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EFFECTS OF AN EXTRACT OF *SALVIA MILTIORRHIZA* ON A PENICILLIN-INDUCED EPILEPSY MODEL IN RATS

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In a penciling-induced epilepsy model, Wistar rats (16 males, 16 females) were i.p. administered by an extract of *Salvia miltiorrhiza* (SmE; total dose 50mg/kg) once a day, during 15 days. The rats were divided into four equal groups, control and SmE-treated for each sex. After the treatment period, an epilepsy model was produced by penicillin G (500 IU) injection into the motor cortex; the electrocorticogram (EcoG) was recorded for 120 min, and statistical analysis was performed. In the male control group with penicillin-induced epilepsy, the spike frequency was significantly ($P < 0.05$) higher than that in the female control group. The frequency values have been significantly ($P < 0.01$) increased within the observation period in the female SmE-treated group, while the respective values significantly ($P < 0.05$) decreased in the analogous male group. There were insignificant differences in the amplitude values and latency to onset of the spike/wave events between female/male SmE and female/male control groups ($P > > 0.05$). Thus, the SmE exerts anticonvulsant effects in the male rat group, while its effect should be characterized as proconvulsant in the female group in penicillin-induced epilepsy model. The difference (related to the presence of estrogen analogs in the SmE) is determined by dissimilar hormonal backgrounds in males and females. The SmE may be considered the base for development of anticonvulsant drugs for clinical therapy of epilepsy in the future.

Keywords: *Salvia miltiorrhiza*, electrocorticography, penicillin-induced epileptiform activity, rats.

INTRODUCTION

Epilepsy is one of the most serious neurological disorders, and the disease is observed at a high incidence in the world [1, 2]. A number of studies have been devoted to the pathogenesis of epilepsy. Epilepsy is determined by abnormally excessive and/or higher-synchronized neuronal activity in the brain. The mechanism underlying these events can be determined as excessive excitation and/or insufficient inhibition in the brain areas where the abnormal discharges start. Thus, the uncontrolled and abnormally synchronized electrical discharges can occur as a result of increased glutamate release (which is an excitatory neurotransmitter) and/or decreased GABA release (which is an inhibitory neurotransmitter) in one or more brain areas [3]. Epileptic seizures are transient events accompanied by the epilepsy symptoms. In many reports, it was shown that there are considerable sex differences in the sensitivity to diverse convulsants in animal models [4–7].

Different experimental studies in animal models play an important role in the research of the epilepsy pathogenesis; epileptic seizures are mimicked in these models [8,9]. A penicillin-induced experimental model of epilepsy has been frequently utilized by various researchers. Penicillin applications cause acute focal epileptic activity similar to the epileptic activity related to the above-mentioned imbalance between inhibitory and excitatory neurotransmitters [10–13].

A *Salvia miltiorrhiza* extract (SmE) contains considerable amounts of acetylcholinesterase (AChE)

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and butyrylcholinesterase (BChE); this extract is a promising mean in the treatment of various disorders of the CNS. As was shown, this extract positively influences memory and other cognitive activities [14-16]. The SmE has been used as an antihydrotic, spasmolytic, antiseptic, and anti-inflammatory mean in the treatment of mental and neurological disorders [16, 17]. Some authors reported on its antioxidant properties, which is essential for scavenging free radicals (due to the presence of phenolic compounds such as carnosic, rosmarinic, caffeic, salvianolic acids, and other phenolic structure-based compounds) [18-22]. Various types of this extract demonstrated antibacterial, cytotoxic, and antiviral effects [23]. Additionally, SmE showed a cardioprotective effect (against ischemic injuries); an important property of this extract is that it provides vasodilation in the coronary arteries [24]. Furthermore, as was found in several studies, SmE contains estrogen-derived compounds. As was shown, estrogens reduce seizure-induced cell death, whereas these compounds can facilitate the onset of seizures [16, 25, 26].

According to our knowledge, the effects of SmE on epileptiform activities have not been investigated; this, in particular, is related to the sex differences in an experimental penicillin-induced rat epilepsy model. We tried to evaluate the effects of this mean on the model of epileptic activity in the groups in both female and male rats.

METHODS

Animals, Experimental Procedure, and SmE Extract Treatment. Thirty-two Wistar albino rats (aged 4-5 months, body mass 200-250 g) were used in the experiments. They were maintained at a 12 h light-dark cycle, with free access to standard laboratory food and water. The rats were housed in metabolic cages at a temperature of 22 ± 2 °C and relative humidity of 50-60%; their body temperature was maintained around 37 ± 0.5 °C during the study. The rats were separated into the following four groups, 8 animals in each group: group 1, female control group treated with physiological (0.9%) saline (0.5 ml, i.p); group 2, female SmE-treated group (SmE, 50 mg/kg, i.p); group 3, male control group treated with physiological saline (0.5 ml, i.p), and group 4, male SmE-treated group (SmE, 50 mg/kg, i.p).

The SmE was supplied by the University of Abant Izzet Baysal, (Dept. of Biology). The ethanolic SmE was prepared according to the technology described by Eidi et al. [27]. Treated groups received i.p injections of the extract once a day during 15 days up to the 50 mg/kg total dose.

Penilicin G-Induced Epilepsy Model and Electrocorticography. After 15-day-long treatment with SmE or saline, all rats were weighed, anesthetized with 1.20 g/kg urethane (Sigma Aldrich, USA, i.p), and immobilized in a streotaxic apparatus (Harvard Apparatus, USA). The scalp was incised rostro-caudally approximately 2-4 cm in length, and a hole (2 mm in diameter) was drilled 1.5 mm left from the bregma; the bone particles and *dura mater* were carefully removed.

The left cerebral cortex was exposed. Then, two Ag-AgCl ball electrodes were placed over the left motor cortex (2 mm lateral to the sagittal suture, 1 mm anterior, and 5 mm posterior to the bregma). The common reference electrode was fixed on the left pinna. The ECoG signals were amplified and filtered (0.1-50 Hz bandpass) using BioAmp amplifiers (AD Instruments, Australia) and digitized at a sampling rate of 1024 sec^{-1} using a four-channel data acquisition system (PowerLab 8/SP; AD Instruments, Australia). The baseline activity in each group was recorded within initial five minutes.

An epileptiform activity was induced by intracortical injection of 2.5 ml penicillin G (500 IU, Merck, USA) in all rats. Using a Hamilton injector (type 701 N; USA), penicillin was injected into the left sensorimotor cortex (2 mm posterior to the bregma, 3 mm lateral to the sagittal suture, and 2 mm ventral to the brain surface) at an infusion rate of 0.5ml/min. The ECoG activity was continuously recorded during 120 min, displayed, and stored using a computer. The frequency (sec^{-1}) and amplitude (mV) values of spike/wave complexes and the latency (min) of onset of the first spike/wave event for each animal were automatically measured using a data acquisition Chart v.5.1.1 system (PowerLab software; AD Instruments, Australia) and analyzed offline.

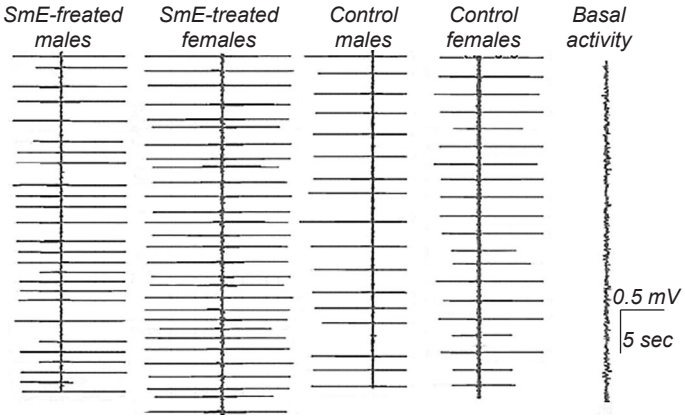
Statistical Analysis. The frequency (sec^{-1}), amplitude (mV) values for spike/wave complexes and the latency (min) to onset of the first spike/wave activity were gathered from animals in all groups and converted to a scaling percentage in a time-dependent manner. All statistical procedures were performed using Statistical Package for the Social Science (SPSS) version 15.0 (SPSS Inc., USA). Numerical data are expressed below as means ± s.d. The data were analyzed by one-way analysis of variance (ANOVA)

followed by the least significant difference (LSD) *post hoc* test for multiple comparisons. Statistical significance was accepted at $P < 0.05$.

RESULTS

Effects of SmE on Penicillin G-Induced Epileptiform Activity. Penicillin-induced epileptiform discharges were characterized by bilateral spikes and spike/wave complexes generated against the background ECoG activity. Epileptic activity reached a constant level in 30 min after the administration of penicillin G and lasted for 3-5 h. The SmE was last time injected 30 min after injection of penicillin (Fig. 1).

As was mentioned above, the frequency and amplitude of spike/waves and the latency to onset of the fist spike/wave were calculated from the



F i g. 1. Changes in ECoG activity after administration of penicillin G in the SmE-treated and control animals.

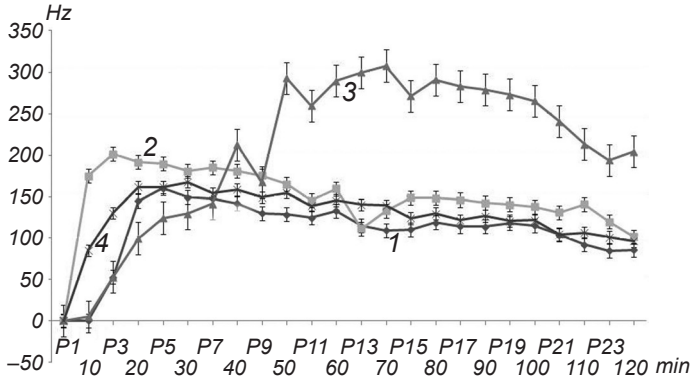
Р и с. 1. Зміни ЕКоГ-активності після введення пеніциліну G у контрольних тварин та тих, котрим уводили SmE.

T a b l e 1. Spike-wave frequency (Hz) in the control and *Salvia* extract-treated groups

Т а б л и ц я 1. Середні значення частоти в комплексах пік–хвиля у контрольних тварин та тих, яким уводили екстракт шавлії

Time, min	Female control (n= 8)	Female SmE group (n = 8)	Male control (n = 8)	Male SmE group (n = 8)
5	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10	0.0 ± 0.0[a]	174.0 ± 35.0[a]	5.0 ± 4.5[b]	84.8 ± 21.8[b]
15	52.5 ± 8.9[a]	200.8 ± 22.2[a]	52.4 ± 31.0[c]	129.8 ± 28.3[c]
20	144.2 ± 11.9	191.0 ± 24.3	99.3 ± 34.7	160.7 ± 19.5
25	159.6 ± 16.8	188.8 ± 27.9	123.8 ± 35.2	160.8 ± 11.0
30	148.9 ± 14.6	180.0 ± 26.3	129.2 ± 28.2	166.8 ± 10.0
35	147.3 ± 13.3	184.6 ± 20,9	140.7 ± 27.2	153.4 ± 7.1
40	141.5 ± 9.6	180.0 ± 13.6	211.8 ± 45.5	158.0 ± 17.3
45	129.7 ± 8.9	174.6 ± 16.6	166.7 ± 35.6	148.5 ± 17.5
50	128.0 ± 10.4	164.3 ± 17.2	292.4 ± 71.3[d]	154.2 ± 17.8
55	124.0 ± 12.6	144.6 ± 15.0	258.8 ± 27.2[e]	138.5 ± 20.9
60	132.5 ± 23.1	158.8 ± 21.8	288.8 ± 28.1[e]	144.8 ± 19.4
65	114.2 ± 15.3	111.0 ± 23.1	299.3 ± 31.4[e]	139.7 ± 18.6
70	108.7 ± 14.8	132.5 ± 14.5	307.3 ± 33.5[e]	138.7 ± 18.2
75	109.8 ± 10.8	148.3 ± 26.9	270.6 ± 37.4[e]	123.5 ± 22.6
80	118.2 ± 14.9	147.5 ± 26.7	290.3 ± 42.5[e]	129.1 ± 20.2
85	114.0 ± 19.1	145.5 ± 26.2	282.7 ± 45.0[e]	121.1 ± 16.3
90	113.3 ± 28.4	141.8 ± 23.5	278.2 ± 44.3[e]	126.2 ± 20.9
95	117.7 ± 34.7	139.6 ± 26.1	272.2 ± 45.4[f]	120.4 ± 19.8
100	114.7 ± 33.0	137.3 ± 29.7	264.8 ± 47.0[f]	121.1 ± 18.4
105	103.7 ± 27.8	130.5 ± 32.0	240.0 ± 49.8[f]	104.0 ± 19.0
110	91.8 ± 23.5	140.1 ± 40.9	212.6 ± 45.6[g]	106.1 ± 18.9
115	84.3 ± 22.3	119.3 ± 30.6	193.1 ± 44.8[g]	100.7 ± 18.0
120	85.3 ± 20.4	101.0 ± 20.9	203.5 ± 45.3[e]	96.1 ± 13.3

All values are shown as means ± s.d. for each group; n is the number of examined rats. Comparisons: (a) female control vs female SmE group ($P < 0.01$); (b) male control vs male SmE ($P < 0.01$); (c) male control vs male SmE ($P < 0.05$); (d) male control vs other groups ($P < 0.05$); (e) male control vs other groups ($P < 0.01$); (f) male control vs female control and male SmE groups ($P < 0.01$); (g) male control vs female control and male SmE groups ($P < 0.05$).



F i g. 2. Values of the spike/wave frequency (Hz) in the control and SmE-treated groups.

Р и с. 2. Динаміка частоти комплексів пік–хвиля в контрольних групах та групах, котрим уводили SmE.

recorded ECoGs. In the male control group, the spike/wave frequency was significantly ($P < 0.05$) higher than that in the female control group. In the female SmE-treated group, the spike/wave frequency significantly ($P < 0.01$) exceeded the respective index in the female control group within nearly entire period of observation. At the same time, the spike/wave frequency in the male SmE-treated group was significantly ($P < 0.01$) lower than that in the male control group at most examined time intervals. Finally, the spike/wave frequency was significantly ($P < 0.01$) greater in the female SmE-treated group as compared with the value that has been significantly ($P < 0.05$) decreased in the male SmE-treated group (Fig. 2, Table 1). In other words, SmE exerted an anticonvulsant effect in the male group, while the proconvulsant effect was observed in the female group in the penicillin G-induced epilepsy model.

When we evaluated the effect of SmE on the spike/wave amplitude values (mV), we found no significant differences among all groups at most time intervals of observation ($P > 0.05$), although this amplitude in the male control group was higher significantly ($P < 0.05$) than that in the female control group at the 20th min of the period of recording (Table 2, Fig. 3).

When we also evaluated the effect of SmE (according

T a b l e 2. Amplitudes of the spike-wave complexes (mV) in the control and SmE-treated groups

Т а б л и ц я 2. Середні значення амплітуд комплексів пік–хвиля у контрольних тварин та тих, яким уводили екстракт шавлії

Time (minutes)	Female control ($n = 8$)	Male control ($n = 8$)	Female SmE group ($n = 8$)	Male SmE group ($n = 8$)
5	0.40 ± 0.1	1.21 ± 0.7	0.72 ± 0.1	0.76 ± 0.1
10	0.40 ± 0.1	1.25 ± 0.8	1.65 ± 0.3	1.05 ± 0.2
15	0.40 ± 0.1	1.86 ± 0.9	2.01 ± 0.4	1.50 ± 0.2
20	0.33 ± 0.1[a]	2.48 ± 1.1[a]	2.18 ± 0.4	1.63 ± 0.2
25	1.85 ± 0.2	2.42 ± 1.0	2.30 ± 0.4	1.80 ± 0.3
30	2.55 ± 0.3	2.72 ± 1.1	2.17 ± 0.3	1.82 ± 0.3
35	2.96 ± 0.4	2.76 ± 1.0	2.33 ± 0.5	1.88 ± 0.3
40	3.10 ± 0.4	3.08 ± 1.0	2.21 ± 0.4	1.93 ± 0.3
45	3.27 ± 0.5	3.02 ± 1.0	2.40 ± 0.5	1.98 ± 0.3
50	3.26 ± 0.5	3.25 ± 1.0	2.27 ± 0.4	2.00 ± 0.3
55	3.25 ± 0.5	3.23 ± 0.9	2.26 ± 0.4	2.00 ± 0.3
60	3.17 ± 0.5	3.40 ± 1.0	2.31 ± 0.4	2.07 ± 0.3
65	3.19 ± 0.5	3.36 ± 0.9	1.84 ± 0.2	1.83 ± 0.3
70	3.03 ± 0.5	3.34 ± 0.9	1.77 ± 0.2	1.89 ± 0.3
75	2.93 ± 0.5	3.00 ± 0.9	1.82 ± 0.3	1.99 ± 0.3
80	2.92 ± 0.4	3.11 ± 0.9	1.84 ± 0.3	1.96 ± 0.3
85	2.79 ± 0.4	3.00 ± 0.9	1.92 ± 0.3	1.97 ± 0.3
90	2.83 ± 0.4	3.03 ± 0.9	1.79 ± 0.3	2.00 ± 0.3
95	2.64 ± 0.4	2.87 ± 0.9	1.94 ± 0.4	2.00 ± 0.3
100	2.55 ± 0.5	2.82 ± 0.9	1.92 ± 0.4	1.98 ± 0.2
105	2.70 ± 0.5	2.91 ± 0.9	1.86 ± 0.5	1.89 ± 0.3
110	2.69 ± 0.5	2.96 ± 0.9	1.98 ± 0.5	1.95 ± 0.3
115	2.61 ± 0.5	2.87 ± 0.9	1.60 ± 0.4	1.94 ± 0.3
120	2.58 ± 0.5	2.80 ± 0.8	1.66 ± 0.4	1.90 ± 0.3

(a) Comparision of the female control *vs* male control group ($P < 0.05$). Other designations are similar to those in Table 1.

to the sex groups) on the latency (sec) to onset of the first spike/wave event, there was an insignificant difference ($P > 0.05$) between the mean value of this index in the female SmE group (288.50 ± 46.15 sec) and female control group (246.25 ± 98.27 sec). In the male groups, there was also no significant difference ($P > 0.05$), while the value in the male SmE group (635. 42 ± 344.21 sec) was smaller than in the male control group (757. 5 ± 461.36 sec). However, the spike/wave latency in the SmE-treated group (635.42 ± 344.21 sec) was significantly longer ($P < 0.05$) than this time index in the female SmE group (288.50 ± 46.15 sec) of rats. The analogous difference between the latencies to onset of the first spike/wave was observed in the control groups (757.5 ± 461.36 sec *vs* 246.25 ± 98.27 sec in females; $P < 0.01$).

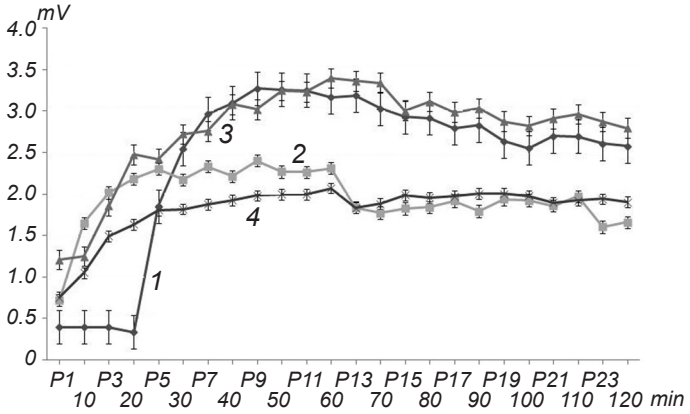


Fig. 3. Values of the amplitude of the spike/wave complexes (mV) in the control and SmE-treated groups.

Рис. 3. Динаміка амплітуди комплексів пік–хвиля в контрольних групах та групах, котрим уводили *SmE*.

DISCUSSION

Epilepsy is a common chronic neurologic disorder characterized by spontaneous recurrent seizure events in various cerebral regions [1, 2]. So far, many researchers tried to discover the pathogenetic mechanism of epilepsy, but this problem has not been finally resolved. In general, the development of epilepsy is based on excessive excitation and/or excessive inhibition in one or another brain area, and this situation results in uncontrolled and abnormally synchronized electrical discharges in the brain neuronal networks. Increased glutamate and/or decreased GABA releases probably cause these events [3]. In many studies, the existence of sex-related differences in the sensitivity to various convulsants was demonstrated in animal models of epilepsy [4-7].

Previous studies suggested that chemoconvulsants act on the GABA receptor complexes, and binding sites for different convulsants are dissimilar. Sex- and species-related differences for such GABA-related convulsants as bicuculline and picrotoxin were found in animal experiments [5, 28-30]. Sex and levels of sexual hormones affect the incidence and severity of seizures [26, 31, 32]. In animal models of different experimental epileptiform states, the effects of testosterone, progestrone, and estrogen were shown to be considerably different [26]. For example, progestrone exerts an anticonvulsant effect in females, while in males the effect should be characterized as proconvulsant [33]. Testosterone has a proconvulsant effect in females, while testosterone exerts an anticonvulsant action in males in experimental animal studies [34-36]. However, it was reported in some communications that the effects of estrogen are excitatory, while those of progesterone are inhibitory [37-40].

At present, pharmacological therapies use various anticonvulsant medications, but most these therapies remain insufficient to prevent epileptic seizures completely. Naturally, it is necessary to search for new more effective and safer therapeutic agents. Some studies have shown that *Salvia miltiorrhiza* contains important substances effective in CNS disorders. The extract of this plant provides positive effects on memory and other cognitive activities [14-16]. In many works, it was demonstrated that SmE can be used as an antihydrotic, spasmolytic, antiseptic, and anti-inflammatory mean in the treatment of mental and nervous disorders [16, 17]. Our study is, probably, the first where the effects of SmE on the penicillin G-induced experimental epilepsy model in rats have been examined. It was found that estrogen reduces seizure-induced cell death, while it facilities the onset of seizures [16, 25, 26]. Considering that SmE contains estrogen-derived compounds, we investigated the pro- vs. antiepileptic properties of this mean between the groups of female and male rats in the penicillin model of epilepsy.

In our study, focal epilepsy was produced in rats by penicillin G administration into the sensorimotor cortex. We measured the frequency of generation and amplitude values of spike/wave complexes and latencies of their onset in ECoG in SmE-treated and control animals. Our results indicated that the spike/wave frequency increased in the female SmE-treated

group, while this value decreased in the analogous male group. In addition, we found under conditions of the penicillin G-induced epilepsy model that the spike/wave frequency in the male control group was higher than that in the female control group (Table 1, Fig. 2). In conclusion, these results suggest that SmE provides a considerable anticonvulsant effect in the male group, while the effects should be characterized as proconvulsant in the female group. Thus, the effect of SmE treatment on penicillin G-induced epileptiform activity is clearly sex-specific.

When we evaluated the effect of SmE on the spike/wave amplitude, we found no significant difference among all groups within most time periods ($P > 0.05$), although the amplitude value in the male control group was higher significantly ($P < 0.05$) than that in the female control group at the first 20th min of recording of the activity (Table 2, Fig. 3). As to the latency to onset of the first spike/wave, there were no significant differences ($P > 0.05$) between the female SmE group and female control group. In the male groups, there was also no statistical difference ($P > 0.05$). On the other hand, i.p injections of SmE in male rats significantly increased ($P < 0.05$) the respective values, as compared with the female SmE group. The mean latency to onset of the first spike/wave complex in the male control group was significantly ($P < 0.01$) longer than that in the female control group.

These data indicate that SmE extract exposure has not been generated any effect on the latency to onset of the first spike/wave between the female or male SmE-treated groups. However, rat females demonstrated increased sensitivity of epileptiform activity on account of the latency to onset of the first spike/wave. In both male SmE-treated and male control groups, the latency to onset of the first spike/wave was significantly longer than that in the female SmE-treated and control groups.

We propose that the anticonvulsant activity of SmE extract could be attributed to the interaction of active compounds (such as flavonoid derivatives) with benzodiazepine (BDZ) sites of $GABA_A$ receptors in brain tissue. Active structural components that bind to the chloride channels of the $GABA_A$/BDZ receptor complex may be considered active inhibitory agents influencing the CNS. This is why the $GABA_A$/BDZ receptor system should be significantly involved in the formation of the antiepliептic effects of SmE. A methanolic extract of *Salvia* was shown to exert a strong inhibitory effect on adenylate cylase (AC) in the rat somatomotor cortex. However, we could not explain the mechanism by which the SmE provides proconvulsant effects in the female group. We did not examine the relationship between the effect of SmE and the hormone levels, such as the estradiol (E2) prostaglandin alpha (PGFα) contents in the rat plasma, as well as interrelations of these indices with epileptiform activity. Other SmE-induced effects, such as changes in the index of cell death in different experimental groups, and increased expression of ATP-dependent potassium channel (K-ATP) proteins related to an estrogen effect, should be examined, and the respective results may help ones to interpret the mechanisms of anti- and proconvulsant effects of SmE in the above-mentioned groups treated with this extract.

In conclusion, our results support the hypothesis that the extract of *Salvia miltiorrhiza* (SmE) may be used in the future as a base for potential anticonvulsant drugs for clinical therapy of epilepsy. Further studies on structure-activity relationship between the components of the SmE are needed in order to explain the mechanisms of modulation of epileptiform activity manifested by this drug. The same can be told on the dose-dependence of the SmE effects and specificity of these effects with respect to sex groups.

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All experimental protocols were in agreement with the Ethics Committe guidelines of the Abant Izzet Baysal University and also in accordance with the statements of the Guide for Care and Use of Laboratory Animals of the National Institutes of Health.

The authors of this study, A. Bahadir, S. Demir, H. Orallar, E. Beyazcicek, and F. Oner, confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВПЛИВИ ЕКСТРАКТУ ІЗ *SALVIA MILTIORRHIZA* НА ІНДУКОВАНУ ПЕНІЦИЛІНОМ МОДЕЛЬНУ ЕПІЛЕПТИЧНУ АКТИВНІСТЬ У ЩУРІВ

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Р е з ю м е

В умовах моделювання епілептичної активності (індукція інтракортикальним уведенням пеніциліну) щурам лінії Вістар (16 самців і 16 самиць) уводили екстракт шавлії (*Salvia miltiorrhiza* extract, SmE, загальна доза 50 мг/кг, щоденні ін'єкції протягом 15 діб). Щури були поділені на чотири рівні групи – контрольні та піддані ін'єкціям SmE самці та самиці. Після періоду введень екстракту епілептиформна активність індукувалась уведенням (500 МО) пеніциліну G у моторну кору, після чого відводили електрокортикограму (ЕКоГ) протягом 120 хв та піддавали її статистичному аналізу. В контрольній групі самців частота в ЕКоГ-комплексах пік–хвиля була вірогідно вищою ($P < 0.05$), ніж така в контрольній групі самиць. Значення частоти істотно зростали ($P < 0.01$) у групі самиць котрим уводили SmE, тоді як відповідні значення в аналогічній групі самців вірогідно зменшувалися ($P < 0.05$). Не було виявлено істотних відмінностей між середніми значеннями амплітуд комплексів пік–хвиля та латентних періодів виникнення таких комплексів у групах самиць та самців, котрим уводили SmE, та аналогічних контрольних груп самиць і самців ($P > 0.05$). Отже, SmE проявляє протисудомні впливи в умовах пеніцилінової моделі епілепсії в групі самців-щурів, тоді як у групі самиць ефекти мають кваліфікуватись як просудомні. Різниця в характері впливів, зумовлена наявністю аналогів естрогенів у SmE, визначається різним гормональним фоном у самиць і самців. SmE може розглядатись як основа для розробки антиконвульсантних засобів для терапії епілепсії в майбутньому.

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