

Chronic Exercise and Vitamin C Attenuate Lipid Peroxidation in Distinct Brain Regions of Epileptic Rats

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ABSTRACT

This study aimed to evaluate lipid peroxidation and antioxidant status in different brain regions of epileptic rats subjected to chronic swimming exercise and vitamin C administration.

A total of 48 rats were randomly divided into six equal groups: Control, Swimming, Swimming + Vitamin C, Swimming + Epilepsy, Swimming + Epilepsy + Vitamin C, and Epilepsy. Chronic swimming exercise was performed for 90 days (30 min/day). Vitamin C (ascorbic acid) was administered intraperitoneally at a dose of 100 mg/kg/day. Epilepsy was induced by injecting 500 IU penicillin into the left somatomotor cortex. At the end of the experimental period, brainstem, cerebellum, and brain tissue tissues were collected. Malondialdehyde (MDA, nmol/ml) levels were measured as an indicator of lipid peroxidation, while reduced glutathione (GSH, μ mol/ml) levels were determined to assess antioxidant capacity.

In the epilepsy groups, a significant increase in MDA levels and a marked decrease in GSH concentrations were observed compared to the control and Swimming+Vitamin C groups ($p < 0.05$). Combined exercise and vitamin C administration suppressed lipid peroxidation and partially improved antioxidant defense in brain tissue in epileptic rats ($p < 0.05$). These findings suggest that epilepsy is associated with increased oxidative damage and impaired antioxidant defenses in multiple brain regions. Chronic swimming exercise together with vitamin C supplementation may exert protective effects by reducing lipid peroxidation and improving antioxidant capacity in the epileptic brain.

Keywords: Epilepsy, Oxidative stress, Swimming exercise, Vitamin C, Antioxidant defense

Introduction

Epilepsy is a neurological disorder characterized by unexplained seizures affecting more than 50 million people worldwide. Seizures in epilepsy involve pathological processes including abnormal electrical activity, impaired antioxidant activity leading to lipid peroxidation, and neuronal damage. Therefore, a range of biochemical and molecular disorders can contribute to disease progression and comorbidities in epilepsy (1). Oxidative stress in brain tissue is considered a pathophysiological mechanism playing a role in epileptogenesis (2). Oxidative stress results from increased activity of prooxidants against

antioxidants and leads to peroxidation of lipids, proteins, and nucleic acids in brain tissue (1, 2). In experimental epilepsy models, elevated levels of MDA, a marker of oxidative damage, and widespread suppression of many antioxidant parameters, including reduced glutathione (GSH), an indicator of antioxidant activity, have been reported, which points to the role of oxidative imbalance in seizure-induced tissue damage (2).

Regular physical exercise is considered not only an activity that improves mood in epilepsy patients but also an auxiliary treatment element that reduces seizure frequency. The effect of regular exercise in reducing seizure frequency in epilepsy is also related to its being a stimulus of

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antioxidant activity (3). Chronic exercise, in particular, is drawn to the role of strengthening antioxidant systems in epilepsy patients. As a result, aerobic activities such as regular swimming stimulate neuroprotective signaling pathways by increasing mitochondrial efficiency and reduce seizure frequency (3). While exercise alone can increase oxidative damage as a stress factor, moderate and chronic exercise strengthens antioxidant defenses, inhibiting oxidative stress parameters in various tissues, especially brain tissue (3). Experimental evidence already shows that chronic exercise can reduce seizure-induced oxidative stress in epileptic animal models (4).

It has been reported that seizure frequency in epileptic patients can affect not only the hippocampus but also multiple brain regions (5,6). It has been reported that seizure frequency frequently affects regions such as the brainstem, cerebellum, and brain tissue in epileptic patients, making these regions susceptible to oxidative damage (5, 6). In experimental animal models, it has been proven that epileptic seizures show tissue damage-specific changes in oxidative stress and antioxidant parameters in brain regions. This evidence shows that tissue damage occurring in epilepsy is not evenly distributed throughout the brain (6).

Vitamin C, also known as ascorbic acid, is an important water-soluble antioxidant. Due to its ability to easily cross the blood-brain barrier, it accumulates in brain tissue, preventing oxidative stress and stimulating antioxidant activity (7). In epileptic seizure models, vitamin C supplementation has been shown to significantly reduce tissue damage (8). This effect of vitamin C occurs by increasing the level of GSH, an antioxidant parameter, and supporting neuroprotection (8).

The common emphasis of the information presented above is the interaction between epilepsy, oxidative stress, and neuroprotective strategies. However, it is also certain that the effects of chronic exercise and vitamin C, separately or in combination, on oxidant/antioxidant markers in different brain regions are not fully understood. This study aims to evaluate the effects of chronic swimming exercise and vitamin C supplementation (alone or in combination) on lipid peroxidation and antioxidant capacity in different brain regions (brainstem, cerebellum, and brain tissue) in a penicillin-induced epileptic rat model.

Materials and Methods

Animals and Ethical Approval: This study was carried out at the Experimental Medicine Research and Application Center of Ondokuz Mayıs University using adult male Wistar rats obtained from the same facility. All experimental procedures were approved by the local Ethics Committee of the same centre (2010/36). Biochemical tissue analyses were conducted at the Molecular Physiology Laboratory, Faculty of Medicine, Selcuk University. A total of 48 rats were included in the study and randomly allocated into six equal groups (n = 8 per group).

Experimental Design and Grouping (G)

The experimental groups were defined as follows:

G1 (Control): Rats maintained on a standard diet without any experimental intervention.

G2 (Swimming): Rats subjected to swimming exercise for 30 minutes per day for a period of three months.

G3 (Swimming + Vitamin C): Rats that underwent the same swimming protocol 10 days prior to the completion of a three-month exercise period and received intraperitoneal (ip) vitamin C (100 mg/kg/day) (9).

G4 (Swimming + Epilepsy): Rats exposed to the swimming protocol for three months, followed by induction of epileptiform activity 24 hours after the final exercise session.

G5 (Swimming + Epilepsy + Vitamin C): Rats that received vitamin C supplementation (100 mg/kg/day, ip) 10 days prior to the end of the swimming protocol and in which epileptiform activity was induced 24 hours after the last vitamin C administration (9).

G6 (Epilepsy): This group received intracortical administration of 500 units (IU) of penicillin in a volume of 2.5 µl to induce epileptiform activity, and was fed a normal diet.

Animal Housing and Experimental Conditions:

Animals were housed in stainless steel cages that were cleaned daily. Standard pellet chow was provided in stainless steel feeders, and tap water was supplied ad libitum in glass bottles. The housing environment was maintained under controlled conditions with a 12 h light/12 h dark cycle and a constant ambient temperature of 21 ± 1 °C.

Vitamin C was administered to animals in Groups 3 and 5 by oral gavage at a dose of 100 mg/kg/day for 10 consecutive days prior to the completion of the swimming exercise period. All

experimental procedures, including swimming sessions, were performed between 10:00 and 12:00 to minimize circadian variability.

Experimental Applications

Exercise Training Program: All animals were adapted to water for swimming exercise before the experiment began. Rats were kept in shallow water at 32°C between 10:00 and 12:00 AM, seven days a week, for adaptation. Adaptation to water continued throughout the experiment. The aim of adaptation to water was to reduce stress without promoting physical training adaptation (9).

Swimming was performed in water at 32-33°C between 10:00 and 12:00 AM. The training period lasted 90 days and consisted of daily sessions of 30, minutes, seven days a week, without workload. Exercise was performed by swimming in two training glass tanks (100 cm long, 50 cm wide, 50 cm deep) containing tap water.

Surgical Procedure and Penicillin Administration: Food was withheld from the rats for 12 hours prior to surgery. Anesthesia was induced via intraperitoneal injection of urethane at a dose of 1.2 g/kg. Following anesthesia, the animals were secured in a stereotaxic frame after shaving the scalp. A midline rostrocaudal incision approximately 3 cm in length was made, and bleeding from superficial tissues was controlled using electrocautery.

Soft tissues overlying the left somatomotor cortex were retracted, and the skull was thinned with a high-speed drill before carefully removing the parietal bone. Stainless steel recording electrodes were positioned epidurally over the cortex, one in the frontal area (2 mm anterior, 3.5 mm lateral to bregma) and another in the parietal area (6 mm posterior, 4 mm lateral to bregma), based on stereotaxic atlas coordinates. Hemorrhage from the bone was controlled with bone wax as needed. To minimize heat-related tissue damage during drilling, the skull surface was intermittently cooled using saline-soaked sponges. After complete removal of the parietal bone, the dura mater was gently exposed (10).

Penicillin G potassium (dissolved in distilled water) was used to induce epileptiform activity. A total of 500 IU in a volume of 2.5 μ L was administered intracortically at a rate of 0.5 μ L/min (10).

Tissue Collection and Biochemical Analysis: At the end of the experimental protocol, animals were sacrificed and brain tissues, including the whole brain, cerebellum and brain tissue were rapidly excised. Tissue samples were stored at -80

°C until biochemical analysis. Malondialdehyde (MDA) and reduced glutathione (GSH) levels were subsequently measured to assess oxidative stress and antioxidant status.

Biochemical Analyses

Measurement of Malondialdehyde (MDA)

Levels: MDA levels in brain tissue samples, including the whole brainstem, cerebellum and brain tissue were assessed as an index of lipid peroxidation using the thiobarbituric acid-reactive substances (TBARS) method (11). The concentration of MDA was calculated and expressed as nmol per milliliter of protein.

Determination of Reduced Glutathione (GSH)

Levels: GSH levels in the brainstem, cerebellum and brain tissues were determined using the Ellman's reagent method (12). GSH concentrations were expressed as μ mol per milliliter.

Statistical Analysis: The statistical interpretation of the findings was performed using the SPSS 26.0 computer package program, and the arithmetic means and standard deviations of all parameters were calculated. The Shapiro-Wilk test was performed to determine the homogeneity of the data, and it was determined that the data showed a normal distribution. One-way analysis of variance (ANOVA) test was used to determine the difference between groups, and the Duncan test, a multiple comparison test, was used to determine which group the differences originated from. Differences at the $p < 0.05$ level were considered significant.

Results

MDA and GSH Parameters in Brainstem

Tissue: The highest MDA levels in the brainstem were observed in the epilepsy groups (G4, G5, and G6) compared with the control groups ($p < 0.05$). The lowest MDA level was detected in the control group without any intervention (G1) ($p < 0.05$, Figure 1, Tables 1-2).

Regarding antioxidant status, the lowest GSH levels in the brainstem were found in the epilepsy group subjected to swimming exercise alone (G4) and in the untreated epilepsy group (G6) ($p < 0.05$). The GSH level in the epilepsy group that underwent both swimming exercise and vitamin C supplementation (G5) was significantly higher than in G4 and G6 ($p < 0.05$), but remained lower than in the control groups ($p < 0.05$, Figure 2, Tables 1-2).

Table 1: Comparison of MDA and GSH Levels in Brainstem Tissue of Study Groups

Groups	N	MDA nmol/ml	GSH μmol/ml
G1 Control	8	5,614±0,368d	0,672±0,136a
G2 Swimming + Control	8	7,854±0,0177b	0,610±0,165b
G3 Swimming + Vitamin C	8	6,751±0,280c	0,677±0,161a
G4 Swimming + Penicillin	8	10,740±0,659a	0,440±0,141d
G5 Swimming + Penicillin + Vitamin C	8	9,800±0,767a	0,500±0,158c
G6 Penicillin	8	10,813±0,758a	0,445±0,140d

a>b>c>d: Differences between means with different letters in the same column are significant (P<0.05).

MDA P Values 1-2:0,000; 1-3:0,000; 1-4:0,000; 1-5:0,006; 1-6:0,000; 2-3:0,044; 2-4:0,000

2-5:0,000; 2-6:0,000; 3-4:0,000; 3-5:0,008; 3-6:0,000; 4-5:0,890; 4-6:0,992; 5-6:0,882

GSH P Values 1-2:0,002; 1-3:0,242; 1-4:0,008; 1-5:0,006; 1-6:0,008; 2-3:0,044; 2-4:0,040

2-5:0,034; 2-6:0,004; 3-4:0,028; 3-5:0,046; 3-6:0,000; 4-5:0,044; 4-6:0,992; 5-6:0,042

Table 2: Comparison of MDA and GSH Levels in Cerebellar Tissue of Study Groups

Groups	N	MDA nmol/ml	GSH μmol/ml
G1 Control	8	6,990±0,799d	0,648±0,163a
G2 Swimming + Control	8	8,050±0,310c	0,511±0,085b
G3 Swimming + Vitamin C	8	7,012±0,333d	0,652±0,097a
G4 Swimming + Penicillin	8	11,147±0,683a	0,316±0,109b
G5 Swimming + Penicillin + Vitamin C	8	9,990±0,599b	0,330±0,077b
G6 Penicillin	8	11,127±0,943a	0,302±0,099b

a>b>c>d: Differences between means with different letters in the same column are significant (P<0.05).

MDA P: Values 1-2:0,000; 1-3:0,217; 1-4:0,000; 1-5:0,006; 1-6:0,000; 2-3:0,044; 2-4:0,000

2-5:0,000; 2-6:0,000; 3-4:0,000; 3-5:0,008; 3-6:0,000; 4-5:0,000; 4-6:0,992; 5-6:0,000

GSH P Values:1-2:0,002; 1-3:0,242; 1-4:0,008; 1-5:0,006; 1-6:0,008; 2-3:0,044; 2-4:0,054

2-5:0,062; 2-6:0,078; 3-4:0,028; 3-5:0,046; 3-6:0,000; 4-5:0,804; 4-6:0,992; 5-6:0,802

Table 3: Comparison of MDA and GSH Levels in Brain Tissue of Study Groups

Groups	N	MDA nmol/ml	GSH μmol/ml
G1 Control	8	6,176±0,690c	1,089±0,218a
G2 Swimming + Control	8	6,715±0,533c	1,060±0,169a
G3 Swimming + Vitamin C	8	6,850±0,797c	1,047±0,157a
G4 Swimming + Penicillin	8	10,105±0,895a	0,279±0,044b
G5 Swimming + Penicillin + Vitamin C	8	8,649±1,204b	0,293±0,158b
G6 Penicillin	8	9,913±0,634a	0,308±0,086b

a>b>c>d: Differences between means with different letters in the same column are significant (P<0.05).

MDA P Values 1-2:0,821; 1-3:0,644; 1-4:0,000; 1-5:0,000; 1-6:0,000; 2-3:1,000; 2-4:0,000

2-5:0,001; 2-6:0,000; 3-4:0,000; 3-5:0,003; 3-6:0,000; 4-5:0,024; 4-6:0,998; 5-6:0,038

GSH P Values:1-2:0,999; 1-3:0,994; 1-4:0,000; 1-5:0,000; 1-6:0,000; 2-3:1,000; 2-4:0,000

2-5:0,001; 2-6:0,000; 3-4:0,000; 3-5:0,001; 3-6:0,000; 4-5:0,804; 4-6:0,999; 5-6:0,880

MDA and GSH Parameters in Cerebellar Tissue: In cerebellar tissue, the highest MDA levels were observed in the epilepsy group subjected to swimming exercise alone (G4) and in the untreated epilepsy group (G6) (p<0.05). MDA levels in the combined treatment group (G5) were significantly lower than in G4 and G6 (p<0.05), but still higher than in the control groups (p<0.05, Figure 3, Tables 3-4).

The highest GSH levels in the cerebellum were detected in the control group (G1) and in the control group that underwent swimming exercise and received vitamin C supplementation (G3) (p<0.05, Figure 4, Tables 3-4).

MDA and GSH Parameters in Brain Tissue: In brain tissue, the highest MDA levels were found in the epilepsy group subjected to swimming exercise alone (G4) and in the untreated epilepsy

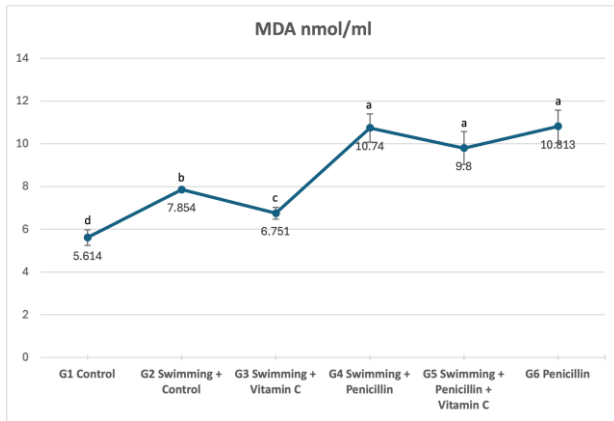


Fig. 1. MDA Levels in Brainstem Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b > c > d$). The unit is presented as nmol/ml

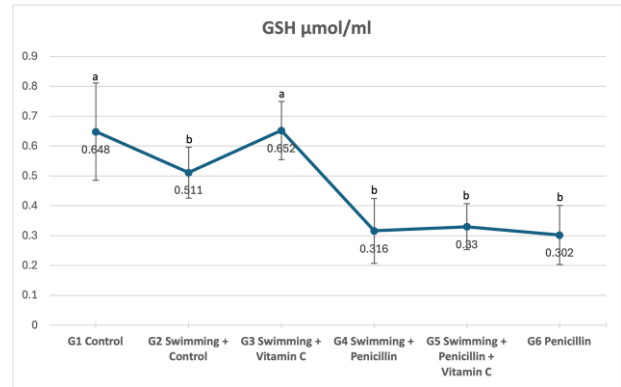


Fig. 4. GSH Levels in Cerebellar Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b$). The unit is presented as μ mol/ml

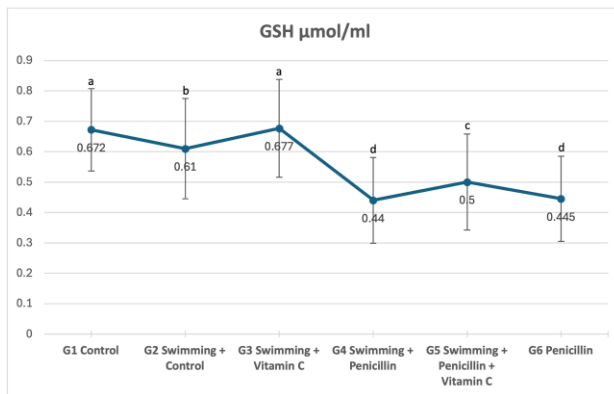


Fig. 2. GSH Levels in Brainstem Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b > c > d$). The unit is presented as μ mol/ml

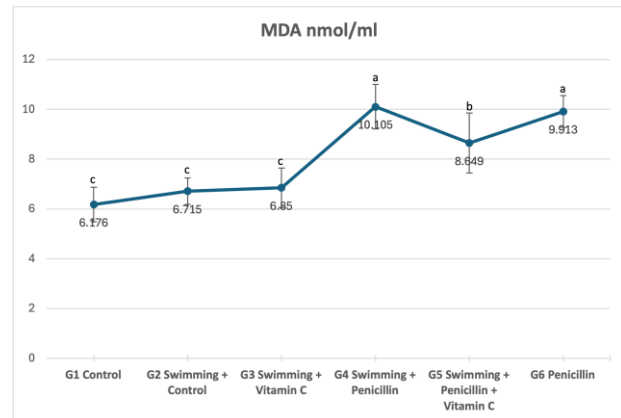


Fig. 5. MDA Levels in Brain Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b > c$). The unit is presented as nmol/ml

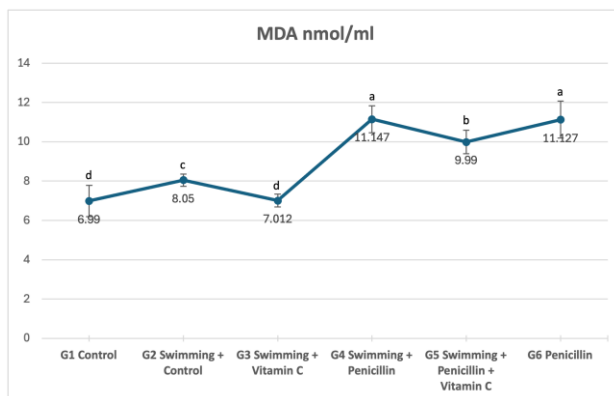


Fig. 3. MDA Levels in Cerebellar Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b > c > d$). The unit is presented as nmol/ml

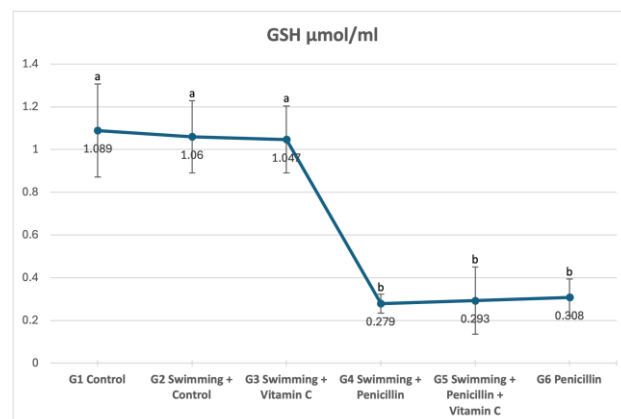


Fig. 6. GSH Levels in Brain Tissue of Study Groups. Results are presented as mean \pm SEM. There are statistically significant differences between groups labeled with different letters ($p < 0.05$; $a > b$). The unit is presented as μ mol/ml

group (G6) ($p < 0.05$). The combined treatment group (G5) showed significantly lower MDA levels than G4 and G6 ($p < 0.05$), although values remained higher than those in the control groups ($p < 0.05$, Figure 5, Tables 5-6).

GSH levels in the brain tissue were significantly higher in all control groups (G1, G2, and G3) compared with the epilepsy groups (G4, G5, and G6) ($p < 0.05$, Figure 6, Tables 5-6).

Discussion

Discussion of MDA and GSH Parameters in the Brainstem: In our study, the highest MDA levels in the brainstem were detected in the epilepsy groups (G4, G5, G6). Thus, the results of the current study show that chronic swimming exercise or vitamin C applications cannot prevent the increase in MDA parameters in the brainstem. Within the brainstem, GSH concentrations reached their minimum levels across all epileptic cohorts (G4, G5, and G6). These results are consistent with previous studies showing that recurrent seizures trigger tissue damage and lead to depletion of antioxidant defenses by increasing oxidative stress products in subcortical brain regions despite applications that increase antioxidant activity (13). However, the most significant difference we obtained in the epilepsy groups regarding the GSH parameter in the brainstem occurred in G5, where swimming and vitamin C were applied in combination. The combined application of swimming and vitamin C led to an increase in the GSH parameter in G5 compared to other epileptic groups (G4 and G6). The brainstem, which has a high metabolic activity, is also more susceptible to oxidative damage due to its dense neural networks. In our study, the lowest GSH levels observed in epileptic rats exposed only to swimming exercise (G4) and in untreated epileptic rats (G6) show that oxidative damage associated with epilepsy cannot be prevented when compared with antioxidant activity. Although it has been reported that chronic moderate exercise increases antioxidant capacity under physiological conditions (14), the current results show that exercise alone is insufficient to reverse seizure-induced oxidative damage in the brainstem. In contrast, the higher GSH levels found in epileptic rats (G5) that received both swimming exercise and vitamin C supplementation compared to other epileptic groups are still significant. This result demonstrates the limited role of the combined application of chronic exercise and vitamin C in

increasing antioxidant activity, as well as highlighting the importance of exogenous antioxidants in strengthening antioxidant defenses during epileptic conditions (15).

Discussion of MDA and GSH Parameters in Cerebellar Tissue: The highest MDA levels in cerebellar tissue were observed in the epilepsy group that underwent swimming exercise (G4) and the untreated epilepsy group (G6). MDA levels in the combined treatment group (G5) were significantly lower than in other epileptic groups, but still higher than in the control groups.

Contrary to reports (16) that oxidative damage occurring in the brain during epilepsy can be prevented by exercise activity, in our study, exposure to swimming exercise alone could not prevent increased MDA levels in the cerebellar tissue of epileptic rats. This finding parallels reports showing that cerebellar tissue is highly sensitive to oxidative stress during epileptic activity (17). In our study, combined swimming exercise and vitamin C supplementation significantly reduced cerebellar MDA levels compared to other epileptic groups. This finding is important because the combined application of moderate physical activity and vitamin C can be suggested as an adjunct in epilepsy treatment to prevent cerebellar tissue damage that occurs in epilepsy. Again, in the present study, we obtained the lowest GSH levels in the epilepsy groups. These results may be due to exercise duration and/or vitamin C dose. Nevertheless, these results are consistent with reports suggesting that antioxidant defenses are effectively maintained only in the absence of epileptic pathology (15, 18).

Discussion of MDA and GSH Parameters in the Brain Tissue: In brain tissue, the highest MDA levels were found only in the epilepsy group treated with swimming exercise (G4) and the untreated epilepsy group (G6) ($p < 0.05$). The combined treatment group (G5) showed significantly lower MDA levels compared to G4 and G6, but the values remained higher than those in the control groups. Consistent with other regions, the epilepsy-induced groups (G4, G5, and G6) exhibited the most depleted GSH profile in the brain tissue.

Cortical neurons are known to be highly susceptible to oxidative damage due to increased seizure frequency during epileptic discharges (19). Although the combined application of swimming exercise and vitamin C reduced MDA levels in brain tissue compared to other epileptic groups in our study, these values remained higher than the control values. This finding suggests that the

combined application of chronic exercise and vitamin C provides partial neuroprotection, and that achieving more optimal results may require longer intervention times or multi-targeted therapeutic strategies for epilepsy-induced oxidative damage (20).

When the results obtained in our study are evaluated as a whole, it is seen that there are regional variations, albeit limited, in terms of oxidative stress parameters throughout the brainstem, cerebellum, and brain tissue. This regional variation may be due to differences in neural composition, distribution of antioxidant defense, and metabolic demand.

It can be said that epileptic seizure activity increases free radical production, consequently leading to lipid peroxidation and antioxidant depletion (21). The most important point to discuss here is that 30 minutes of chronic exercise per day alone does not show protective efficacy under the experimental conditions of the current study. This suggests that swimming as a type of exercise and/or 30 minutes of chronic swimming does not strongly stimulate antioxidant activity. However, future studies involving various types and durations of exercise may provide us with more accurate information.

According to our results, although the protective effects of moderate chronic exercise alone appear to be limited, its application together with vitamin C for perhaps a longer period may show potential neuroprotective effects by preventing tissue damage in an epileptic rat model (22). Further studies could encourage the clinical investigation of chronic exercise and vitamin C supplementation.

Limitations: There are some limitations in the current study. First, this study was limited to the analysis of MDA and GSH in brain regions. The analysis of these parameters was not supported by histopathological changes. Second, the current study did not evaluate behavioral consequences related to epileptic seizure severity.

However, future further studies incorporating molecular, structural, and functional assessments, and integrating the neuroprotective potential of antioxidants and chronic exercise, could provide a deeper perspective on the subject.

The findings of this study suggest that impaired antioxidant activity and increased brain tissue damage in epilepsy can be partially reversed by the combined application of chronic exercise and vitamin C. In epilepsy, a disease that negatively impacts quality of life, the widespread clinical

research into chronic exercise and antioxidant minerals may provide promising information regarding epilepsy, brain tissue damage, and antioxidant activity.

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