimer’s, and Alzheimer’s+Folate nano-liposomes groups. Moreover, a significant difference was found between Alzheimer’s group and Alzheimer’s+resistance training, and Alzheimer’s+resistance training+Folate nano-liposomes groups (Figure 3).

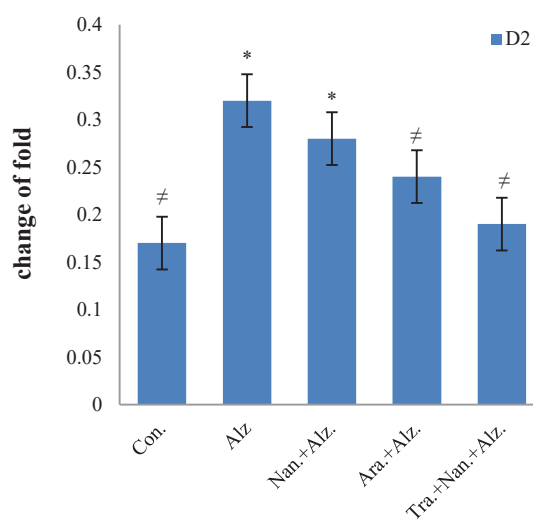
**Discussion**

**Response D1 and D2 Receptors to Folate Nano-liposomes and Resistance Training**

The findings of the present study demonstrated that resistance training and Folate nano-liposomes have synergistically increased the expression of dopamine D1 and decreased D2 receptor genes. The effects of exercise and nano-liposomes appear to reduce the harmful effects of Alzheimer’s on cognitive phenomena in rats (23). In this research, resistance training could increase blood flow in the brain, slow down the process of brain cell loss, improve brain function, and enhance general health. Thus, resistance training improved the nervous system and better coordination of the muscles and nerves (24). Folate nano-liposomes (an antioxidant) counteract beta-amyloid peptide (an oxidative stress agent), reducing neuronal apoptosis and controlling AD; hence, the presence of iron is necessary for the proper growth of neurotransmitters (25). The results of Toval et al are in



**Figure 2.** Comparison of Mean±SD of Gene Expression Values and Significant D1 Changes Between Five Experimental Groups in Male Rats. Note. SD: Standard deviation. \* $P \leq 0.05$  represents a significant difference between control group and another group. ≠ $P \leq 0.05$  denotes a significant difference between Alzheimer’s group and another group.



**Figure 3.** Comparison of Mean±SD of Gene Expression Values and Significant D2 Changes Between Five Experimental Groups in Male Rats. Note. SD: Standard deviation. \* $P \leq 0.05$  shows a significant difference between the control group and another group. ≠ $P \leq 0.05$  implies a significant difference between Alzheimer’s group and another group.

line with the findings of this study and support the effects of physical activity on brain function (26). Additionally, our results are consistent with those of the research by Lou et al (27). Possible mechanisms of the effect of exercise on Alzheimer’s are effects on the metabolism of amyloid beta precursor proteins, learning, and memory (28, 29).

Cholinergic activity is also involved in an exercise in exercise-induced neuronal plasticity, and exercise may improve behavioral disorders by reducing A $\beta$  peptide levels. These reductions are important for neuronal survival, neuronal proliferation, and neural plasticity, as well as reducing A $\beta$  plaque exercise activities and improving memory learning and nerve tissue formation in Alzheimer's mice (30).

However, Matta et al found that exercise increases dopamine D2 receptors. The activation of dopamine D1 or D2 receptors increases the release of acetylcholine in the hippocampus (31). Compounds that enhance the effect of the cholinergic system improve memory, and conversely acetylcholine antagonist damage memory. Thus, the increase in dopamine D2 and D1 receptors may have improved impaired memory by increasing the release of acetylcholine in the hippocampus. Acetylcholine released by the activation of hippocampal dopamine receptors can activate muscarinic and nicotine receptors in the dorsal hippocampus, which activates both receptors (31). In addition, Piri and Zarrindast concluded that the activation of presynaptic nicotinic receptors can even increase the release of glutamate and thus improve memory (32). Further, the activity of dopaminergic receptors D1 and D2 affects the proliferation, migration, and differentiation of neurons. Dopamine receptors also affect brain growth (33).

Another mechanism is that neurons increase dopamine in response to an increase in intracellular calcium, and proteins that are calcium sensors sense the level of calcium in a nerve cell and trigger the release of dopamine. Exercise increases the concentration of calcium in the cell and therefore is effective in the secretion of dopamine (34).

The structure of the Folate nano-liposome destroys and reduces amyloid accumulations through various mechanisms and is also used to transport drug particles through the blood-brain barrier. The human brain naturally contains iron oxide nanoparticles, which are the result of the metabolism and storage of iron in brain cells. Due to the magnetic properties of this substance, it seems to play a role in information storage, and the accumulation of these particles has been observed in AD. Iron oxide magnetic nanoparticles and microtubules in the axons of neurons can interact magnetically, which is essential for the transmission and storage of brain data. However, this interaction is disrupted with the accumulation of these nanoparticles in the brain, and nanoparticles bind to microtubules and tau proteins, leading to the instability of microtubular polymers and disturbance of the correct orientation of microtubules. In this study, it seems that the reduction in the number of receptors due to exercise and nano-liposomes has prevented the continuation and progression of the disease, which is due to the synergistic effects of exercise and supplementation.

Furthermore, iron plays a major role in the transport

of oxygen and physical activity, and its deficiency causes fatigue and irritability. Iron deficiency reduces dopamine levels in the body. Therefore, consumption of Folate nano-liposome and exercise training increase access to oxygen and release more dopamine. As a result, it will have a positive effect on cognitive status and improve Alzheimer's (35).

The results of the present study showed that resistance training can reduce inflammatory factors in Alzheimer's and modulate dopamine receptors. These changes can be due to the beneficial effects of physical activities in preventing or reducing the harmful effects of pathological conditions. Oxidative stress and the production of reactive oxygen species (ROS) and an imbalance in the antioxidant capacity of cells are the possible causes of Alzheimer's. ROS is produced during the respiratory chain, which is why mitochondria are the most important sources of these compounds in the cell (23). Beta-amyloid protein can enter the mitochondria and disrupt the mitochondrial electron transport chain, leading to ROS production, inhibition of adenosine triphosphate production, mitochondrial dysfunction, and neuronal damage. Due to the dependence of oxidative reactions to mitochondria on iron compounds and Folate nano-liposomes may have been effective in providing low levels of B12 and iron Folate .

The strengths of this research are the study of the simultaneous effects of exercise and supplementation, the use of controlled animal subjects, and the study of a supplement of nano-drugs. On the other hand, weaknesses of this research include the use of an aggressive experimental method, high cost of experiments, a small number of samples, and non-use of human subjects.

## Conclusion

The results of the present study revealed that resistance training with Folate nano-liposomes modulated D1 and D2 gene expression in rats. Exercise as a non-invasive method and Folate nano-liposomes can have undeniable effects on the function of many organs of the body. Of course, it should be noted that several cellular messaging pathways can be involved in the persistence of these changes that need further investigation.

## Author Contributions

Laboratory studies and tests, study and review, as well as analysis and interpretation of data: FN and FF.

## Conflict of Interests

The authors declare that there is no conflict of interests.

## Ethical Approval

All stages of the research were implemented in accordance with the rules of ethics in research and the Helsinki Declaration, under the supervision, and a code of ethics (IR. IAU.VARAMIN. REC.1399.041) was obtained from the Medical School of the Islamic Azad University for this purpose.

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