UDC 616.8:615.322

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GENDER SPECIFICITY OF GENISTEIN TREATMENT IN PENICILLIN-INDUCED EPILEPTIFORM ACTIVITY IN RATS

Received December 25, 2015

We investigated gender-dependent differences of genistein (isoflavone phytoestrogen) treatment in a penicillin-induced experimental epilepsy rat model. Twenty-eight adult Wistar Albino rats (14 females and 14 males) were devided into four groups, control and genistein-treatmed males and females. Genistein (100 μg/kg, i.p) or saline was given during 15 days before the electrocorticography (ECoG) recordings. The epileptiform activity was induced by penicillin G potassium solt (500 IU, i.c) injections into the left somatomotor cortex. Significant differences among the groups were found in the latency to onset of epileptiform activity. This value in the female control group was significantly longer than the latencies in the male control, male genistein, and female genistein groups (respectively, $P = 0.002$, 0.015, and 0.032). There were no significant differences regarding the spike/wave frequencies and amplitudes in epileptiform activity between female/male genistein and control groups within all observation intervals ($P > 0.05$). Thus, genistein exerts a proconvulsant effect in the penicillin-induced epilepsy model, and the effect demonstrates the clear gender specificity related to the specificity of hormonal backgrounds in males and females.

Keywords: genistein, epileptiform activity, electrocorticography (ECoG), penicillin, rat.

INTRODUCTION

Epilepsy is one of the most common neurological diseases with a high incidence in the world. The disease is based on changes in the neuronal excitation/inhibition balance. It is usually characterized by the occurence of prolonged recurrent and unprovoked seizures [1]; this is mostly related abnormal hypersynchronous electrical activity of cerebral cortical neurons [2]. The development and manifestations of epileptiform activity are, to a significant extent, based on alteration of GABAergic transmission; it should be taken into account that GABAergic transmission could be responsible for both seizure-suppressing and seizure-promoting actions [3]. Despite extensive research of epilepsy and the respective seizure mechanisms, successful mechanism-based treatment approaches have not been developed until now. Many researchers examine and try to understand the pathogenesis of epilepsy using different experimental epilepsy models, including the penicillin-induced epilepsy model [4, 5].

The mentioned disease is more complicated in women compared to that in men; there are some interactions between epileptic manifestations and the level of female hormones [6, 7]. There are indication that sex gonadal hormones of both females and males exert significant effects on the neuronal excitability and seizure suspectibility in epilepsy. Thus, effects of gender specificity should be taken into account in different experimental epilepsy models [7–9]. In this context, some clinical and experimental studies have been declared that estrogen hormones provide proconvulsant effects, while progesterone exerts an anticonvulsant effect on epileptic seizures [8–10]. However, the data on the effects of estrogens on epileptiform activity are controversial [9–13]. Results of both clinical and experimental studies indicated that estrogens are mostly proconvulsant effects [9–11], while others reports emphasized the predominance of anticonvulsant effects [12, 13]. Opposite effects of estrogens may depend on many factors, such as a hormone type, differences between

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natural or synthetic hormone preparations, regional distiribution of hormone receptors, treatment duration, estrogen dose, hormonal status, regions of the nervous or neurotransmitter systems involved, seizure type in the model used, and sex [7, 13].

Phytoestrogens are rather similar in their effects to animal estrogen; they can directly bind to estrogen receptors (ERs) mainly ERβ. These compounds mimic estrogen functions in particular modulation of gene expression. Isoflavone phytoestrogens can act as agonists or antagonists of ERs. These substances manifest estrogenic and/or anti-estrogenic properties owing to phenolic rings in the chemical structure of their molecules. Genistein (4', 5,7-trihidroksiflovan) is an isoflavone phytoestrogen; its main source are soybeans. Isoflavones, particularly genistein and daidzein, have agonist, with respect to estrogen, effects; they selectively bind to ERs and mimick some effects of estrogen [14]. Thus, these agents were proposed to be used as an alternative to natural compounds in estrogen replacement theraphy (ERT). It was also shown that genistein exerts inhibitory effects on protein tyrosine kinase (PTK), which plays an important role in intracellular signal pathways, via modulation of the functions of ion channels [15, 16]. Additionally, genistein was reported to exert a negative regulatory effect on GABA activity [17].

The aim of our study was to investigate the effects of genistein with special attention to gender-dependent differences in the action of this phytoestrogen, observed in a penicillin-induced experimental epilepsy model in rats.

METHODS

Animals. Experiments were performed on 28 adult Wistar albino rats (14 females and 14 males) weighing 300-350 g. Animals were housed three to four per cage under a 12 h light/dark cycle at room temperature of 22-25°C and 40-50% humidity, with free access to water. The rats were kept at 80-85% of their free-feeding body mass during the experiment.

Chemicals and Experimental Groups. Genistein (> 97%) was purchased from Sigma Aldrich (USA) and dissolved in dimethyl sulfoxide (DMSO). Booth genistein and saline (control) were given i.p. during a 15-day-long treatment period in the genistein and saline groups, respectively. The epileptiform activity was induced by 2.5 µl intracortical penicillin G potassium injection (500 IU, Sigma Chemical, USA) to all rats.

In our study, a relatively low dose (100 µg/kg, i.p.) genistein not showing any cytotoxic and apoptotic effects was used, as previously reported [18]. Animals were divided into two main groups, male and female ones (M and F). Each gender group was additionally divided into two groups, control and genistein treated (C and G). Thus, animals were randomly divided into the following four equal groups (n = 7 in each), MC, MG, FC, and FG.

Electrocorticography. All rats were anesthetized with 1.2 g/kg urethane (Sigma Aldrich, USA, i.p) and placed in a stereotaxic apparatus (Harvard Apparatus, USA) before surgical operation. After controlling the anesthesia depth, eye and claw reflexes were checked. An incision (length 2-4 cm) was made on the skull in the rostro-caudal direction. The left cerebral cortex was exposed by craniotomy (2 mm posterior to the bregma and 3 mm lateral to the sagittal line); bone particles and *dura mater* were carefully removed. Two Ag/AgCl ball electrodes were placed over the left somatomotor cortex (first electrode, 2 mm lateral to the sagittal suture and 1 mm anterior to bregma, second electrode, 2 mm lateral to the suture and 5 mm posterior to the bregma). The common reference electrode was fixed on the left pinna.

The ECoG activity was continuously monitored on a recorder (PowerLab 8/SP, AD Instruments, Australia); ECoG signals were amplified and filtered (0.1-50 Hz bandpass) using BioAmp amplifiers (AD Instruments, Australia) and digitized at a sampling rate 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 the first 5 min.

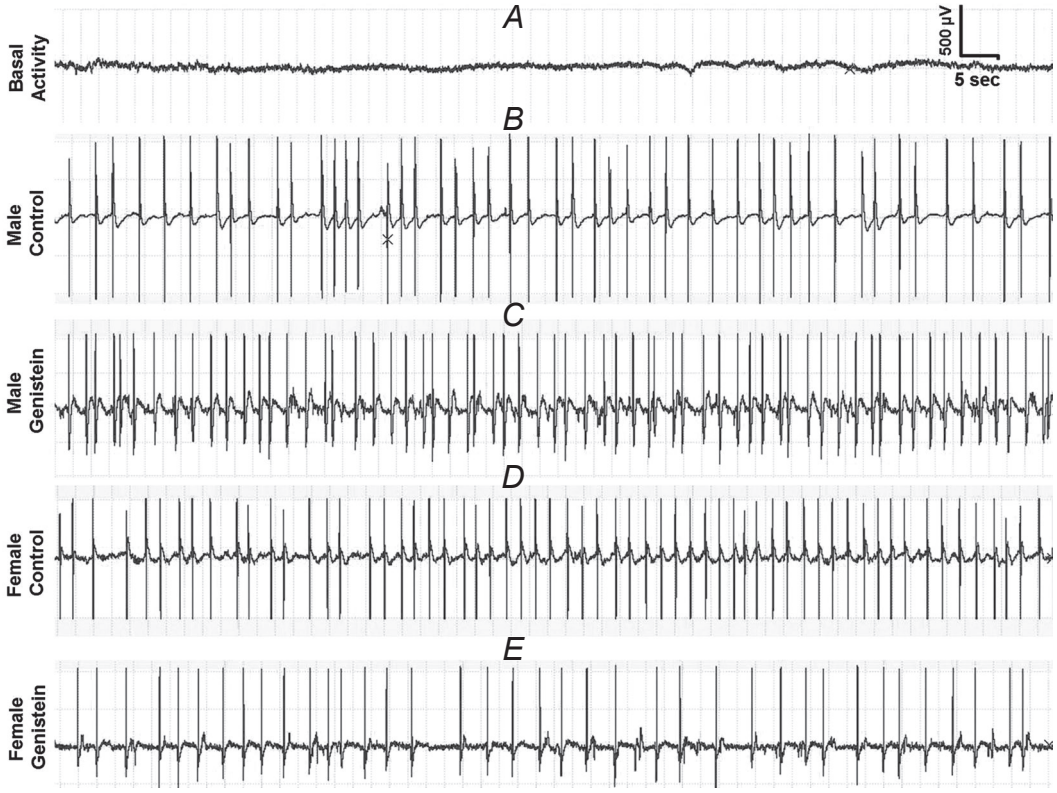
After observation of basal activity within the above interval, epileptiform activity was induced by intracortical (i.c) injection of 2.5 µl penicillin G potassium salt dissolved in sterile physiological saline into the left sensorimotor cortex (2 mm posterior to the bregma, 3 mm lateral to the sagittal suture, and 2 mm ventral to the brain surface) using a Hamilton microinjector at the infusion rate 0.5 µl/min in all rats. The ECoG activity was continuously recorded during 180 min, displayed, digitized, and stored for post-experimental computer analysis. The frequency (min^{-1}) and amplitude (µV) values of the spike/wave complexes and the latency (sec) of onset of the first spike/wave event in each animal were automatically measured using a data acquisition Chart v. 6.0 system (Power Lab software; AD Instruments, Pty Ltd., Australia) and analyzed offline.

Statistical Analysis. The epileptiform activity was

analyzed after numerical conversion within every 10-min-long interval during 180 min recording. The above-mentioned ECoG parameters were gathered from all groups, and these values were analyzed using PASW package (ver. 18). Descriptive values were computed as means ± s. d. and medians. The Kruskal-Wallis test was used for comparing each group with respect to the spike-wave latency, frequency, and amplitude within each period. In addition, the *post-hoc* Dunn's test followed the Kruskal-Wallis test were used. Bonferroni-corrected *P* values were used for comparing these indices among different groups. The $P < 0.05$ values were considered to be statistically significant.

RESULTS

Effects of Genistein on Penicillin G-Induced Epileptiform Activity. The epileptiform activity characterized by spikes and spike-wave complexes started 2-5 min after penicillin injection, reached constant levels of the frequency and amplitude in 30 min, and lasted for 3-5 h (Fig. 1). Data comprising the mean spike/wave frequency and amplitude values and latencies to onset of epileptiform activity in all experimental groups during a 180-min-long recording period following penicillin injection are presented as Fig. 1.



F i g. 1. Examples of ECoG activity before (A) and after (B–E) penicillin G injections in different experimental groups.

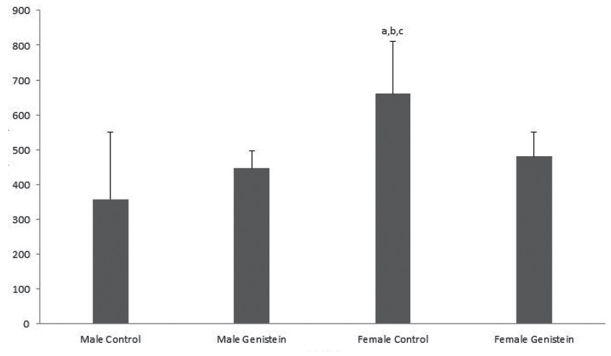
Р и с. 1. Приклади ЕКоГ активності перед ін'єкцією пеніциліну G (*A*) та після такої ін'єкції (*B–E*) в чотирьох досліджених групах.

T a b l e 1. Values of the Latency, sec (Onset Time of the First Epileptic Phenomenon) in the Experimental Groups

Т а б л и ц я 1. Середні значення латентного періоду першого епізоду епілептичної активності в експериментальних групах

Groups	*N*	Mean	Median	s.d.	Minumum	Maximum	*P*-value
Male control	7	445.86	358.00	193.15	240.00	801.00	
Male genistein	7	419.71	446.00	51.41	330.00	468.00	0.013
Female control	7	649.00	660.00[a,b,c]	150.17	480.00	903.00	
Female genistein	7	456.85	480.00	71.61	300.00	510.00	

n – number of examined rats; s.d. – standard deviation; [a] – female control group compared with female genistein ($P < 0.032$); [b] – female control group compared with male control ($P < 0.015$). [c] – female control group compared with male genistein ($P < 0.002$).



F i g. 2. Median latencies (sec) in the experimental groups. a) female control group compared with female genistein ($P < 0.032$). b) female control group compared with male control ($P < 0.015$). c) female control group compared with male genistein ($P < 0.002$).

Р и с. 2. Медіанні значення латентного періоду першого комплексу пік/хвиля в експериментальних групах.

We was mentioned, we used a low dose of genistein (100 μg/kg) in both female and male treated groups (FC and MC) which was determined in the previous study [18]. There was significant difference ($P = 0.013$) observed between the values of the median latency (sec) to the first epileptic event among the experimental (G) and control (C) groups. Additionally, the median latency value in the FC group was significantly longer than the median latency in the MC, MG, and FG groups (respectively, $P = 0.002$, 0.015, and 0.032; Fig. 2, Table 1). In other words, genistein manifested a clear proconvulsant effect by lowering the threshold of onset of epileptic seizures. At the same time, shortening of the latency on the epileptic activity induced with penicillin was observed in the female group (FG) only.

T a b l e 2. Values of the Frequency of the Spike/Wave Complexes in the Experimental Groups within the Observation Period

Т а б л и ц я 2. Частота комплексів пік/хвиля в експериментальних групах протягом періоду спостереження

Time, min	Male control		Male genistein		Female control		Female genistein		*P* value
	Mean ± s.d.	Median	Mean ± s.d.	Median	Mean ± s.d.	Median	Mean ± s.d.	Median	
10	82.6 ± 106.9	26.0	35.9 ± 38.2	33.0	33.1 ± 43.9	31.0	67.7 ± 134.0	19.0	0.855
20	201.1 ± 170.6	174.0	202.3 ± 188.9	242.0	207.0 ± 177.3	207.0	163.3 ± 152.4	127.0	0.975
30	229.9 ± 140.8	177.0	196.7 ± 143.5	155.0	205.9 ± 121.0	278.0	222.9 ± 143.1	268.0	0.956
40	253.3 ± 150.2	271.0	239.9 ± 147.6	239.0	302.9 ± 86.7	304.0	340.9 ± 94.9	352.0	0.406
50	282.3 ± 113.1	236.0	270.3 ± 152.3	231.0	276.4 ± 102.8	269.0	378.3 ± 121.1	367.0	0.314
60	304.0 ± 102.2	248.0	264.9 ± 153.5	221.0	237.7 ± 66.1	258.0	362.3 ± 148.3	344.0	0.341
70	286.9 ± 77.5	286.0	295.6 ± 124.6	283.0	213.1 ± 72.0	216.0	335.0 ± 143.3	347.0	0.231
80	270.6 ± 42.7	279.0	294.3 ± 153.5	216.0	228.7 ± 78.4	255.0	323.3 ± 176.4	302.0	0.639
90	250.4 ± 42.8	256.0	287.1 ± 162.5	188.0	235.0 ± 86.4	240.0	295.3 ± 175.3	274.0	0.922
100	219.3 ± 91.2	228.0	217.7 ± 158.5	175.0	316.4 ± 126.3	266.0	244.1 ± 110.9	224.0	0.551
110	197.4 ± 90.1	210.0	238.9 ± 175.2	169.0	306.4 ± 149.2	291.0	228.7 ± 87.0	185.0	0.623
120	173.3 ± 89.9	178.0	194.7 ± 116.8	168.0	306.7 ± 161.7	261.0	197.9 ± 94.4	179.0	0.291
130	154.0 ± 74.2	168.0	183.9 ± 94.2	147.0	266.7 ± 147.9	257.0	167.6 ± 70.5	206.0	0.376
140	154.9 ± 94.7	170.0	252.1 ± 148.2	182.0	269.0 ± 140.6	240.0	150.1 ± 79.9	176.0	0.223
150	164.1 ± 97.0	183.0	245.6 ± 166.9	188.0	243.1 ± 142.6	188.0	159.6 ± 60.6	183.0	0.645
160	136.7 ± 71.2	151.0	230.6 ± 155.2	175.0	201.9 ± 115.1	159.0	150.4 ± 54.0	151.0	0.632
170	162.3 ± 93.8	167.0	226.9 ± 165.3	169.0	231.9 ± 136.2	193.0	153.3 ± 49.9	155.0	0.772
180	132.6 ± 72.6	146.0	145.7 ± 89.9	168.0	185.4 ± 118.4	155.0	135.4 ± 71.1	132.0	0.958

F o o t n o t e: all intergroup differences did not reach the level of significance within all time periods.

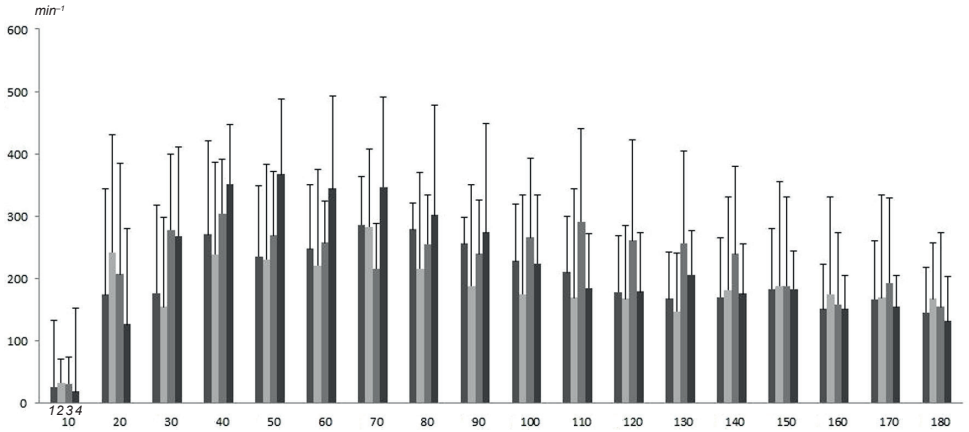
At the same time, no significant differences were found regarding the median spike/wave frequency (min^{-1}) and median amplitude (μV) values of the epileptiform activity all examined groups (both gender and genistein/control) within all time periods ($P > 0.05$). It should be, however, mentioned that the respective intergroup differences of all indices, confirming the conclusion on the proconvulsant effect of ginesteine (while not reaching the significance level), were quite clear (Figs. 3, 4; Tables 2, 3).

T a b l e 3. Values of the Spike/Wave Amplitudes (μV) in the Experimental Groups within the Observation Period

Т а б л и ц я 3. Значення амплітуд (мкВ) комплексів пік/хвиля в експериментальних групах протягом періоду спостереження

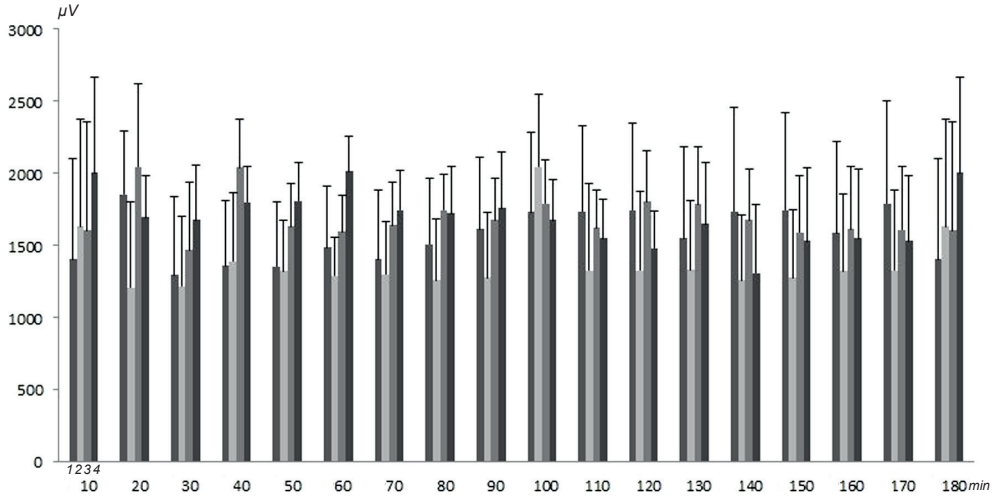
Time (min)	Male control		Male genistein		Female control		Female genistein		*P* value
	Mean ± s.d.	Median	Mean ± s.d.	Median	Mean ± s.d.	Median	Mean ± s.d.	Median	
10	1346.1 ± 700.7	1406.0	1454.7 ± 743.4	1633.9	1290.0 ± 758.0	1604.1	1655.9 ± 660.8	2006.6	0.780
20	1653.9 ± 443.0	1854.8	1276.9 ± 590.2	1210.5	1632.3 ± 574.9	2048.0	1641.1 ± 285.5	1695.3	0.401
30	1357.8 ± 544.6	1298.2	1360.5 ± 483.4	1221.0	1433.9 ± 468.6	1470.4	1545.3 ± 380.5	1677.0	0.876
40	1374.8 ± 451.7	1588.5	1434.9 ± 475.6	1394.2	1807.8 ± 329.6	2043.3	1817.1 ± 246.5	1803.0	0.094
50	1518.5 ± 450.2	1355.9	1375.5 ± 350.7	1321.7	1745.0 ± 294.9	1633.2	1799.1 ± 264.0	1810.0	0.078
60	1588.4 ± 423.5	1488.0	1316.0 ± 265.3	1291.7	1732.7 ± 255.9	1597.0	1850.9 ± 240.0	2013.7	0.084
70	1549.5 ± 478.7	1407.6	1446.4 ± 368.9	1300.9	1688.6 ± 302.7	1641.3	1787.4 ± 275.1	1748.3	0.221
80	1552.5 ± 458.0	1508.7	1447.5 ± 427.2	1261.0	1801.0 ± 250.7	1744.5	1729.7 ± 326.2	1724.0	0.126
90	1519.0 ± 495.8	1613.8	1451.9 ± 454.2	1280.2	1683.8 ± 285.3	1677.7	1673.9 ± 392.7	1758.3	0.731
100	1470.3 ± 550.5	1731.3	1668.9 ± 499.1	2047.8	1761.8 ± 299.8	1790.8	1561.1 ± 281.9	1676.8	0.536
110	1425.2 ± 594.2	1738.0	1463.6 ± 596.8	1329.5	1696.1 ± 262.5	1625.8	1483.7 ± 274.6	1549.1	0.817
120	1403.9 ± 600.0	1745.4	1496.2 ± 547.4	1326.2	1667.7 ± 351.4	1806.6	1418.7 ± 258.9	1482.8	0.651
130	1298.7 ± 636.8	1549.4	1555.8 ± 474.8	1334.0	1625.0 ± 396.0	1788.7	1588.0 ± 425.6	1651.7	0.758
140	1334.1 ± 723.8	1738.0	1427.6 ± 449.3	1261.0	1646.4 ± 351.6	1677.7	1471.8 ± 475.2	1308.9	0.700
150	1330.4 ± 672.5	1745.4	1444.7 ± 467.4	1280.2	1610.3 ± 395.3	1592.5	1532.1 ± 504.9	1530.8	0.897
160	1458.8 ± 636.6	1588.6	1510.1 ± 531.2	1323.9	1557.1 ± 431.1	1614.9	1510.6 ± 478.7	1549.1	0.971
170	1493.5 ± 711.3	1794.2	1499.0 ± 552.7	1329.5	1558.6 ± 435.8	1611.7	1525.6 ± 454.4	1533.9	0.964
180	1346.1 ± 700.7	1406.0	1454.7 ± 743.4	1633.9	1290.0 ± 758.0	1604.1	1655.9 ± 660.8	2006.6	0.878

F o o t n o t e: all intergroup differences did not reach the level of significance within all time periods.



F i g. 3. Dynamics of the medians of the spike/wave frequency (min^{-1}) in different experimental groups within the observation period. Columns 1–4, male control, male genistein, female control, female genistein groups, respectively.

Р и с. 3. Динаміка медіанних значень частоти комплексів пік/хвиля ($хв^{-1}$) в експериментальних групах.



F i g. 4. Dynamics of the medians of the spike/wave amplitude (μV) in different experimental groups within the observation period. Designations are similar to those as in Fig. 3.

Р и с. 4. Динаміка медіанних значень амплітуди комплексів пік/хвиля (мкВ) в експериментальних групах**.**

DISCUSSION

Estrogens and phytoestrogens regulate the neuronal excitability by either their influence on the release of neurotransmitters from presynaptic terminals (such as acetylcholine, dopamine, GABA, and glycine) or direct effects on different ion channels in the postsynaptic membrane structures. Moreover, it has been reported that these hormones influence both the seizure threshold and frequency of epileptic activity [7, 9]. Also, sex gonadal hormones have different effects according to sex-dependent differential influences on the severity of seizures in experimental rat models [10-12]. It has been indicated that phytoestrogens of the soy extract may mimic the estrogen proconvulsant effect in a PTZ-induced seizure model. Both low and high doses of soy extract treatment affected the seizure severity in the model, but their effects were different in the presence or absence of ovarian hormones [19].

Genistein, a relatively selective ER β-agonist, is an isoflavone phytoestrogenic molecule; its structure is rather similar to 17β-estradiol [20]. It exhibits PTK activity; this enzyme plays important roles in many cellular processes, as was shown in *in vivo* and *in vitro* studies [15, 16]. It was reported that genistein exerts neuroprotective effects against neurodegenerative diseases [21, 22]. In addition, genistein was described as an effective agent in both prophylaxis and treatment of hormone-dependent cancers, in particular, those of breast and endometrium [23]. Accordingly, many studies suggested that genistein may be used as an alternative to ERT; it reproduces the neuroprotective effect of estrogen without cancer-promoting adverse effects of the latter [24, 25]. However, the mechanisms of the effects of genistein on epileptic activity have not been finally determined until now.

Our study was performed to investigate the effects of genistein in penicillin-induced epilepsy model and to evaluate possible gender-dependent differences. To our knowledge, this is the first study to address changes of the epileptiform activity after genistein treatment to female and male rats in the above-mentioned epilepsy model.

Genistein penetrates the blood-brain barrier in a dose-dependent manner, and can be defined in the brain tissue. It's concentration in this tissue was found to be lower than the levels observed in other tissues [26, 27]. In our study, genistein was given during 15 days to the female and male treated rat groups before cortical injections of penicillin G that induced epileptiform activity. We took into account that genistein shows a relatively low penetration rate through the blood-brain barrier. Thus, our results illustrate chronic effects of small doses of genistein in experimental epilepsy model. Genistein can be dissolved in various solvents, such as DMSO, ethanol, propylene glycol, olive oil, or sesame oil, and this also can affect the obtained experimental results.

We found that genistein facilitated the onset of epilepsy in female group (FG) of the rat model, and we used DMSO as solvent for genistein. Besides, Choi and Lee [18] demonstrated that chronic administration of high doses of genistein (20 mg/day) induced cytotoxic effects and apoptosis, while low doses of genistein (2 mg/day) had no cytotoxic effect in the rat cerebral tissue. Considering this, in the present study we used a rather low dose (100 μg/kg) of genistein showing no cytotoxic and apoptotic effects according [18].

In our study, we observed significant differences in the latency to onset of epileptiform activity among all female and male genistein/control groups. We found that low dose genistein treatment facilitated starting of epileptiform seizures but only in a female group (FG), while such treatment did not changed significantly the onset time of first epileptic manifestation in the male group (MG). In other words, the latency in the FG group was significantly shorter than that in both male groups (MC and MG) and female control group (FC). The proconvulsant effect of genistein arises from its estrogen-like activity, and these findings may be related to two possible mechanisms. Genistein may exert a negative regulatory effect on the GABA-system activity [17]. Other mechanism may be the following; flavonoids like genistein partly inhibit acetylcholinestherase. Thus, it delays degradation of the respective neurotransmitter [28]. We think that the proconvulsant effect of genistein may result from both above reasons.

Furthermore, in the present study, genistein treatment did not demonstrate significant differences with regard to the spike/wave frequency or amplitude values between both female and male rats, while the respective trends were noticeable. These results may arise from interaction of three different mechanisms. The first one may be based on inhibition of voltage-gated sodium currents by genistein. This was shown in rat superior cervical ganglion (SCG) neurons and realized through PTK-dependent and kinase-independent signal pathways [15]. Thus, genistein suppress the neuronal excitability by reducing the depolarization rate in neuronal units. The second mechanism may be due to changes in the

depolarization state of the cell by estrogen-induced blocking of Na^+,K^+-ATPase pump activity. It was reported that functioning of this pump is significantly increased under conditions of an estrogen deficiency in ovariectomized rats [29]. The third mechanism may arise from the formation of membrane hyperpolarization resulting from an increase in ATP-dependent potassium channel (K_{ATP}) activity related to estrogen effect in neuronal cells [30]. We believe that the absence of significant differences in the genistein effects on the frequency and amplitude ECoG values, observed in our studies, are determined by a combined nature of the nature of genistein effects and complex interactions between the factors of this treatment in both female and male groups. Further research is needed of explain the exact reason observed pattern of proconvulsant effects of genistein observed in our experiments.

Our study, naturally, has a number of considerable limitations. We did not study the dose-dependence of genistein treatments in non-cytotoxic doses and the influence of different solvents. Additionally, female rats were tested randomly for epileptic activity regardless of their ovulation cycle stage. Individual hormonal cycle stages may play a significant role in seizure susceptibility. One another disadvantage was that we had no data on the effects of genistein depending of the level of ovarian hormones. In further research, application of genistein under various estrogen conditions (females, i.e., standard estrogen condition, males, i.e., naturally low-estrogen condition, and ovariectomized rats, artificially induced estrogen deficiency) is expedient. We did not examine the relationship between the effects of genistein and hormone levels such as estradiol (E2), and progesterone (P4) contents, in the rat plasma, as well as interrelations of these indices with epileptiform activity.

In any case, we suggest that genistein, according to the results of our study, may not be a good candidate in ERT, because it can noticeably increase the epileptic seizure susceptibility in female individuals.

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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 University (Decision No: 2014/08).

The authors of this study, A. Bahadir, S. Demir, H. Orallar, E. Beyazcicek, A. Cetinkaya, S. Ankarali, and H. Ankarali, 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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ГЕНДЕРНІ ВІДМІННОСТІ ВПЛИВІВ ҐЕНІСТЕЇНУ НА ІНДУКОВАНУ ПЕНІЦИЛІНОМ ЕПІЛЕПТИФОРМНУ АКТИВНІСТЬ У ЩУРІВ

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Р е з ю м е

Ми досліджували залежні від статі відмінності впливу ґеністеїну (ізофлавоноїдного фітоестрогена) в умовах індукованої пеніциліном експериментальної моделі епілепсії у щурів. 28 дорослих щурів лінії Вістар (14 самиць і 14 самців) були поділені на чотири групи – контрольних та лікованих геністеїном самців і самиць. Ґеністеїн (100 мкг/кг, внутрішньоочеревинно) або фізіологічний розчин уводився тваринам протягом 15 діб, після чого у них відводились електрокортикограма (ЕКоГ). Епілептиформна активність індукувалась ін'єкцією пеніциліну G калієвої солі (500 МО) в ліву соматомоторну кору. Істотні міжгрупові відмінності були виявлені щодо латентного періоду початку епілептиформної активності ($P = 0.013$). Ця величина в контрольній групі самиць була істотно більшою, ніж аналогічні значення в контрольній групі самців та групах самців і самиць, лікованих ґеністеїном ($P = 0.002$, 0.015 та 0.032 відповідно). Не було виявлено істотних відмінностей щодо частоти комплексів пік/хвиля та амплітуди епілептиформної активності у всіх чотирьох груп у межах інтервалу спостережень ($P > 0.05$). Зроблено висновок, що ґеністеїн впливає на пеніцилініндуковану модель епілепсії як проконвульсант; відповідні ефекти демонструють значну гендерну специфіку, очевидно, залежну від гормонального фону в самців і самиць.

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