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Short-duration swimming exercise decreases penicillin-induced epileptiform ECoG activity in rats

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The aim of the present study is to understand the basic relationship between swimming exercise and natural course of epilepsy in animals by performing an electrophysiological study. For this purpose, male Wistar rats were submitted to daily swimming exercise program of three different durations. Animals were swim-exercised for 90 days with either 15 minutes, 30 minutes or 60 minutes/day. Thereafter, the epileptiform activity was induced by a single microinjection of penicillin (500 units) into the left somatomotor cortex. Short-duration swimming exercise (15 min per day for 90 days) decreased the mean frequency and amplitude of penicillin-induced epileptiform activity in the 70 and 90 minutes after penicillin injection compared to penicillin administered group, respectively. Moderate-duration (30 min per day for 90 days) and long-duration (60 min per day for 90 days) swimming exercise did not alter either the frequency or amplitude of epileptiform activity. The results of the present study provide electrophysiologic evidence that short-duration swimming exercise partially inhibits penicillin-induced epileptiform activity. These data also suggest that moderate and long-duration swimming exercise do not increase either the frequency or severity of seizure in the model of penicillin-induced epilepsy.

Key words: ECoG, epilepsy, epileptiform activity, swimming exercise

INTRODUCTION

Epilepsy is one of the most common and chronic neurologic disorder worldwide. Epileptogenic processes have been associated with imbalance between excitatory and inhibitory control systems in selective regions of the brain (Brailowsky and Garcia 1999). For many years, people with epilepsy have been discouraged from participation in a regular physical activity or sport recreation for the possibility of inducing seizures or increasing seizure frequency (Denio et al. 1989, Nakken et al. 1990, Setkowicz and Mazur 2006, Arida et al. 2008). Therefore, people with epilepsy prefer sedentary life by trying to minimize their physical activity based on a common belief that physical activity exacerbates seizure, which causes a greater body weight, poorer muscle strength and lower respiratory capacity (Jalava and Sillanpaa 1997). For this purpose, clinical and experimental studies have analyzed the effect of physical exercise on epilepsy. Although, several studies from adult animals have demonstrated that different types of physical activities have many benefits for mental and physical health, the implications of exercise for epilepsy are still controversial. Long-term exercise program (15 weeks) decreased seizure frequency in women with intractable epilepsy (Eriksen et al. 1994). Four-week of intensive training caused a decrease in the occurrence of epileptiform discharges in EEG of people with epilepsy (Nakken et al. 1997). Arida and coauthors (1999) reported that the physical training did not induce epileptic seizures in the model of temporal lobe epilepsy in rats and they also showed that chronic exercise increased the threshold in the model of kindling development (Arida et al. 1998). An aerobic physical training on a treadmill reduced CA1 hyperresponsiveness and modified synaptic plasticity in the pilocarpine model of limbic epilepsy in rats (Arida et al. 2004). Furthermore, it was reported that treadmill exercise improved learning capacity by modulating hippocampal regenerative sprouting and related gene expression in a development rat model of

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penicillin-induced recurrent epilepticus (Ni et al. 2009). There are also studies reported that swimming exercise decreased the susceptibility to subsequent pilocarpine-induced seizure (Setkowicz and Mazur 2006) and pentylenetetrazole-induced seizure in male rats (Souza et al. 2009). The results of Setkowicz and Mazur (2006) proved that regular training of moderate intensity could ameliorate the course of the experimentally induced status epilepticus. The trained group showed statistically significant modifications in all behavioral parameters they described (Setkowicz and Mazur 2006). Physical training increased latency and attenuated the duration of generalized seizures induced by intraperitoneal injection of PTZ in rats (Souza et al. 2009). They also showed that physical exercise decreased the spike amplitude of EEG recordings (Souza et al. 2009). Conversely, there are some studies shows that physical exercise increased epileptic activity (Kuijer 1978, Ogunyemi et al. 1988, Ramsden et al. 2003). Kuijer (1978) observed an increase in the number of seizures during physical activity compared to daily activity. In people with epilepsy, seizures were induced and epileptiform abnormalities were activated in EEG after 25 minutes of exercise (Ogunyemi et al. 1988). Exercise caused the reproducible induction of temporal lobe seizures in two patients (Sturm et al. 2002). Even tough, the high levels of physical activity increased neuronal vulnerability via altered neurochemistry in hippocampus to kainate excitotoxicity in female rats (Ramsden et al. 2003).

The aim of this study was to determine the impact of different intensities of swimming exercise on the brain susceptibility to penicillin-induced epileptic activity. For this purpose, we decided for the first time, to investigate the effects of swimming exercises (15 min, 30 min and 60 min/day for 90 days) on penicillin-induced epileptiform activity in adult rats. We used penicillin to induce epileptiform activity in rats in the present study, which is a widely used method for inducing epileptiform activity by applying penicillin to the cerebral cortex (Holmes et al. 1987). Penicillin can also induce recurrent prolonged seizures in developmental animals (Ni et al. 2009). The application of penicillin to the neocortex results in synchronous discharge of neurons which, bears an electrophysiologic resemblance to human focal interictal epileptic discharges (Purpura et al. 1972).

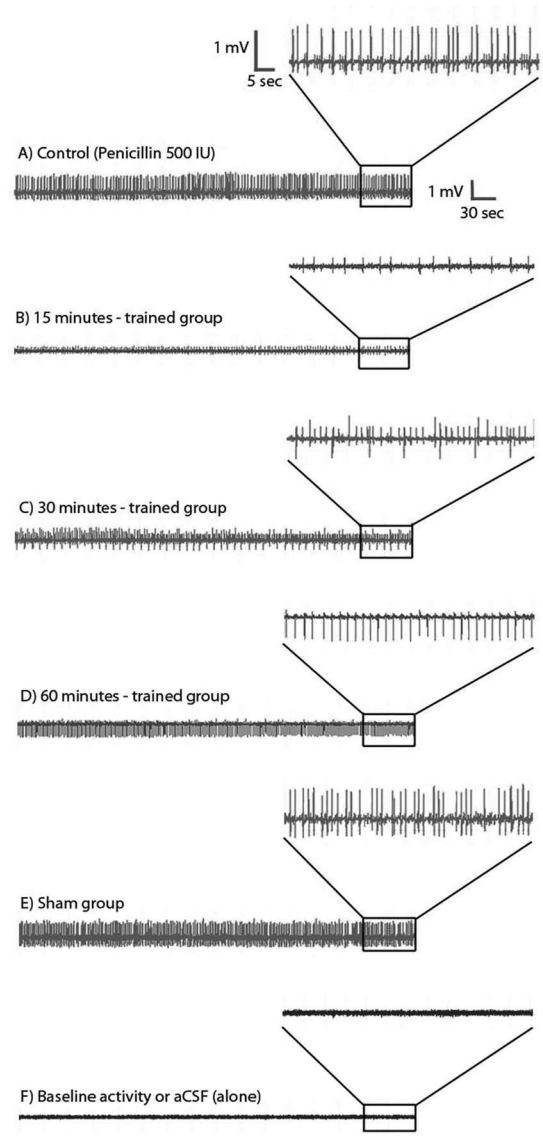

Fig. 1. (A) The intracortical injection of penicillin (500 IU) induced epileptiform activity on ECoG. (B) The mean frequency and amplitude of penicillin-induced epileptiform ECoG activity significantly decreased in the 70 and 90 minutes after penicillin injection in 15 minutes-trained group (swimming exercise 15 min per day, for 90 days), respectively. (C) The mean frequency and amplitude of penicillin-induced epileptiform ECoG activity did not change in 30 minutes-trained group (swimming exercise 30 min per day, for 90 days). (D) The mean frequency and amplitude of penicillin-induced epileptiform ECoG activity did not change in 60 minutes-trained group (swimming exercise 60 min per day, for 90 days) (E) The mean frequency and amplitude of penicillin-induced epileptiform ECoG activity did not change in adapted to water group (sham group). (F) Presents baseline ECoG activity before penicillin or the injection of aCSF.

METHODS

Adult male Wistar rats weighing 180–220 g (Ondokuz Mayis University of Turkey) were used throughout this study after at least 1 week of acclimatization. All described procedures were approved by the local ethics committee. Animals were housed in groups of 3–4 and were allowed free access to food and water, except for the short time that the animals were removed from their cages for the experiments. All animals were kept in a temperature controlled (22±1ºC) environment on a 12-h light/dark cycle. Rats were assigned to the following experiments and groups: intracortical (i.c.) delivery of (Group 1) 2.5 µl artificial cerebrospinal fluid [aCSF containing (mM): NaCl, 124; KCl, 5; KH_2PO_4, 1.2; $CaCl_2$, 2.4; $MgSO_4$, 1.3; $NaHCO_3$, 26; glucose, 10; HEPES, 10; pH 7.4 when saturated with 95% O_2 and 5% CO_2] (i.c.); (Group 2) 500 units penicillin (2.5 µl, i.c.); (Group 3) 15 minutes-trained for 90 days + 500 units penicillin (2.5 µl, i.c.); (Group 4) 30 minutes-trained for 90 days + 500 units penicillin (2.5 µl, i.c.); (Group 5) 60 minutes-trained for 90 days + 500 units penicillin (2.5 µl, i.c.); (Group 6) adapted to the water + 500 units penicillin (2.5 µl, i.c.). Each animal group was composed of seven rats.

Adaptation to the water

All animals were adapted to the water before the beginning of the experiment. The rats were kept in shallow water at 32ºC for seven days/week, from 10.00 A.M. to 12.00 A.M. for adaptation. The adaptation to the water proceeded during experimental period. The purpose of the adaptation to water was to reduce stress without promoting a physical training adaptation (Souza et al. 2009).

Exercise training program

The swimming performed in water at a temperature of 32-33ºC between 10.00 A.M -12.00 A.M. Training period lasted 90 days and consisted of 15, 30, and 60 minutes daily sessions for seven days/week without workload. Exercise performed by swimming in two training glass tanks (length 100 cm, width 50 cm, depth 50 cm) containing tap water. After 90 days swimming, rats were prepared for induction of epileptiform activity in the next training time.

Induction of epileptiform activity

The animals were anesthetized with urethane (1.25 g/kg, i.p.) and placed in a stereotaxic frame. Rectal temperature was maintained between 36 and 37ºC using a feedback-controlled heating system. A polyethylene cannula was introduced into the right femoral artery to monitor blood pressure, which was kept above 110 mm-Hg during the experiments. All contact and incision points were infiltrated with procaine hydrochloride to minimize possible sources of pain. The left cerebral cortex was exposed by craniotomy (5 mm posterior to bregma and 3 mm lateral to sagittal sutures). The epileptic focus was produced by 500 units of penicillin G potassium injection (1 mm beneath the brain surface by a Hamilton microsyringe type 701N; infusion rate 0.5 µl/min) (Kozan et al. 2009).

Penicillin was prepared in the sterile distilled water and administered intracortically in a volume of 2.5 µl.

Electrocorticography recordings

Two Ag–AgCl ball electrodes were placed over the left somatomotor cortex (electrode coordinates: first electrode, 2 mm lateral to sagittal suture and 1 mm anterior to bregma; second electrode, 2 mm lateral to sagittal suture 5 mm posterior to bregma). The common reference electrode was fixed on the pinna. The electrocorticography (ECoG) activity was continuously monitored on a four-channel recorder (PowerLab, 4/SP, AD Instruments, Castle Hill, Australia). All recordings were made under anesthesia and stored on a computer. The frequency and amplitude of epileptiform ECoG activity was analyzed off-line.

Data analysis

The results are given as the means ± standard error of the mean (SEM). Statistical differences between all groups were first checked by Kruskal-Wallis non-parametric ANOVA test. After confirmation of significance statistical differences between groups were tested by the non-parametric Mann-Whitney U-test with the Bonferroni adjustment. The level of significance was corrected according to Bonferroni in mul-

tiple comparisons among four groups (p<0.05/4 =0.0125). Statistical analyses were performed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

We used the penicillin model of epilepsy, which was previously used in our laboratory (Ayyildiz et al. 2007). As already observed in previous experiments, intracortical injection of penicillin (500 units) induced an epileptiform ECoG activity characterized by bilateral spikes and spike-wave complexes (Fig. 1A) (Ayyildiz et al. 2007, Bosnak et al. 2007). Epileptiform activity began within 2–4 min. It reached a constant level as to the frequency and amplitude in the 30 min and lasted for 3 h. The means of spike frequency and amplitude were 29±2 spike/min and 1,007± 193 μV, respectively (Fig. 1A).

Figure 2 shows the effect of physical training on the frequency of penicillin induced epileptiform activity in male rats. The mean frequency of ECoG epileptiform activity significantly decreased in the 70 minutes after penicillin injection in the group 3 compared to group 2 (Fig. 2). The mean amplitude of ECoG epileptiform activity also decreased in the 90 minutes after penicillin injection in group 3 compared to group 2 (Fig. 3). The mean frequency and amplitude of ECoG epileptiform activity did not significantly change in the group 4, group 5 swimming training groups, and group 6 compared to group 2 (Fig. 2). The mean spike frequency of epileptiform activity was 12.4±6.9, 33.2±11.8, 32.8±12.4, 30.2±6.5 spike/min, and the mean amplitude was 443±149, 714±69, 667±80, 717±17 μV after 70 minutes from penicillin injection in the group 3, group 4, group 5 swimming training groups and group 6, respectively (Fig. 1 B–E). The intracorti-

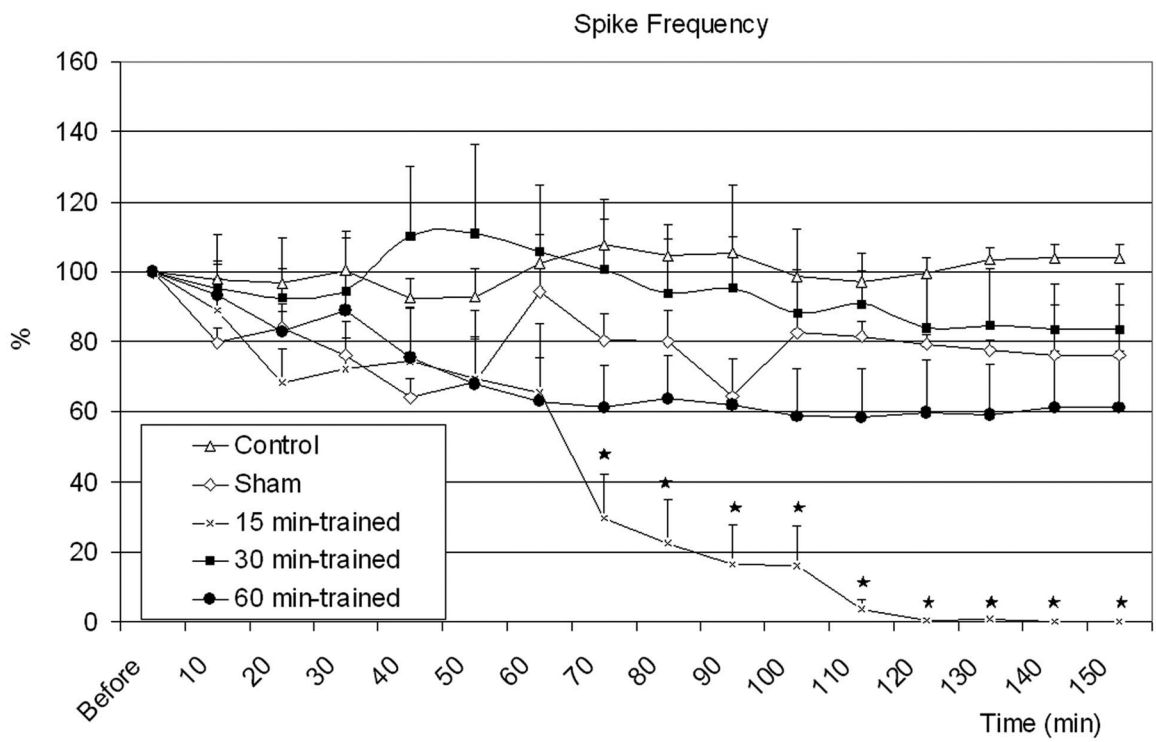

Fig. 2. The effects of swimming exercise on the mean spike frequency of penicillin-induced epileptiform ECoG activity. The mean frequency of ECoG epileptiform activity significantly decreased in the 70 minutes after penicillin injection in the 15 minutes swimming training group. The mean frequency of ECoG epileptiform activity did not significantly change in the 30 min, 60 min swimming training groups, and sham group. (*p<0.0125)

The percentage frequency of epileptiform ECoG activity value depends on both the frequency of epileptiform ECoG activity before and after 30 minutes as it is defined as:

$$\text{Frequency Value \%} = \frac{\text{The mean of spike frequency after 30 minutes}}{\text{The mean of spike frequency before 30 minutes}} \times 100$$

cal injection of aCSF (2.5 µl), did not cause any change in the frequency or amplitude of ECoG activity with respect to the control base line in the non-penicillin injected animals (Fig. 1F).

DISCUSSION

Several clinical and experimental studies have been performed to answer the question whether the physical activity influences the brain susceptibility to seizures. Although there is convincing evidence indicating that physical exercise has the positive role in reducing the frequency and severity of seizures in several models of experimental epilepsy (Arida et al. 1998, 2004, Setkowicz and Mazur 2006, Souza et al. 2009), this subject is still a matter of controversy. Therefore, we evaluated the effects of different durations of swimming exercise on penicillin induced epileptiform activity in male rats. The present study demonstrated that short-duration swimming exercise decreased the mean frequency and amplitude of epileptiform activity, whereas moderate and long- duration swimming exercise did not affect.

A variety of animal seizure models have been designed to evaluate the relationship between exercise and epilepsy. Arida and coauthors (1998) demonstrated that chronic exercise (40 min running on the treadmill at 20 m/min, 7 days per week, for 45 days) inhibited development of amygdale kindling in rats. The frequency of seizure significantly reduced in the training (40 min running on the treadmill at 20 m/min, 7 days per week, for 45 days) groups compared to control and sham groups in a model of temporal lobe epilepsy in rats (Arida et al. 1999). They also observed that after 45 days of exercise, CA1 hyperresponsiveness reduced and synaptic plasticity modifies in rats submitted to the pilocarpine model of limbic epilepsy (Arida et al. 2004). Furthermore, physical exercise (treadmill)

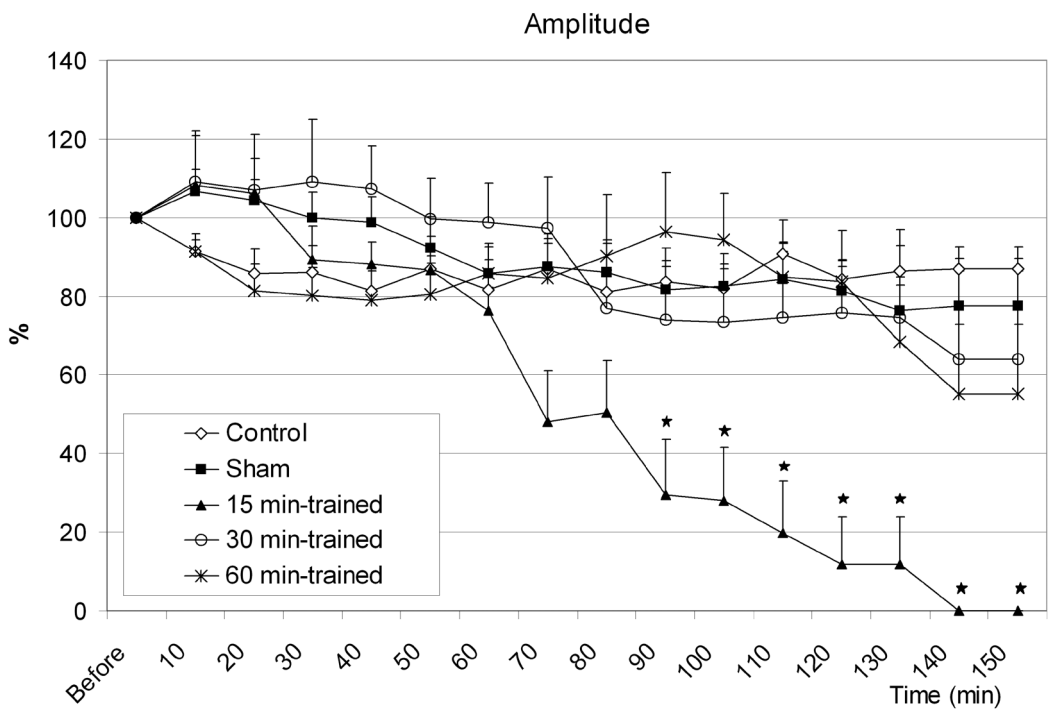

Fig. 3. The effects of swimming exercise on the mean spike amplitude of penicillin-induced epileptiform ECoG activity. The mean amplitude of ECoG epileptiform activity significantly decreased in the 90 minutes after penicillin injection in the 15 minutes swimming training group. The mean amplitude of ECoG epileptiform activity did not significantly change in the 30 min, 60 min swimming training groups, and sham group. (*p<0.0125)

The percentage amplitude of epileptiform ECoG activity value depends on both the amplitude of epileptiform ECoG activity before and after 30 minutes as it is defined as:

$$\text{Frequency Value \%} = \frac{\text{The mean of spike frequency after 30 minutes}}{\text{The mean of spike frequency before 30 minutes}} \times 100$$

improved the learning deficits caused by recurrent penicillin-induced seizures during brain development of rats by modulating GABA-A and CCK expression in hippocampus (Ni et al. 2009). However, only a few works have applied a programmed swimming exercise in the epileptic activity (Setkowicz and Mazur 2006, Souza et al. 2009). Occurrence of maximal seizures in trained group (20 min/day for 45 day) was significantly delayed and the whole time of seizure manifestation was significantly shorter than in the non-trained rats (Setkowicz and Mazur 2006). They also reported that trained group showed a significant delay of the first pilocarpine-induced symptoms (Setkowicz and Mazur 2006). Interestingly, the frequency and intensity of the symptoms considerably increased in their both trained (treadmill and swimming) groups (Setkowicz and Mazur 2006). The six weeks of swimming training (60 min per day, 5 days/week) increased the latency for the first PTZ-induced convulsion in male rats (Souza et al. 2009). In addition, swimming training decreased the occurrence of electroencephalographic (EEG) seizure activity induced by all doses of PTZ (Souza et al. 2009). However, it is important to note that only the high doses of PTZ (45 or 60 mg/kg) caused the appearance of generalized tonic-clonic seizures (Souza et al. 2009). The protection of physical training against PTZ-induced seizures strongly correlated with non-protein sulfhydryl content (Souza et al. 2009). In agreement with previous studies, the results of present study show that a short time of swimming exercise (15 min per day, for 90 days) significantly decreased the mean frequency and amplitude of penicillin-induced epileptiform ECoG activity in rats. The moderate-duration and long duration swimming exercise (30 min per day and 60 min per day, for 90 days) did not alter both the mean of frequency and amplitude of penicillin-induced epileptiform activity in the present study. In contrast, the survey of Denio and others (1989) showed that thirty-six of 66 epilepsy patients had no regular exercise; thirty of them participated in regimens of running, walking, cycling, swimming, weight lifting, aerobics classes, or martial arts on three or four occasions per week. They reported that exercise increased seizure frequency in people with epilepsy suggesting more comprehensive trial, including EEGs (Denio et al. 1989). Seizures were induced by exercise, and epileptiform abnormalities were activated by exercise in three people with epilepsy (Ogunyemi et al. 1988). Sturm and coworkers (2002) determined that temporal lobe seizures were triggered by physical activity in two patients by recording ictal and interictal EEG recordings, as well as temporal hypometabolism on PET (Sturm et al. 2002). Kuijer (1978) also showed an increased in paroxysmal abnormality on EEG and seizure in the period after exercise. Nakken and colleagues (1990) noted seizures only in 6 patients of 21 with epilepsy during 4 week intensive physical training program (45 min three times a day) without recording EEG. However, most of the seizures during the training period occurred when the patients were resting in their study (Nakken et al. 1990). Moreover, physical exercise increased the neuron loss associated with kainate lesion in hippocampal region CA2/3 of female rats (Ramsden et al. 2003). They did not found an apparent relationship between the level of exercise and the extent of neuron loss in hippocampus (Ramsden et al. 2003). It is important to note that moderate and long-duration of swimming exercise did not cause an increase in the frequency and amplitude of epileptiform activity in the present study.

The imbalance between excitatory and inhibitory control system in brain was suggested as one of the main reason for epileptogenic processes (Corda et al. 1991, Löscher 1993). Macdonald and Barker (1977) reported that even, at low concentrations, penicillin specifically blocks synaptic transmission by the inhibitory neurotransmitter. Furthermore, Tsuda and coauthors (1994) suggested that penicillin exerts its proconvulsant effect by inhibiting GABA-gated chloride ion influx. On the other hand, it is well established that physical exercise is able to alter the release of neurotrophins, neurotransmitters, and neuropeptides in different brain areas including prefrontal cortex (Chaouloff et al. 1987, Neeper et al. 1995, Arida et al. 2009). Therefore, the type of physical exercise may produce different effects on brain function (Brown et al. 1979, Vissing et al. 1996). Souza and others (2009) suggested that the increase of antioxidant defenses and reduction of basal production of oxidants elicited by physical training may protect against Na^+, K^+-ATPase inhibition induced by PTZ. Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) release during moderate and long-term physical training (Widenfalk et al. 1999, Cotman and Berchtold 2002). An antiepileptic role of BDNF has been reported via triggering expression of neuropeptide Y (NPY) in the different models of epilepsy (Takahashi et al. 1999, Vezzani et al. 1999). In addi-

tion, long-term exercise activity enhances the ability to synthesize NPY (Scott and Crutcher 1994, Levenson and Moore 1998). It is also well established that NPY has anticonvulsant properties in various experimental models of epilepsy, including electrically- and chemically-induced seizures tests (Woldbye et al. 1996, Nagaki et al. 2000, Silva et al. 2005). NPY may also regulate the spread of excitability into other brain structures via tonic inhibition of glutamate (Schwarcz and Meldrum 1985, Xapelli et al. 2006, Noè et al. 2008). However, we have not determined the certain mechanism of these effects in the present study. Therefore, further more advanced electrophysiologic and neurochemical studies are required to determine the mechanisms involved.

CONCLUSIONS

The present study evidences for the first time that short-duration, long-term swimming exercise decreased the mean frequency and amplitude of penicillin-induced ECoG epileptiform activity, suggesting an interaction between swimming exercise and model of penicillin-induced epileptiform activity used in this study. Moderate-duration and long- duration, long-term swimming exercise did not affect either the frequency or amplitude of epileptiform activity. These results suggest that swimming exercise; including long-duration does not increase either the frequency or amplitude of epileptiform actvivity at least, in the penicillin model of epilepsy.

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