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Original Research

Hippocampal ZnT3 (SLC30A3) Levels Reflect Hippocampal Tissue Damage in Chronic Exercising Diabetic Rats

Abdulkerim Kasim Baltaci[1], Mehmet Yasli[1], Saltuk Bugra Baltaci[2], Rasim Mogulkoc[1], Esma Menevse[3], Omer Unal[4]

[1] Faculty of Medicine, Department of Physiology, Selçuk University, Konya, Turkey
[2] Department of Physiology, Regenerative and Restorative Medical Research Center, Istanbul Medipol University, Istanbul, Turkey
[3] Faculty of Medicine, Department of Biochemistry, Selçuk University, Konya, Turkey
[4] Faculty of Medicine, Department of Physiology, Kirikkale University, Kirikkale, Turkey

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Correspondence
Abdulkerim Kasim Baltaci, MD
Address: Department of Physiology, Faculty of Medicine, Selcuk University, Konya- Türkiye
E mail: baltaci61@yahoo.com

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ABSTRACT

Objective: In this study, it was investigated how chronic exercise affects hippocampus tissue damage and ZnT3 levels in diabetic rats.

Methods: The 40 adult rats were used in the study were divided into 4 equal groups: Control (G1), Exercise Control (G2), Diabetes (G3), Diabetes+Exercise (G4). Diabetes was induced in animals in G3 and G4 by injecting intraperitoneal streptozotocin (STZ) twice, 24 hours apart. The animals in G2 and G4 were runed on the rat treadmill for 45 minutes daily for 4 weeks. MDA (spectrophotometric method) and ZnT3 (ELISA method) levels were determined in hippocampus tissue samples obtained from animals sacrificed at the end of the experimental procedures.

Results: In the current study, the highest MDA and lowest ZnT3 levels in the hippocampus tissue were obtained in the diabetes group (G3) ($P<0.05$). Chronic exercise prevented increased hippocampal tissue damage in diabetic rats and reversed decreased ZnT3 levels ($P<0.05$).

Conclusion: The results of our study showed that 4 weeks of chronic exercise could be prevent increased tissue damage in the hippocampus tissue of diabetic rats and ameliorate the decreased ZnT3 levels. The data obtained in this study indicate that ZnT3 levels in diabetic rats may be an indicator of hippocampal tissue damage.

Keywords: Chronic exercise, diabetes, MDA, hippocampus, ZnT3.

INTRODUCTION

Diabetes Mellitus, a chronic metabolic disease characterized by hyperglycemia, insufficient secretion or insufficient action of endogenous insulin, which is a global public health problem [1]. It constitutes 12.2% of all-cause global deaths [2]. As a result of metabolic dysregulation in diabetes, various complications including both macro and micro vascular disorders develop [1, 2]. Oxidative stress increases in both type-1 and type-2 diabetes states. As a result, increased tissue damage plays a role in the development of cardiovascular system-related diseases which is associated with both types of diabetes [3].

Alzheimer's disease (AD) and Type-2 diabetes are both defined as chronic degenerative diseases. In both disease groups, there is a coexistence of pathophysiological events such as insulin resistance, inflammatory stress and amyloid aggregation [4].

Both Diabetes mellitus and Alzheimer's disease increase alarmingly with aging. Accordingly, there is a strong relationship between type 2 diabetes and increased dementia risk [5,6].

AD is also called Type-3 diabetes mellitus (DM) because diabetes is a neuroendocrine disorder that leads to the progression of AD [7]. The term type 3 diabetes is a term used to draw attention to the insulin deficiency and resistance that occurs in the brain in AD [8]. Insulin neurotransmitter release makes synaptic modulation and thus creates learning and long-term memory effects [9]. Autopsies of Alzheimer's patients show decreased insulin in the brain [10]. The risk of Alzheimer's disease is doubled in patients with insulin resistance, metabolic syndrome and type 2 diabetes [10,11].

Especially in diabetic patients, glycation products formed as a result of high plasma sugar that causes neuronal damage due to oxidative stress in the hippocampus [10, 11]. Amyloid plaques are associated with neuronal and synaptic loss in Alzheimer's disease [12]. Regular exercise reduces the signs of Alzheimer's disease in individuals with brain amyloid findings. As a result, it has been reported that physical activity reduces the risk of Alzheimer's disease and has a positive effect on mortality [12, 13].

ZnT3, a zinc transporter protein, is critical in the transport of zinc to the synaptic vesicles of a group of glutamatergic neurons in the brain tissue, especially the hippocampus and neocortex [14]. ZnT3 contributes to the protection from aging-related cognitive losses due to its critical role in zinc regulation [15]. ZnT3 gene expression decreases significantly with age [16], Alzheimer's disease [17, 18], Parkinson's disease and dementia [14]. Consistent with these results, aged mice lacking the ZnT3 gene have loss of cognitive performance. As a result, these mice show difficulties in learning and memory [19-21]. It has been reported that ZnT3-KO mice show decreased progenitor cell proliferation and neuroblast production induced by hypoglycemia [22]. It has also been reported that there are fundamental changes in the expression of proteins and genes important in neuronal transmission in Znt3-KO mice [23]. Zinc deposited in synaptic vesicles by ZnT3 has been shown to play a fundamental role for presynaptic Erk 1/2 signaling during hippocampus-dependent learning [21]. In addition, studies with mice with mutated zinc-binding domains of neurotransmitter receptors have shown that synaptic zinc activated by ZnT3 is important [24]. Synaptic zinc may contribute to amyloid deposition in an age-dependent manner [19]. Thus, appropriate delivery of zinc to synaptic vesicles by ZnT3 may play a critical role in preventing the onset of Alzheimer's disease.

Main Points;

- In our study, increased hippocampal MDA and decreased hippocampal ZNT3 levels in diabetic rats were reversed by 4 weeks of moderate-intensity chronic exercise.
- The data obtained in our study suggest that hippocampal ZnT3 levels may be a marker of hippocampal tissue damage.
- The current study is the first study to evaluate diabetes-exercise-hippocampus and ZnT3 together.

The aim of this study was to investigate the relationship between hippocampus ZNT3 levels and hippocampal tissue damage in diabetic rats undergoing chronic running exercise.

MATERIALS AND METHODS

Study Groups and Animal Material

The research was carried out at Board of Selcuk University Experimental Medicine Research and Application Center. The study protocol was approved by the (2018-14). Ethics Committee (Decision Number: 2018-14, Meeting date 27.04.2018). 40 adults male Wistar rats were used in the study and divided into 4 equal groups. Control (G1), Exercise Control (G2), Diabetes (G3), Diabetes+Exercise (G4).

Induction of Diabetes in Experimental Animals

Diabetes groups were formed by randomly selecting 20 rats used in the study. Rats were injected intraperitoneally with 40 mg/kg streptozotocin (STZ) "Sigma, S-0130" twice, the same dose at 24-hour intervals. Six days after the second injection, blood glucose levels were measured from the tail veins of the animals using a diagnostic glucose kit. Animals with blood sugar levels of 300 mg/dl and above were considered diabetic [25].

Running Exercise

Chronic running exercises in experimental animals were performed on a rat treadmill.

The treadmill mechanism, where the running exercises were performed, was designed so that eight animals, separated from each other by glass partitions, could run at the same time. The treadmill was equipped with technical equipment that allowed the electrical impulse stimulation to be set at low intensity to

encourage the rats to run. The exercises were started 48 hours after diabetes was established in the rats and were performed as chronic running exercise for forty-five minutes a day for four weeks. Exercises performed in rats between 30 minutes and 60 minutes are defined as moderate intensity exercise [26]. Consistent with exercise intensity, this sports activity causes moderate stress in rats [26]. Based on this point, we planned the exercise duration of the rats as 45 minutes of daily running exercises. This application was made to minimize stress factors in rats. To accustom the rats to both the treadmill and running exercises, the animals were trained to run at a speed of 15 m/min for 15 minutes for two days before starting chronic running exercises.

Afterwards, the animals were run at 20 m/min for 45 minutes per day for 4 weeks [27]. With intramuscular administration of a combination of Ketalar (60 mg/kg), Parke-Davis and xylazine (5 mg/kg) "Rompun, Bayer" to avoid animal suffering 24 hours after the last running exercise, the animals were sacrificed under general anesthesia. Hippocampus tissue samples were taken from sacrificed animals. Chronic exercise practices; It was applied to Exercise Control (G2) and Diabetes+Exercise (G4) animals. Control (G1) and Diabetes control (G3) animals were not exercised.

Biochemical Analysis

Determination of Tissue Malondialdehyde (MDA) Levels

Although MDA is not a specific analysis method for fatty acid oxidation, it correlates strongly with the degree of lipid peroxidation. For this reason, it is a very common measurement method. In our study, we determined MDA levels in the hippocampus tissue as an indicator of tissue damage. We used the TBA (thiobarbituric acid) technique, which is the analysis method of Uchiyama and Miharama [28], which is also the most used method in MDA analysis. Tissue MDA results were determined as nmol/gr tissue in spectrophotometer [28].

Analysis of ZnT3 in Hippocampus Tissue by ELISA

After weighing the hippocampus tissue to be analyzed, it was put into tubes. It was homogenized with phosphate buffer at pH=7.4 in Misonix's Microsan Ultrasonic Homogenizer at 4˚C. The obtained homogenates were centrifuged according to the analysis. Analyzes were performed with the Elisa test kit, brand Bioassay Technology Laboratory, catalog number E235Ra.ZnT3 levels were calculated as ng/g tissue.

Statistical Evaluations

Statistical analysis of the data obtained in the study was performed with a computer package program (SPSS 22.0). The arithmetic mean and standard deviations (SD) of all data were calculated. The homogeneity of the data was confirmed by applying the "Shapiro-Wilk" test. One-Way Analysis of Variance was used to determine the difference between groups, and the Bonferroni test was used to determine which group caused the difference. Differences at $P<0.05$ level were considered significant.

RESULTS

In our study, the highest hippocampal MDA values and the lowest hippocampal ZnT3 values were obtained in the diabetes control group (G3) ($P<0.05$). Hippocampal MDA and ZnT3 values of the control (G1), exercise control (G2) and exercise diabetes (G4) groups were not different from each other (Figures 1, 2).

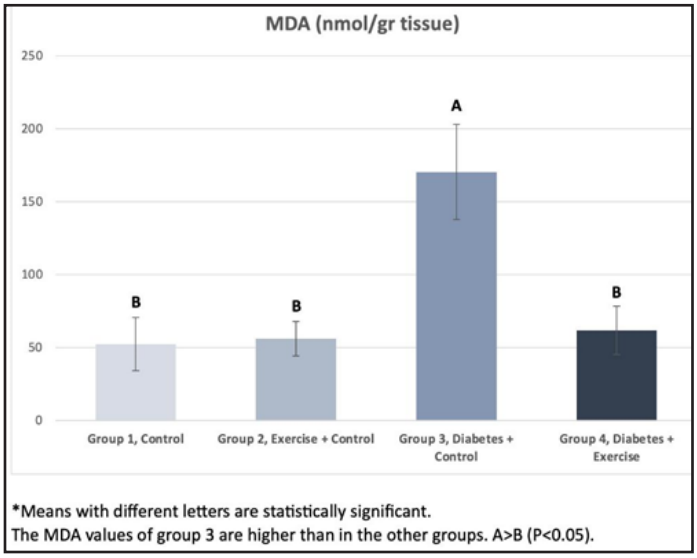


Figure 1. Hippocampal tissue MDA levels of study group

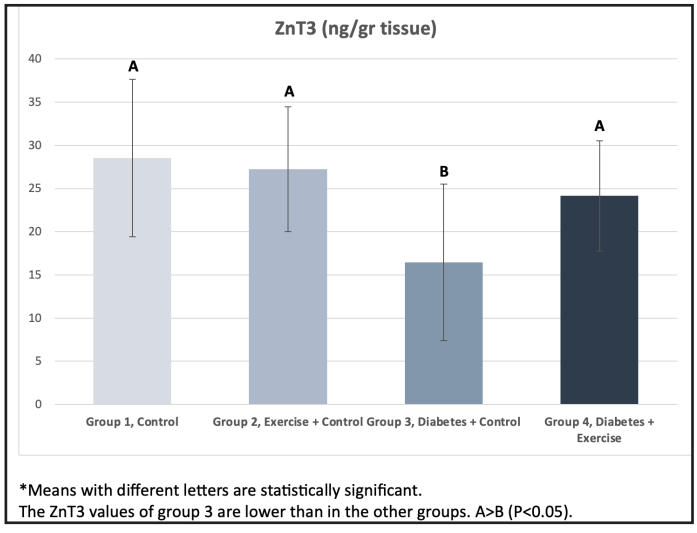


Figure 2. Hippocampal tissue ZnT3 levels of study group

Discussion of the Hippocampus MDA Parameters of the Study Groups

Hyperglycemia in diabetes weakens the antioxidant capacity in the body and facilitates the production of free radical products. For this reason, diabetic patients are more sensitive to oxidative stress [29]. In addition, hyperglycemia can lead to protein modification through the production of reactive oxygen species (ROS) during protein glycation, indicating that lipid peroxidation products may play a role in the complications of diabetes [29]. One of the structures most sensitive to diabetes is the hippocampus. Diabetes-related complications may cause degeneration of synaptic plasticity in the hippocampus [30]. Additionally, diabetes and related complications are shown as a risk factor for the deterioration of cognitive performance [30]. With the prolongation of the life expectancy of diabetic patients (especially those with Type 2 diabetes), cognitive impairment and dementia have become new complications of diabetes patients. Interestingly, diabetic patients are at approximately 60% higher risk of developing dementia than those without diabetes [31, 32]. Therefore, there is an increasing interest in investigating the relationship between diabetes and the hippocampus [32]. In our study, diabetes resulted in increased MDA levels in the hippocampus of rats. Possible mechanisms linking diabetes and depression have recently been found. One of these mechanisms is the increase in lipid peroxidation in the hippocampus [33]. Similarly, Kim et al. [29] showed that diabetes increases lipid peroxidation in the hippocampus. The results of our study show that diabetes increases hippocampal tissue damage within a period of 4 weeks in rats. This finding is in line with the findings of the above researchers, who suggested that diabetes affects hippocampal functions by causing neuronal damage. Again, our study shows that 4-week chronic exercise prevents oxidant damage in the hippocampus in diabetic rats. In our study, 4 weeks of moderate-intensity chronic exercise led to a significant decrease in hippocampal MDA levels when compared to non-exercise diabetic rats. Newsholme et al. [34] reported that exercise can improve metabolic and inflammatory outcomes by preventing oxidative stress in diabetes. This finding is consistent with the decreased MDA levels we obtained in exercised diabetic rats in our study. Reporting that increased hippocampal tissue damage in diabetes can be prevented by treadmill exercise [29] is an important finding that supports the decreased hippocampal MDA levels we obtained in diabetic rats that underwent chronic running exercise in our study.

Discussion of the Hippocampus ZNT3 Parameter of the Study Groups

In our study, the lowest ZnT3 levels in the hippocampus were obtained in diabetic rats. We could not find any studies directly on the relationship between diabetes, hippocampus and ZnT3 in Medline scans. However, it has been reported that there are changes in the levels of some zinc transport proteins, including ZnT3, in diseases such as Alzheimer's and diabetes [35]. It has also been shown that ZnT3 can also be expressed in pancreatic beta cells outside the brain [36]. In addition, it has been reported that there is a significant decrease in ZnT3 expression in brain tissue due to aging, which may be important in the relationship between aging and AD [37]. In this study, the idea of determining the hippocampal ZnT3 parameter in rats with diabetes was born for two reasons. First, diabetic patients exhibit features such as cognitive impairment and dementia [31, 32]. The second is that the risk of developing Alzheimer's disease is 60% higher in diabetic patients than in people without diabetes [8, 38]. Therefore, the decreased ZnT3 levels we obtained in diabetic rats can be considered as a very interesting and important finding. It is already known that the role of ZnT3 in cognitive functions and events such as Alzheimer's is critical [16]. The formation of beta amyloid plaques lies at the basis of the pathology of Alzheimer's disease. Beta amyloid plaques (amyloid fibrils) accumulate especially in the hippocampus and neuronal cortex [39]. Loss of function of ZnT3 has a critical place in the formation of amyloid plaques. Presynaptic glutamatergic vesicles contain high levels of zinc through ZnT3, which is localized in the vesicles [36]. As a result, one of the important factors leading to the formation of amyloid plaques in Alzheimer's disease is abnormal changes in free zinc levels [40]. It was suggested that this abnormal zinc regulation occurs in two phases. First, inhibition of zinc uptake leads to changes in zinc homeostasis. The corresponding increase in presynaptic zinc leads to increased oligomerization and insolubility with amyloid β [41]. Second, dysregulation of zinc homeostasis results from an inhibition of zinc transport leading to high intracellular zinc levels [42]. Recently, Deshpande et al. [43] showed that the formation of hippocampal amyloid β plaques was significantly increased in mice lacking the ZnT3 gene compared to normal mice, revealing the importance of ZNT 3 in the development of Alzheimer's. In conclusion, the low hippocampal ZNT3 levels we obtained in diabetic rats are a very critical and original finding in this respect.

More interestingly, 4 weeks of moderate-intensity chronic exercise in our study prevented the decrease in hippocampal ZnT3 levels when compared to non-exercise diabetic rats. Amyloid plaques are associated with neuronal and synaptic loss in Alzheimer's disease [12]. Regular exercise reduces the signs of Alzheimer's disease in individuals with brain amyloid findings. As a result, it has been reported that physical activity reduces the risk of Alzheimer's disease and has a positive effect on mortality [12]. With this aspect, the fact that 4 weeks of moderate-intensity chronic exercise in diabetic rats prevents the decrease in hypompal ZNT3 levels in diabetic rats may be critical information in the relationship between diabetes-Alzheimer's-exercise. In the study of Kim et al. [29]; the findings that diabetes increases lipid peroxidation, whereas treadmill exercise can reduce diabetes-induced oxidative damage in the hippocampus is a report that indirectly supports the increased hippocampal ZNT3 levels we obtained in diabetic rats in our study. Based on the fact that chronic exercise prevents hippocampal tissue damage caused by diabetes in the current study, it can be suggested that chronic exercise may be beneficial in delaying Alzheimer's disease, which is more common in diabetic elderly people.

Limitation

The limiting factor in the current study is that the effect of chronic exercise on histological changes in hippocampal tissue in diabetic rats was not demonstrated. Revealing the relationships between histological changes in hippocampus tissue and diabetes and chronic exercise may provide us with more original information.

CONCLUSION

In our study, increased hippocampal MDA levels in diabetic rats were prevented by 4 weeks of moderate-intensity chronic exercise. Again in the present study, significantly suppressed hippocampal ZnT3 levels in diabetic rats were reversed by 4 weeks of moderate-intensity chronic exercise. Based on the data obtained in our study, we suggest that hippocampal ZnT3 levels may be a marker showing hippocampal tissue damage. Based on Medline scans; We can say that our study is the first study in which diabetes-exercise-hippocampus- and ZnT3 were evaluated together.

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Conflict of interest: The authors declare that they have no potential conficts of interest to disclose.

Informed Consent: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University Experimental Medicine Research and Application Center (2018-14). This research was performed on the animals (rat). Meeting date 27.04.2018).

Author Contributions: Conception: SBB;RM;AKB – Design:RM; AKB - Supervision:RM; AKB- Fundings: -Materials:MY - Data Collection and/or Processing:EM; SBB; OU - Analysis and/or Interpretation:EM; SBB; OU-Literature:MY; SBB - Review:MY; SBB - Writing:SBB- Critical Review:RM;AKB.

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