



## THE EFFECTS OF ADMINISTRATION OF VALPROIC ACID ON BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) AND DEPRESSION OF ANIMAL ALZHEIMER'S DISEASE DURING EIGHT WEEK LONG ENDURANCE EXERCISES

Seyd Rasoul HOSSEINI<sup>1,\*</sup>, Mohammad Amin Edalat MANESH<sup>2</sup>

<sup>1</sup>Department of Physical Education, Fars Science and Research Branch, Islamic Azad University, Marvdasht, Iran

<sup>2</sup>Department of Physical Education, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran

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**Abstract.** The objective of the present study is to analyze the effects of administration of valproic acid on Brain Derived Neurotrophic Factor (BDNF) and depression of alzheimer's disease of desert rat during eight week long endurance exercises. In order to administer the study, 140 Sprague Dawley desert rats (70 of which are male and the other half, female) are categorized randomly into seven research groups, which includes 1) control group 2) sham group and testing groups 3) long distance training group 4) valproic acid 100 group 5) valproic acid 200 group 6) training group of valproic acid 100 7) training group of valproic acid 200. During the eight week period, research desert rats of groups 3, 6 and 7 run for 15 minutes and 30 seconds on zero gradient laboratory treadmill, with the speed of 15 to 20 meters per minute in each training lapse. The lapses are frequented five times a week. Furthermore, for a 14 day period, groups 4 and 6 are daily administered with 100 milligrams valproic acid on kilogram and groups 5 and 7 are daily administered with 200 milligrams valproic acid.

**Research Methodology.** For research data analysis, one-way variance test and post hoc Tukey's test are utilized. The findings indicate that the level of BDNF in all the research groups is significantly higher than the sham group ( $p<0.05$ ) and Tumor Necrosis Factor Alpha (TNF) and depression level of all the research groups are significantly lower than the sham group ( $p<0.05$ ).

**Research Findings.** According to the research findings, it is indicated that endurance exercises, valproic acid and their synthetic administration increase the level of BDNF and decrease the levels of TNF and depression in desert rats with alzheimer's disease.

**Keywords:** Endurance Exercise, Valproic Acid, Brain Derived Neurotrophic Factor (BDNF), Alzheimer's Disease

### Introduction

Alzheimer's disease is the most prevalent factor of memory and mind deterioration and is considered to be one of the controversial maladies in people who are older than 65 years. This disease creates numerous difficulties for its inflicted patients and their families (Brun, 2007). Scientific observations of patients with alzheimer's indicate emergence of depression as a circumstantial malady of alzheimer's disease. Depression can function as a risk factor for such patients. Generally, those adults with depressive experiences show specific cognitive complications. On the other hand, circumstantial symptoms of depression can be camouflaged by primary symptoms of alzheimer's clinically. Prevalent degeneration of alzheimer's disease is due to the lack of monoamines in different parts of brain including hippocampus, locus coeruleus, brain stem and raphe (Anisman et al., 2008). It is scientifically observed that autonomous administration of physical exercises and anti-depressant drugs can increase the hippocampal level and subsequently the level of BDNF through formation of neurogenic tissues (Engesser et al., 2009). Physical education acquires high efficiency on cognitive

\* Corresponding author. Seyd Rasoul HOSSEINI

skills. Regular administration of physical exercises improves cognitive function through deteriorating risk factors of cognitive damages (Winter et al., 2006).

Valproic acid (also known as valproic sodium, valproic acid-mono-sodium) is utilized as an anti-paroxysm drug in the clinical treatment of epilepsy. Valproic acid increases neuron density in CA1 part of hippocampus and prevents loss of hippocampal cells (Zang et al., 2012). Scientific observations depict that valproic acid is utilized as an anti-paroxysm and a mental stabilizer prevalently and acquires clinical potentiality of neuron protection against alzheimer's. This clinical potentiality is materialized through signaling neuron generation in cultural and active environments of stem cells (Zang et al., 2012).

Considering various studies registered in scientific data centers, the present study deduces that there has been no comprehensive study regarding endurance exercises and chronic administration of valproic acid in treatment of depressive complications of alzheimer's disease, which is clinically induced by prescription of Trimethyltin chloride. Therefore, the present study intends to analyze the effects of chronic administration of valproic acid on mitigation of depressive behaviors of animal alzheimer's disease. The present study hopes that such an analysis can be regarded as a pioneering step towards treatment of complications of alzheimer's disease. It should be noted that various researches have been administered analyzing each aspect surveyed in the present study comprehensively.

### **Research Historical Background**

Mirzayee et al. (2011) analyze the effects of an eight week long endurance exercises period on BDNF level of blood plasma of Wistar desert rats. The results of their study indicate that administration of 30 minutes and 60 minutes endurance exercises increases BDNF level of blood plasma and there is no significant difference between effectuality of the allocated exercising lapses of their study.

In "Meta-Analytic Study of Effects of Physical Education on BDNF Level of Human Subjects", Cannabin et al. (2008) report the fact that a single exercising lapse can not impact BDNF level significantly. Furthermore, their study indicates that there is significant difference in BDNF level during administration of both strength and aerobic exercises.

In "Endurance Training Enhances BDNF Release from the Human Brain", Seifert et al. (2011) deduce that while there is no variance in BDNF level of the participants of the control group, the testing groups of their research show significant increase of BDNF level after administration of regular endurance exercises.

Huang et al. (2006) believe that obligatory physical education result in positive accommodation of BDNF level of hippocampus. Pahlevanzadeh et al. (2006) analyze depression in athlete and non-athlete university students. The results of their studies depict that 96% of athlete university students acquire normal humor clinically. At the same time, only 66% of non-athlete university students acquire normal humor clinically. Furthermore, it should be noted that in their studies, it is depicted that remaining 4% of athlete university student acquire mild depressive complications.

### **Research Questions**

Does individual and synthetic administration of endurance exercises and valproic acid impact TNF level of hippocampal degeneration?

Does individual and synthetic administration of endurance exercises and valproic acid impact depressive factors of hippocampal degeneration?

# The Effects of Administration of Valproic Acid On Brain Derived Neurotrophic Factor (Bdnf) And Depression of Animal Alzheimer's Disease During Eight Week Long Endurance Exercises

## Research Plan and Methodology

Considering scientific nature of research objectives subject matter, the present study is a basic experimental research. Since the study surveys cause and effect relationships, independent variables should be modified so that their distinctive efficiency on dependant variables can be analyzed. The research plan is administered under post hoc tests and is oriented towards control research groups. The statistical population of the present study includes all Wistar desert rats. From the population, 140 desert rats (70 of which are male and the other half female) are selected randomly as research statistical sample.

## Research Findings

### Clinical Preparation of Valproic Acid

In order to prepare 100 and 200 valproic acid dosage solutions, 1000 and 2000 milligrams valproic acid are dissolved in 10 milliliters normal saline respectively. Through administration of this solution through peritoneum, 1 milliliter of the solution is allocated for each kilogram of body weight of rats (For instance, 250 milliliters of the solution are administered for a rat with the weight of 250 grams). In order to analyze the ameliorating effects, valproic acid is daily administered through peritoneum of rats of testing groups in 14 day long period.

### Descriptive Data Analysis of Research Findings

In order to analyze normal distribution of research findings among testing groups, the results of Kolmogorov-Smirnov test are represented through tables 1-4.

**Table 1-4.** The Results of Kolmogorov-Smirnov in the Analysis of Normal Distribution of Research Findings.

Research Variable	Z	P-Value
Serum Level of BDNF (Male Subjects)	1/253	0/086
Serum Level of BDNF (Female Subjects)	1/645	0/009
Hippocampal Level of BDNF (Male Subjects)	1/423	0/035
Hippocampal Level of BDNF (Female Subjects)	1/597	0/012
TNF Level of BDNF (Male Subjects)	1/433	0/033
TNF Level of BDNF (Female Subjects)	1/729	0/005
Hippocampal Level of TNF (Male Subjects)	2/186	0/000
Hippocampal Level of TNF (Female Subjects)	2/001	0/001
Tail Suspension Test (Male Subjects)	1/244	0/091
Tail Suspension Test (Female Subjects)	1/144	0/146
Elevated-Maze Test (Male Subjects)	1/251	0/087
Elevated-Maze Test (Female Subjects)	1/682	0/007

## Research Inferential Statistics

### BDNF (Male Subjects)

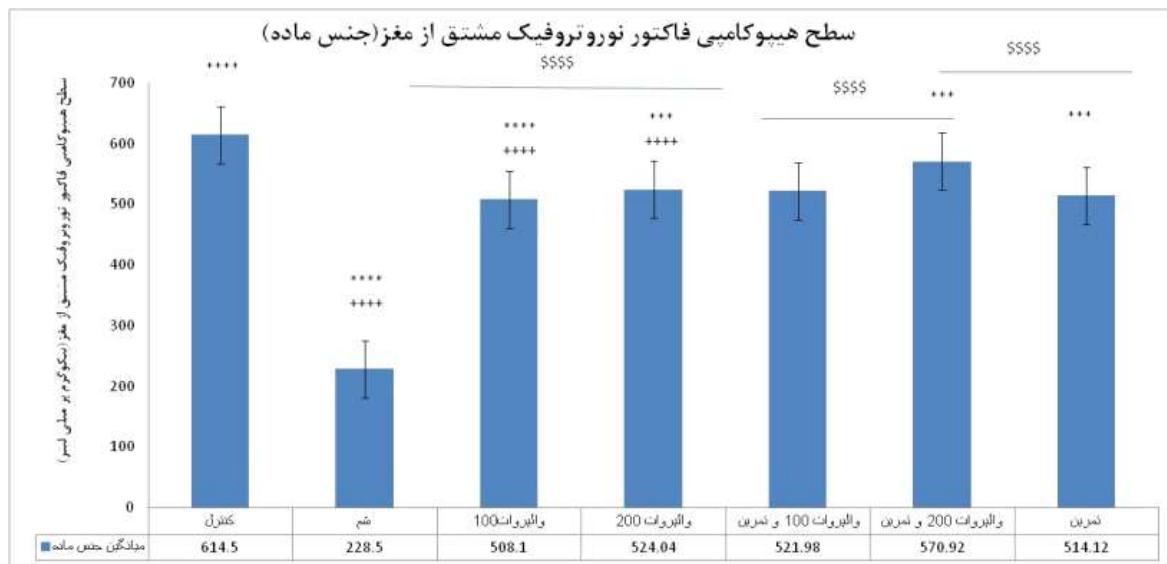
**Table 4-4.** The Results of Analysis of BDNF Level (Male Subjects).

Variance Statistics	Square Root Sum	Degree of Freedom	Square Root Average Rate	F	P-Value
Extra-Groups	815766/768	6	135961/128	0 56/50	0/001
Intra-Groups	1/658		1/658		
Total Sum			7		

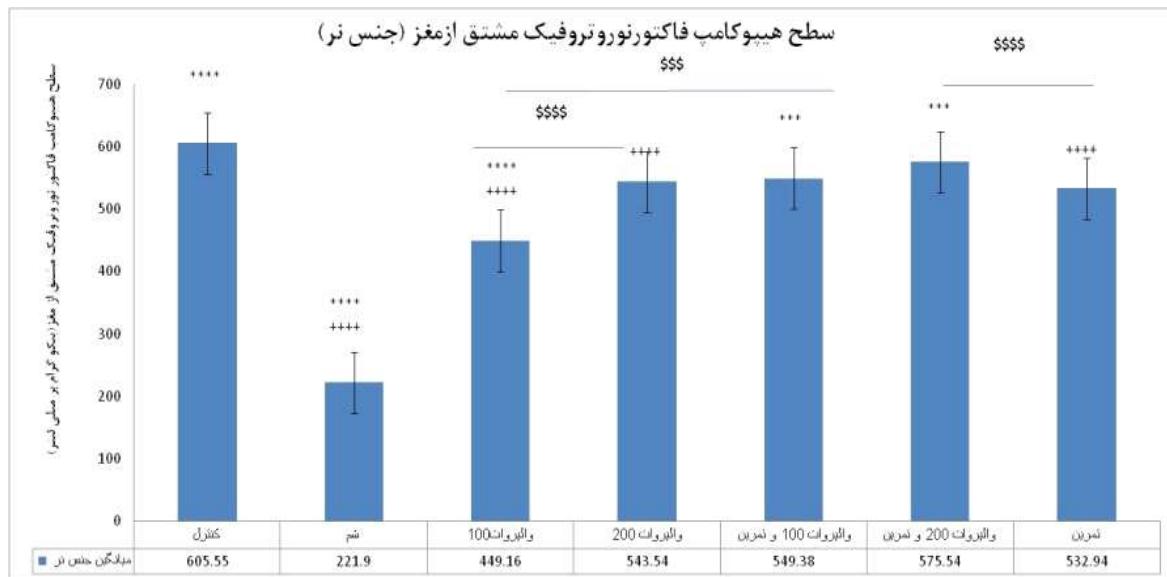
Note: P-value is considered 0.05.

Comparison of the control and testing groups of the study depicts that there is significant difference between control group and 100 milligrams valproic acid group, the endurance exercises group and the synthetic group of endurance exercises and 200 milligrams valproic acid ( $p<0.0001$ ). Furthermore, there is significant difference between control group and 200 milligrams valproic acid group. Through administration of 100 and 200 milligrams of valproic acid and endurance exercises and analysis of the most effective synthesis between the optimal dosage of valproic acid and endurance exercises, the present study indicates that there is significant difference between research sham groups and testing groups ( $p<0.0001$ ). Therefore, the present study deduces that BDNF level is increased in all the research testing groups.

### Hippocampal Level of BDNF (Female Subjects)



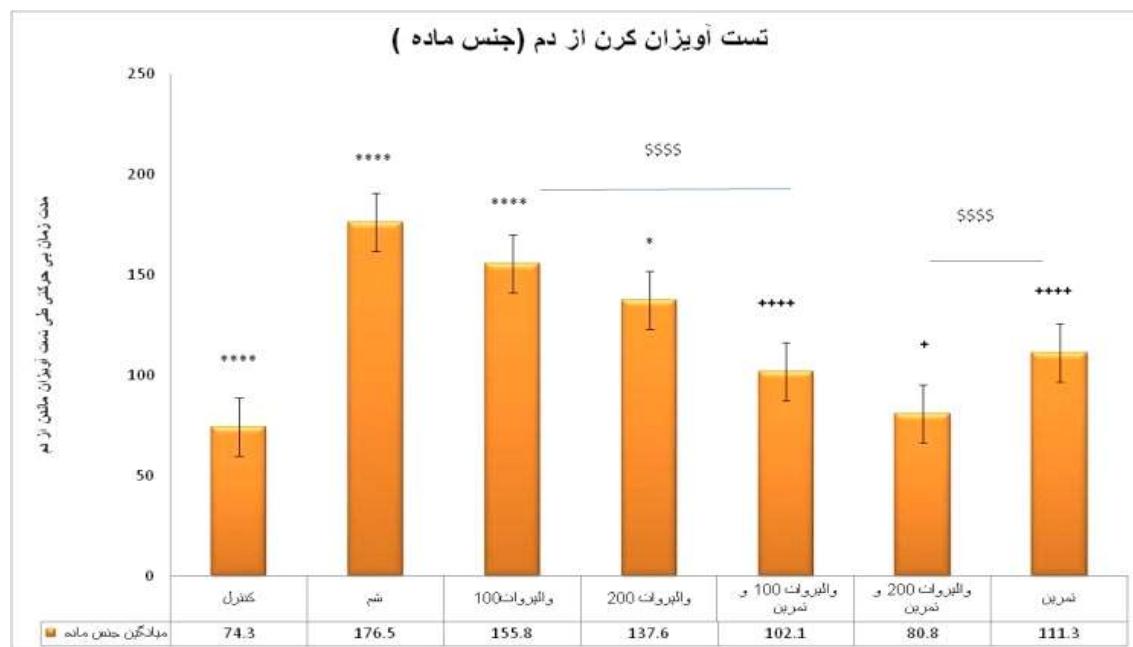
### Hippocampal Level of BDNF (Male Subjects)



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**Tail Suspension Test (Male and Female Subjects)**

**Tail Suspension Test (Female Subjects)**



**Tail Suspension Test (Male Subjects)**



## Conclusion

Considering antecedent studies and research historical background, the present study detects no comprehensive study regarding the analysis of synthetic effects of endurance exercises and valproic acid administration on serum and hippocampal levels of BDNF of hippocampal degeneration. For the fist time, the present study analyzes the synthetic effects of chronic administration of various dosages of valproic acid and an eight week long endurance exercises period on serum and hippocampal levels of BDNF. The results of the present study depict that in comparison with research sham groups, research testing groups acquire higher hippocampal and serum levels due to administration of valproic acid. Furthermore, synthetic effects of administration of various dosages of valproic acid and endurance exercises indicate that administration of valproic acid 200 and endurance exercises can significantly improve hippocampal and serum levels in comparison with other testing groups of the research. The ultimate results of the present study represent efficient impacts of synthetic administration of eight week long endurance exercises period and chronic administration valproic acid on BDNF level of animal models of hippocampal degeneration.

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