

The effects of moderate running exercise and L-tyrosine on penicillin-induced epileptiform activity in rats

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Regular exercise and amino acid supplementation, popular approaches toward the reduction of epileptic seizures, have been extensively researched. This study was conducted to evaluate the effects of treadmill exercise and L-tyrosine treatment on the frequency and amplitude of epileptiform activity in rats. A total of 32 male albino Wistar rats were randomly divided into four groups: control, exercise, L-tyrosine, and exercise + L-tyrosine. L-tyrosine was supplemented by oral gavage (500 mg/kg/day, 2.5 mL solution). The treatments were performed 5 days a week for 10 weeks. The rats were anesthetized and then administered 500 IU penicillin into the left cerebral cortex using a microinjector and electrocorticogram (ECoG) activity was recorded for 3 hours using a Power Lab data acquisition system. The frequency and the amplitude of the ECoG recordings were analyzed offline. Compared to the control group, spike frequency decreased significantly in all other groups. There was no statistically significant difference between the groups in terms of spike amplitude and latency. In this study, the effects of regularly administered treadmill exercise and L-tyrosine use on epileptiform activity were examined and evaluated together for the first time. The results of this study showed that regular exercise and L-tyrosine use decreased epileptiform activity. Further research and clinical trials are needed to investigate the extent to which L-tyrosine and physical activity interfere with the epileptic state by investigating different doses of L-tyrosine and different severity/time/type of exercise protocols.

Key words: L-tyrosine, epilepsy, epileptiform activity, exercise

INTRODUCTION

Experimental research using animal models plays an important role in the investigation of the pathogenesis of epilepsy, where epileptic seizures are stimulated in the models. One frequently used experimental epilepsy model is induced by penicillin (Erfanparast and Tamaddonfard 2015; Zhu et al., 2018; Tokiwa et al., 2018). Penicillin administration causes acute and focal epileptic activity similar to the epileptic activity associated with an imbalance between inhibitory and excitatory neurotransmitters (Tokiwa et al., 2018).

Regular exercise and amino acids are used together as a popular nutritional supplement to reduce these epileptic seizures, and regular daily physical exercise is, thus, important for health. Although the positive or negative effects of physical exercise on seizure frequency remain unclear, it is expected that exercise will have the same positive effects on maximal aerobic capacity, working capacity, and body weight in this patient group as in healthy individuals. However, general health and quality of life can be negatively affected in epileptic patients who do not exercise (Allendorfer and Arida, 2018). Several clinical and experimental studies have found that exercising is beneficial for convul-

sive diseases after a regular sport or physical therapy program, and that patients who regularly exercise feel better, have better seizure control, and experience a significant decrease in number of seizures (Kayacan, 2016; Çakır et al., 2016; Häfele, 2018).

Amino acid supplementation is frequently recommended to increase the recovery rate in tissues and cells after epileptic seizures. Tyrosine is an amino acid that has been shown to reduce fatigue in rats during exercise, leading to increased performance (Chinevere et al., 2002). L-tyrosine is an antioxidant/amino acid that has amphiphilic properties because of its polar and apolar group characteristics (Gemili et al., 2010) and its antioxidant activity results from its side chain that can donate protons to free radicals. This property is similar to aromatic amino acids such as phenylalanine and tryptophan (Kayacan et al., 2017). Research has shown that a tyrosine supplement or food that is nutritionally rich in tyrosine increases dopamine (DA) and norepinephrine release in the brain (Robertson et al., 2016). Additionally, tyrosine is frequently used to reduce adverse effects of conditions that consume dopaminergic resources in the brain in humans (Steenbergen et al., 2015).

Studies investigating tyrosine supplementation administered together with exercise have shown that tyrosine use has an effect that balances body temperature and reduces fatigue (Sutton et al., 2005; Tumilty et al., 2011). It has also been reported to significantly and positively affect cognitive functions (Coull et al., 2015). The purpose of this study is to examine the effects of regular moderate treadmill exercise and L-tyrosine on epileptiform activity in rats. In addition to the above-mentioned physiological and psychological effects of tyrosine, it is thought that tyrosine and exercise may have a positive effect on epileptic activity, because tyrosine is a biochemical precursor of catecholamines such as DA, epinephrine, and norepinephrine. Consideration of the positive effects of exercise in combination with the effect on neurotransmitters in the brain resulting from the use of L-tyrosine suggests that findings from the study may contribute to the development of new treatment methods for epilepsy patients. The present study is the first to evaluate the effect of treadmill exercise and L-tyrosine use on epileptiform activity in rats.

METHODS

Animals

Thirty two 20–24-week-old male Wistar albino rats (n=8 in a group) weighing 280–350 g were supplied by

the Medical and Surgical Research Center of Ondokuz Mayıs University. The study protocol was approved by the Experimental Animal Ethics Committee of University (2016/36). The rats were randomly divided into four groups: control group (C), exercise group (E), L-tyrosine group (LT), and L-tyrosine+exercise group (ELT). L-tyrosine was dissolved (25°C) in saline solution (pH was adjusted to 7.4) and administered by oral gavage (500 mg/kg/day, 2.5 mL solution).

Exercise and L-tyrosine administration were performed 5 days per week for 10 weeks. The CE-certified four-lane animal treadmill (May Time 0804, Animal Treadmill) with adjustable settings for rate, distance, running time, speed, incline, and built-in memory to store data was used for exercise experiments. To avoid any stress that may possibly arise during the course of physical exercise, all rats were preliminarily subjected to a conditioning exercise series at the lowest speed during 5-min-long sessions for 10 days. After the treadmill adaptation period, control-group rats were put in cages under standard conditions until surgery, while the exercised groups continued to be trained according to the treadmill exercise protocol. The exercise workload consisted of running at a speed of 2 m/min for the first 5 min, 5 m/min for the next 5 min, and then 8 m/min for the last 20 min with a zero-degree angle incline.

Experimental protocol

Rats were anesthetized with urethane (1.25 g/kg, intraperitoneally [i.p.]) and placed into a stereotaxic frame under spontaneous respiration. Incision regions were infiltrated with prilocaine hydrochloride to prevent possible occurrence of pain. After shaving the top of the head, a 3-cm-long incision was created on the skull in the rostral-caudal direction. The soft tissue on the skull was removed and the bregma (reference point) was identified. Under stereotaxic guidance, two stainless steel screws were placed over the left somatomotor cortex (first screw, 3 mm lateral and 4 mm rostral to bregma; second screw, 3 mm lateral and 4 mm caudal to bregma) and a well conductor bipolar electrode was connected to the screws (Arslan et al., 2013; Çakır et al., 2016). After observing the brain's basal activity using the PowerLab data acquisition system (ADInstruments – Australia), a 1-mm hole was opened (1.5 mm left lateral and 1.5 mm caudal to the bregma), using a hand drill, to inject the penicillin G potassium (Sigma Chemical Co., St. Louis, MO, USA), which was dissolved in sterile physiological saline. The epileptic focus was produced by intracortical penicillin G potassium 500 IU injection (1 mm vertical direction on the

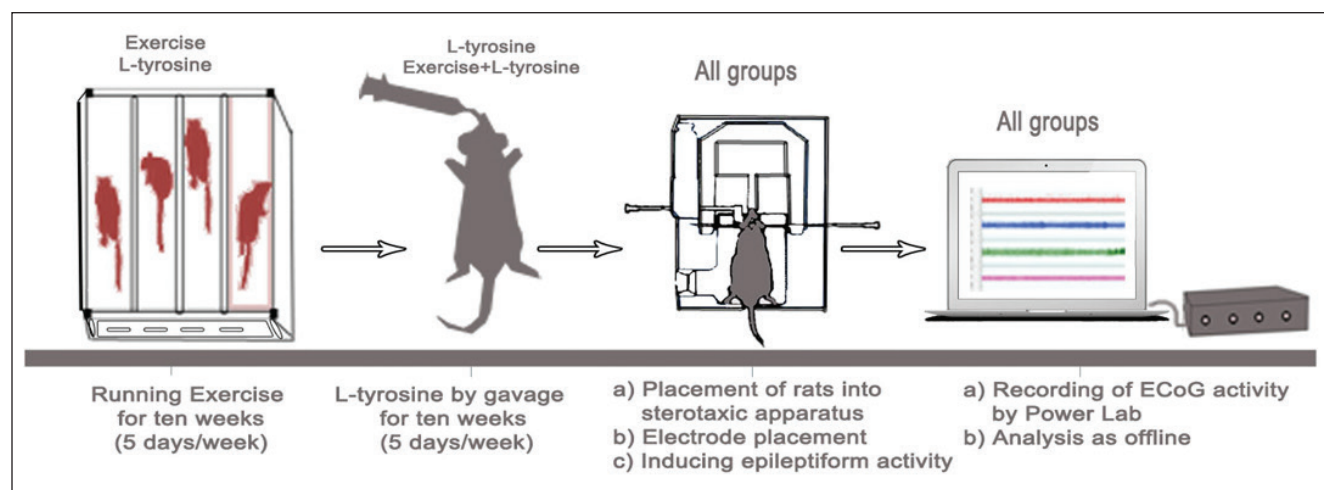


Fig. 1. Experimental application process performed in the present study.

brain surface) using a Hamilton microsyringe (type 701N, 22s-gauge, bevel tip) with a volume of 2.5 μL over 2 min. The ECoG signals were amplified using a BioAmp and transferred to a Power Lab 8/SP (both from AD Instruments, Australia; bioamp range, 5 mV; low pass, 120 Hz; high pass, 0.03 s; notch, 50 Hz) data recording system.

The ECoG activity was continuously recorded for 180 min, displayed, and stored using a computer. The frequency (min^{-1}) and amplitude (mV) values of spike/wave complexes and the latency (s) of onset of the first spike/wave event for each animal were automatically measured using a data acquisition Chart v.5.1.1 system and analyzed offline.

Periodic epileptiform discharges are an uncommon EEG or ECoG pattern characterized by lateralized or generalized; periodic or near periodic; or spike, spike-wave, or sharp-wave complex presentations throughout most or all of the recording. Epileptiform activity was quantified by the number of spike discharges per unit time.

After the animals arrived at the facility, they were exercised for 10 weeks (5 days/week) in the E and ELT groups. L-tyrosine was administered to the appropriate groups via gavage during the same period (10 weeks; 5 days/week) in the LT and ELT groups. After completion of these procedures, the animals were fixed to the stereotaxic apparatus and electrodes were placed in the head of the rat. ECoG recordings were obtained using PowerLab and the data were analyzed offline.

Statistical analysis

The frequency (min^{-1}) and amplitude (mV) of spike/wave complexes, and latency (s) to onset of the

first spike/wave event were gathered from animals in all groups and converted to a scaling percentage in a time-dependent manner. All statistical procedures were performed using the Statistical Package of SPSS, version 21 (SPSS Inc., USA) software. The normality of the data distribution was tested using the one-sample Kolmogorov–Smirnov test before analyses. After verifying the normality, a one-way analysis of variance (ANOVA) and the Tukey–Kramer post-hoc test for multiple comparisons were performed. Numerical data are expressed as the mean \pm standard deviation (SD). For all statistical comparisons, $P < 0.05$ was considered to be significant.

RESULTS

Based on the analysis, the spike frequency of penicillin-induced epileptiform activity was significantly reduced in all groups compared to the control group (Table I). The means of epileptiform activity spike frequencies were determined as follows: C: 6648 ± 689 , E: 3452.37 ± 322 , LT: 2551.5 ± 328 , and ELT: 2133.9 ± 286 (Table I). There was no statistically significant difference between the groups in terms of spike amplitude and latency values (Table II). Fig. 2 shows the change in mean spike frequency at 10-minute intervals generated by treadmill exercise and penicillin induction through L-tyrosine administration. Fig. 3 shows the spike graphs of the groups at the 100th minute.

Table I shows the mean and total spike numbers and significance levels of groups. When compared with the control group, significant differences were found in all groups in terms of spike number ($P < 0.05$). The lowest spike frequency was observed in the ELT group.

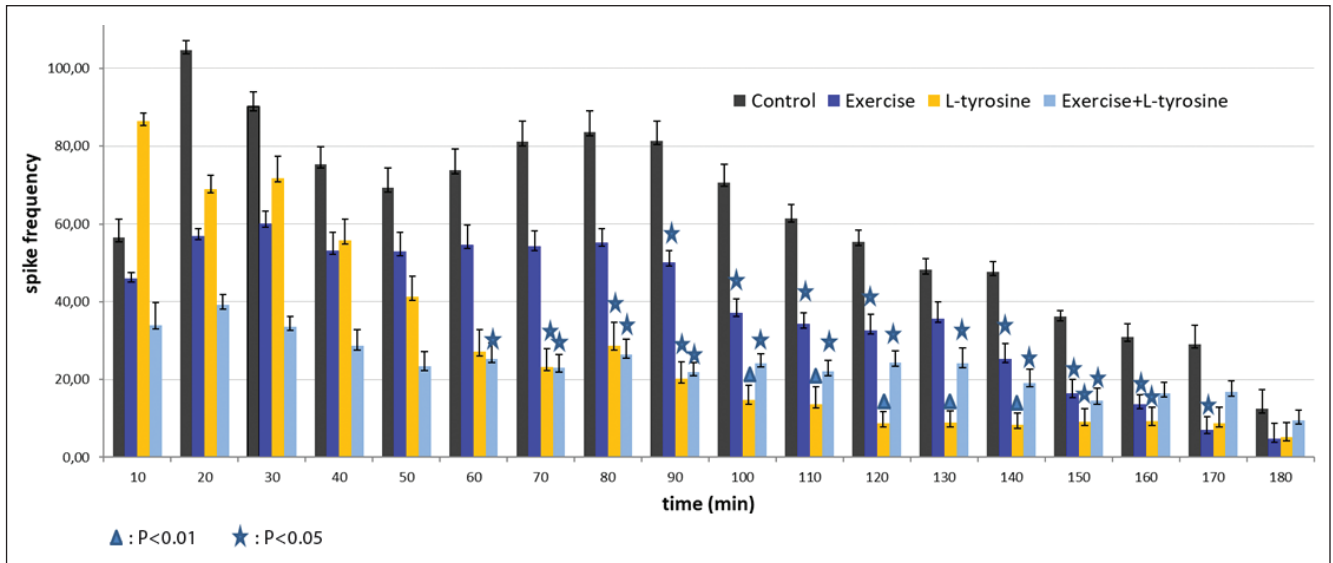


Fig. 2. Spike frequency distributions in all groups at 10-min intervals. The spike frequency of epileptiform activity was significantly reduced in all groups compared to C group (ELT: 60th min.; LT: 70th min.; E: 90th min.).

Table I. The statistical results of the groups according to the total number of spikes.

Groups	SD	Total	Mean	F	P
C	689	6648	61.56a	12.673	<0.05
E	322	3452.37	38.36b		
LT	328	2551.5	28.35b		
ELT	286	2133.9	23.71b		

The letters "a" and "b" indicate the differences among the groups in the same column.

Table II. The statistical results of groups' total amplitude and latency times.

Parameter	Groups	SD	Total	Mean	F	P
Amplitude (mV)	C	0.06	15.58	0.86	10.21	>0.05
	E	0.21	9.30	0.51		
	LT	0.11	8.05	0.44		
	ELT	0.14	10.78	0.59		
Latency (sec)	C	13.08	336	48.21	11.28	>0.05
	E	16.74	342	48.85		
	LT	10.39	384	48		
	ELT	16.89	396	49.5		

There were no statistically significant differences between groups in terms of spike amplitude and latency time after 180 minutes of recording by Powerlab.

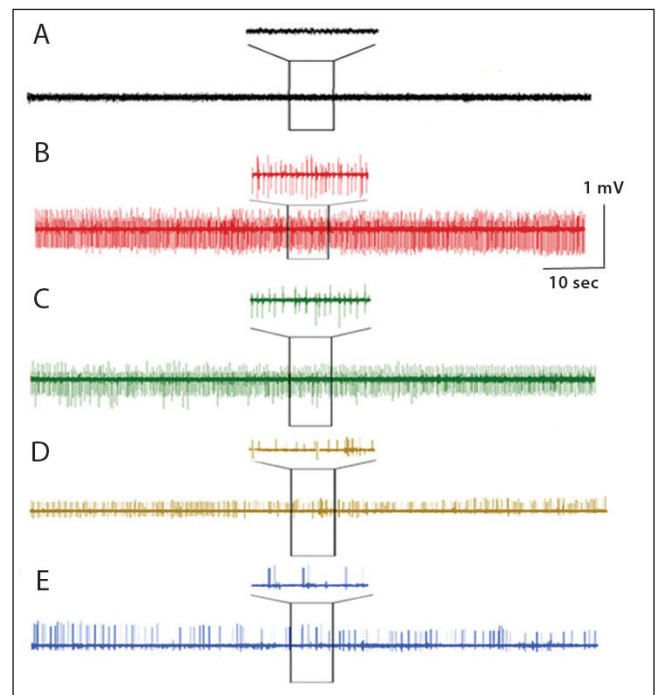


Fig. 3. The spike distributions recorded at the 100th minute. (A) Basal activity; An injection of normal saline (2.5 μ L, i.c.) did not alter the mean frequency or amplitude of the epileptiform activity. (B) Control; The intracortical injection of penicillin (500 IU/2.5 μ L) induced epileptiform activity on ECoG. (C) Exercise; The mean frequency of penicillin-induced epileptiform activity significantly decreased at 90 min after penicillin injection in the treadmill exercise group (P=.041 at the 90th min). (D) L-tyrosine; The mean frequency of penicillin-induced epileptiform activity significantly decreased at 70 min after penicillin injection in the L-tyrosine group (P=.047 at the 70th min). (E) Exercise+L-tyrosine; The mean frequency of penicillin-induced epileptiform activity significantly decreased at 60 min after penicillin injection in the Exercise+L-tyrosine group (P=.03 at the 60th min).

DISCUSSION

In the present study, the effect of treadmill exercise and L-tyrosine on the electrophysiological mechanisms of epilepsy was investigated. In the experimental epilepsy model created using penicillin, spike frequency was significantly decreased in all groups after the creation of the epileptiform activity compared to the control group. Moderate levels of exercise and L-tyrosine were evaluated together in our study because both methods involve similar physiological responses to neurotransmitter release in terms of their effect on epilepsy. Additionally, no studies were found in the literature that evaluated exercise and L-tyrosine supplementation in combination. The definition of epileptiform activity is given in Chatrian's glossary of terms as "distinctive waves or complexes, distinguished from background activity and resembling those recorded in a proportion of human subjects suffering from epileptic disorders" (Chatrian et al., 1974). These waves or complexes can appear as isolated focal spikes or sharp waves, a generalized polyspike, a spike and wave, or paroxysmal fast activity, and sometimes as abrupt rhythmic evolution in the background that heralds seizures. In our procedure, penicillin was administered to Wistar rats to create a model of focal seizure, in which epileptiform discharges were induced in advance by cortical application of the potent epileptogenic substance penicillin G. In this study, treadmill exercise significantly decreased the frequency of epileptiform activity at the 90th minute.

Physical exercise was found to improve motor performance and cognitive ability and contribute to healthy brain aging and a reduction in general oxidative stress (Sumien, 2017). However, regular physical activity has also been reported to play an effective role in reducing epileptic seizures (Kayacan et al., 2016; Çakır et al., 2016). Souza et al. (2009) stated that swimming exercise significantly reduced the duration and amplitude of PTZ-induced generalized seizures. Similarly, Kayacan et al. (2016) found that treadmill exercise significantly reduced the spike frequency of penicillin-modeled epileptiform activity in rats. Although regular exercise causes many physiological responses, research has shown that the oxidant/antioxidant system resulting from exercise is effective in reducing epileptiform activity (Souza et al., 2009; Kim et al., 2013). Recently, oxidative stress was found to be an important factor in various acute and chronic neurological diseases, especially in epileptic seizures. Studies on animals have shown that epileptic seizures may cause free radical production and oxidative damage to cellular proteins, lipids, and DNA. Epileptic seizures are a common feature of mitochondrial dysfunction associated with

mitochondrial encephalopathies (Patel, 2004). However, physical exercise has been reported to be effective in the treatment of oxidative stress and impaired brain function that is associated with oxidative stress (Kim et al., 2013; Kayacan et al., 2017). Accordingly, the mid-level running exercise that was performed in the present study reduced epileptiform activity, which may be caused by oxidative stress. In addition to the above-mentioned effects, regular exercise has been reported to activate the dopaminergic system and to increase DA availability in the striatum in animals (Hattori et al., 1994). In particular, exercise increases functional recovery after striatal lesions and striated grafts (Shi et al., 2017) and stimulates DA synthesis in the striatum of epileptic mice (Robertson et al., 2016). Correspondingly, L-tyrosine and exercise as administered in this research study caused a common physiological response. L-tyrosine is a precursor of neurotransmitter synthesis, similar to DA and norepinephrine (Fenstrom, 2005), and it increases neurotransmitter synthesis that has β -adrenergic-stimulating effects (Hoffman et al., 2009). For catecholamine synthesis, the tyrosine hydroxylase (TH) enzyme is an important control point in the conversion of tyrosine to dihydroxyphenylalanine (DOPA). DOPA is then converted to DA by dopa decarboxylase in the cytosol. Pharmacological studies have reported that increased DA and norepinephrine levels in the brain via L-tyrosine uptake may cause antiepileptic effects (Bozzi and Borrelli 2013; Tchekalarova et al., 2015). However, it has been reported that DA-modulated neurotransmission has a significant antiepileptic effect, especially in temporal lobe epilepsy (Alacantara et al., 2018).

Clinical and experimental studies implicate most neuromodulatory systems in epileptogenesis. The dopaminergic system has a seizure-modulating effect that crucially depends on different subtypes of DA receptors and the brain regions in which they are activated. Specifically, DA plays a major role in the control of seizures arising in the limbic system (Bozzi and Borrelli, 2013). The traditional anticonvulsant action of DA was attributed to D₂ receptor stimulation in the forebrain, while the advent of selective D₁ agonists with proconvulsant properties revealed for the first time that DA could also lower the seizure threshold from the midbrain (Starr, 1996). One important change in the epileptic brain is an imbalance in the excitation-to-inhibition ratio. Although this change is usually because of abnormal activity in glutamatergic and/or GABAergic neurons, neuromodulators such as DA can also affect this ratio by inducing some changes in the activity of glutamatergic and/or GABAergic neurons (Depaulis et al., 1994). A large amount of evidence shows that the dopaminergic system plays a critical role in controlling

neuronal activities during a seizure. Previous studies have shown that significant changes occur in different aspects of the dopaminergic system (such as dopamine release, metabolism, and receptor binding) following epileptic seizures in both humans and laboratory animals (Starr, 1996; Bozzi et al., 2011). Additionally, dopaminergic neurons modulate synaptic plasticity, a phenomenon that is also affected by seizure activity (Hansen and Manahan-Vaughan, 2014). Any abnormal variation in synaptic plasticity may change neuronal responsiveness and lead to seizure-induced impairment in different aspects of brain function in epileptic patients, such as progressive hyper-excitability and cognitive dysfunction (Rezaei et al., 2017). DA synthesis resulting from exercise and L-tyrosine may have been effective in decreasing the epileptiform activity, based on the findings that were identified in the present study. Both mechanisms cause the release of the same neurotransmitter group, and our findings are consistent with those of previous studies. For example, Yoon et al. (2007) found that treadmill exercise (30 min/day) in rats increased dopaminergic neuron activity in the brain. Similarly, Hasegawa et al. (2011) reported that, in rats, body temperature increased with exercise and this physiological response was also associated with DA and norepinephrine release.

In this study, the frequency of epileptiform activity in the exercise and L-tyrosine group decreased significantly. Although it is stated that athletes may be at risk of increased free radicals resulting from highly intense exercise (Avloniti et al., 2017), research shows that regularly exercising people and athletes adapt to such a program over time and are more resistant to oxidative damage (Evans and Omaye, 2017).

Generally, antioxidants clear all free radicals; therefore, an increase in antioxidant consumption can affect a variety of pathways, including cellular signaling pathways that are important for adaptation to exercise (McLeay et al., 2017). Studies in humans and mice have shown that feeding antioxidant vitamins has a positive effect on lipid peroxidation after exercise (Sari-Sarraf et al., 2016; Yang and Zhang, 2017). For example, Şentürk et al. (2001) examined the effect of vitamin C and E supplementation on high lipid peroxidation, which is caused by acute exhaustive running exercise in rats. They found that the vitamin supplementation administered to the exercising group was more beneficial than in the sedentary group and that lipid peroxidation in the exercising group decreased significantly. It was determined that the vitamin supplement administered to the group that exercised was more effective in reducing oxidative stress compared to the sedentary group. Consistent with these findings, McLeay et al. (2017) reported that vitamins E and C consumed to-

gether with exercise may more effectively contribute to reducing cellular damage induced by reactive oxygen types that are released through aerobic exercise in athletes.

The antioxidant enzyme activity is significantly increased in athletes and exercised rats. The increased antioxidant activity then inhibits lipid peroxidation caused by an exercise-induced increase in oxidative stress (Kayacan et al., 2017; 2019). Additionally, individuals exercising regularly have an advantage over sedentary people because training supports the activity of many major antioxidant enzymes and development of the overall antioxidant level. This information appears to be consistent with the findings of the ELT group in the present study.

CONCLUSION

The effects of regularly administered treadmill exercise and L-tyrosine use on epileptiform activity were examined and evaluated together for the first time. The results of this study showed that the use of L-tyrosine and exercise decreased epileptic activity effectively. Further experimental and clinical studies are required to investigate the degree to which L-tyrosine and physical activity interfere with the epileptic state. The results of this study suggest that exercise and nutrition can play a beneficial role in epilepsy. These findings also may be able to aid in the treatment of patients with epilepsy and contribute to the understanding of its electrophysiological mechanisms.

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