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Effect of Resveratrol on a Penicillin-Induced Epilepsy Model in Rats

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Abstract

Objective: Epilepsy, one of the most common chronic neurological diseases, is characterized by spontaneous recurrent seizures. Many studies, using various experimental epilepsy models, have shown that resveratrol reduces epileptiform activity and has neuroprotective effects. Using an epilepsy model created with penicillin, we aimed to investigate the effect of resveratrol on epileptiform activity in rats.

Methods: A total of 40 Wistar albino rats were divided into 5 groups of 8. In the control group, only 2.5 µL of saline was administered intracranially (ic). In the penicillin group, 500 IU of penicillin was given intracranially with no additional procedure. In the resveratrol group, 40 mg/kg of resveratrol was administered intraperitoneally (ip) 20 minutes after penicillin was given intracranially. In the sodium valproate group, 20 minutes after penicillin ic, 300 mg/kg of sodium valproate was administered intraperitoneally. In the resveratrol + sodium valproate group, 20 minutes after penicillin ic, 40 mg/kg of resveratrol was administered intraperitoneally to the right side and 300 mg/kg of sodium valproate ip to the left side. The rats were placed in a stereotaxic device after the procedure and electrocorticogram recordings were captured for 180 minutes.

Results: The number of spikes and the average amplitude of the spikes (peak-to-peak) were calculated from the electrophysiological recording data. In the resveratrol group, there was no statistically significant difference in spike frequency and amplitude values. In the resveratrol + sodium valproate group, the spike frequency values decreased significantly from the 30th minutes ($P = .028 < .05$) and the amplitude decreased significantly from the 60th minutes ($P = .018 < .05$).

Conclusion: In this rat experimental epilepsy model created with penicillin, administration of resveratrol alone did not create a statistically significant difference in epileptiform activity; however, administration of resveratrol with sodium valproate significantly decreased epileptiform activity.

Keywords: electrocorticography, epilepsy, Penicillin epilepsy model, resveratrol, sodium valproate

INTRODUCTION

Epilepsy, characterized by spontaneous recurrent seizures, is one of the most common chronic neurological diseases affecting approximately 65 million people worldwide.[1-3] Epileptogenesis is a process in which the previously normal neuronal network in the brain changes functionally against increased seizure sensitivity and has a high probability of spontaneous recurrent seizures.[4,5] Epileptic seizures occur upon a disruption in the coordination between inhibition and excitation of the central nervous system.[6] The mechanisms involved in epilepsy are still not fully understood. Experimental epilepsy models are used to investigate the basic mechanisms of epilepsy and to elucidate the neuronal mechanisms of normal brain functions.[6] Penicillin is a chemical convulsive agent known to induce experimental epileptic seizures, and the epilepsy model created with penicillin is one of the most frequently used acute models in the field of experimental epilepsy studies. This model, a simple partial seizure type, is also important in analyzing the synchronization and spread of epileptogenic seizure activity.[7-9] It shows the convulsive activity of penicillin through the gamma-aminobutyric acid (GABA) system.[10] Gamma-aminobutyric acid is the major inhibitory neurotransmitter in the mammalian brain, and the changes in its function are critical in the pathophysiology of many brain diseases, including epilepsy. Gamma-aminobutyric acid and glutamate are the most common neurotransmitter substances in the central nervous system.[11,12] It is generally accepted that GABA-ergic inhibitor neurotransmission disorder may lead to convulsions, while GABA-ergic transmission may cause anticonvulsant effects. Gamma-aminobutyric acid acts with 3 types of receptors: GABA-A, GABA-B, and GABA-C. Valproate has proved to have an anticonvulsant effect with various pharmacodynamic results, such as increasing the level of the inhibitory neurotransmitter GABA through GABA-transaminase inhibition.[12-14]

Resveratrol is a phytochemical which was first isolated from the roots of *Veratrum grandiflorum* in 1940. It is found in many nutrients such as red grape skin, raspberry, black mulberry, plum, and pistachio. When plants are exposed to environmental stress such as bacterial and fungal infections, ultraviolet radiation, temperature fluctuations, injury, and ozone, resveratrol is synthesized as phytoalexin. Resveratrol is an anti-ischemic,

anti-inflammatory, antiviral, antiproliferative, neuroprotective, anticarcinogenic, endothelial-protective agent that can treat dyslipidemia and obesity and reduce hyperglycemia and hyperinsulinemia. It also is an antioxidant substance with different biological properties and has an antiepileptic function through various mechanisms demonstrated by researchers.[15-18] In many studies using experimental epilepsy models created with pentylenetetrazole (PTZ), ferric chloride (FC), and kainic acid (KA), the anticonvulsant effect of resveratrol has been demonstrated and as such, it has been emphasized as an important chemical in the treatment of epilepsy.[16,19-23]

Although there are many studies investigating the effectiveness of resveratrol in experimental epilepsy models created with many different chemicals, only 1 study investigated the effectiveness of resveratrol in an experimental epilepsy model created with penicillin. Thus, our study aimed to evaluate the anticonvulsive efficacy of resveratrol in a rat experimental epilepsy model created with penicillin.

METHODS

Animals

Prior to the study, approval was obtained from the Atatürk University Animal Experiments Local Ethics Committee (Date: November 28, 2014, Decision no: 8-134). A total of 40 male Wistar albino rats, 12-16 weeks old, weighing 200 ± 50 g, were used in the study. The animals were obtained from the Atatürk University Medical Experimental Research and Application Center (Erzurum, Turkey) and kept in plastic cages with no restrictions on food and water, under standard laboratory conditions, at a room temperature of 20-22°C and 50% humidity, on a 12-hour day-12-hour night cycle.

The rats were divided into the following 5 groups of 8:

(1) Saline (2.5 µL, ic)
(2) Penicillin (500 IU, 2.5 µL, ic)
(3) Resveratrol (40 mg/kg, ip)+penicillin (500 IU, 2.5 µL, ic)
(4) Sodium valproate (300 mg/kg, ip)+penicillin (500 IU, 2.5 µL, ic)
(5) Resveratrol (40 mg/kg, ip)+sodium valproate (300 mg/kg, ip)+penicillin (500 IU, 2.5 µL, ic)

Surgical Procedure and ECoG Recordings

Following anesthesia administration of 1.25 g/kg urethane (25% solution) ip, the rats were placed in a stereotaxic device (Harvard Apparatus Stereotaxic Instrument, Mass, USA) and an incision with an average length of 3 cm was made in the rostrocaudal plane. After removing the soft tissue on the left somatomotor cortex, the skull was thinned with a drill mill and the skull bone was removed. A positive Ag/AgCl ball electrode was placed 1 mm in front of the bregma and 2 mm lateral to the sagittal suture. A negative electrode was placed 5 mm posterior to the bregma and 2 mm lateral to the sagittal suture. An earth electrode was placed in the right ear by applying the gel. The body temperature of the rats was maintained with a homeothermic blanket (Harvard Institute, USA) connected to a rectal probe and kept stable at 37°C throughout the experiment. The activity recorded by the electrodes was amplified with an MP 100A-CE (BioPac Systems, Santa Barbara, California, USA) interface and transferred to an MP 100 EEG-100C (BioPac Systems) data recording system. Analog signals received from the cortex with the MP 100 were transferred to the computer with a USB cable after being digitalized. Brain activity was monitored with AcqKnowledge 3.9.1 (BioPac Systems) software. After the recordings were completed, the frequency and amplitude of the epileptiform activity were analyzed.

Induction of Epileptiform Activity and Drug Administration

While the rats were in the stereotaxic unit, 2.5 µL of penicillin dissolved in distilled water was administered to the left somatomotor cortex, 3 mm lateral, 2 mm posterior, and 2 mm ventral from bregma[24] using a Hamilton microinjector (710 SNR, infusion rate 0.5 µL/min). Epileptiform activity caused by the internal administration of penicillin started to be recorded 1-2 minutes after the injection. The spike frequencies and amplitudes of this activity reached a steady level approximately 20-30 minutes after penicillin injection and continued for approximately 3-4 hours. Electrocorticogram (ECoG) activity was recorded for 180 minutes after penicillin injection.

The experiment was started with the control group. After administering 2.5 µL of physiologic saline, ECoG was recorded for a period of 180 minutes. Penicillin (500 IU, 2.5 µL, ic) was given to the 2nd group and no additional procedure was performed. Penicillin (500 IU, 2.5 µL, ic) was given to the 3rd group and 30 minutes later resveratrol was injected (40 mg/kg, ip). Penicillin (500 IU, 2.5 µL, ic) was given to the 4th group and 30 minutes later sodium valproate was injected (300 mg/kg, ip). Penicillin (500 IU, 2.5 µL, ic) was given to the 5th group and 30 minutes later resveratrol was injected (40 mg/kg, ip) to the right side and sodium valproate (300 mg/kg, ip) to the left side.

The epileptiform activity occurred within 1-2 minutes after penicillin injection in all animals and reached a steady level after approximately 20-30 minutes. One of the animals died in the middle of the recording after penicillin injection; hence, this animal was excluded from the study.

Statistical Analyses

Since the epileptiform activity reached a stable level 20-30 minutes after penicillin injection, the average of the values between the 20th and 30th min of penicillin injection (10-min period) was accepted as the 1st-minute value in all spike frequency and amplitude evaluations. After the 30th minute, the spike frequency and amplitude of 1-minute slices were averaged at 10-minute intervals. Statistics were evaluated using 1-minute segments taken every 10 minute, and the time indicators in the graphics were adjusted accordingly. Electrophysiological recording data were obtained with AcqKnowledge 3.9.1 (Biopac Systems) software and these data were divided into 1-minute periods. Calculations were made by counting the number of spikes and the average amplitude of the spikes (peak-to-peak) within each minute. After all electrophysiological records were converted into numerical data, these data were analyzed with Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

Since there were more than 2 independent groups, the Kruskal–Wallis test was used to compare the quantitative continuous data between the groups. After the Kruskal–Wallis test, the Mann–Whitney *U*-test was used to determine the differences, and the Wilcoxon test was used to identify the difference between repeated measurements within the group. The obtained findings were evaluated at a 95% CI and a 5% significance level. The data of all experimental groups used in the study were expressed as mean ± standard error (SEM). A P-value < .05 was considered significant.

RESULTS

Penicillin-induced epileptiform activity is characterized by biphasic spike and spike-wave complexes. The epileptic discharge occurred in 61 ± 13 seconds after penicillin (500 IU, 2.5 µL, i.c.) administration

Table 1. Penicillin-Induced Epileptiform Activity's Mean Spike Frequency (Spike/Min)

Groups	1st	30th	60th	90th	120th
Penicillin	86 ± 9	88 ± 17	68 ± 21	61 ± 19	39 ± 17*
Sodium valproate	90 ± 23	43 ± 9*	40 ± 12*	44 ± 22	33 ± 14*
Resveratrol	64 ± 6	61 ± 6	58 ± 12	53 ± 14	52 ± 14
Resveratrol + sodium valproate	84 ± 16	33 ± 8*	20 ± 5*	10 ± 2*	10 ± 3*

Data are presented as mean ± sem (mean ± standard error).
Multiple comparison tests were used.
All groups were compared with the first-minute value.
*$P < .05$.

in the penicillin group. The spike frequency and amplitude of epileptiform activity reached the maximum level in 30 ± 8 minutes. The spike frequency of epileptiform activity began to decrease in 120 ± 18 minutes, and the amplitude of epileptiform activity began to decrease in 90 ± 14 minutes.

Spike Frequency

When the spikes in the penicillin group were compared according to the 1st-minute value, a statistically significant decrease ($P = .028 < .05$) was found in the measurements made at the 120th minute intervals. In a comparison of spikes in the sodium valproate group according to the 1st-minute value, a statistically significant decrease ($P = .043 < .05$) was found in the measurements made at the 30th-, 60th-, and 120th-minute intervals. When the spikes in the resveratrol group were compared according to the 1st-minute value, no statistically significant difference was found. When the spikes were compared in the resveratrol + sodium valproate group according to the 1st-minute value, a statistically significant decrease ($P = .028 < .05$) was found in the measurements made at the 30th minute and following 30-minute recording intervals [Table 1]. When the spikes percentage changes in the penicillin group were compared according to the 1st-minute value, a statistically significant decrease ($P = .028 < .05$) was found in the measurements made at the 120th-minute intervals. In a comparison of spikes percentage changes in the sodium valproate group according to the 1st-minute value, a statistically significant decrease ($P = .028 < .05$) was found in the measurements made at the 60th-, 90th-, and 120th-minute intervals. When the spikes percentage changes in the resveratrol group were compared according to the 1st-minute value, no statistically significant difference was found. When the spikes percentage changes were compared in the resveratrol + sodium valproate group according to the 1st-minute value, a statistically significant decrease ($P = .043 < .05$) was found in the measurements made at the 30th minute and following 30-minute recording intervals [Figure 1]. As shown in Figure 2, all group samples from the 60th and 70th minute of ECoG were obtained from epileptiform activity induced by penicillin. Considering the average frequency of the spike, resveratrol significantly reduced the frequency of epileptiform activity with sodium valproate in the resveratrol + sodium valproate group.

Amplitude

When the amplitudes in the penicillin group were compared to the 1st-minute value, a statistically significant decrease was found in the measurements made at the 90th-minute and at following 30-minute intervals ($P = .018 < .05$). When the amplitudes in the sodium valproate group were compared to the 1st-minute value, a statistically significant decrease was found at the 30th and 60th minute ($P = .018 < .05$). There was no statistically significant difference in the 90th-minute value; however, a statistically significant decrease was found at the 120th minute ($P = .018 < .05$). The decrease in amplitude value in this group was not stable. When the amplitudes in the resveratrol group were compared to the 1st-minute value, there was no statistically significant difference. When the amplitudes in the resveratrol + sodium valproate group were compared to the 1st minute, a statistically significant decrease was found ($P = .018 < .05$) in the measurements at the 60th minute and following 30-minute recording intervals. [Table 2] When the amplitudes percentage changes in the penicillin group were compared to the 1st-minute value, a statistically significant decrease was found in the measurements made at the 120th minute ($P = .018 < .05$). When the amplitudes percentage changes in the sodium valproate group were compared to the 1st-minute value, a statistically significant decrease was found at the 60th, 90th, and 120th minute ($P = .028 < .05$). When the amplitudes percentage changes in the resveratrol group were compared to the 1st-minute value, there was no statistically

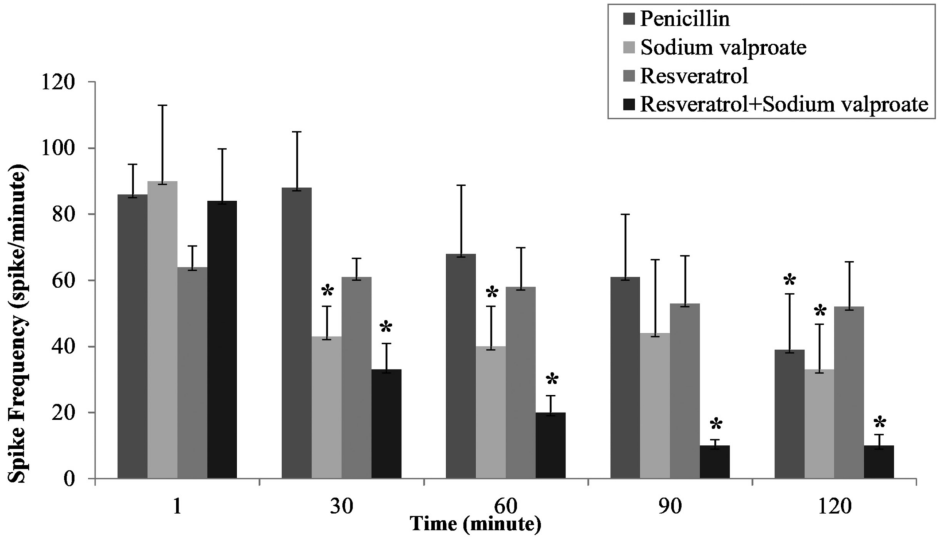

Figure 1 Graph of percentage changes in spike frequency over time in the penicillin, sodium valproate, resveratrol, and resveratrol + sodium valproate groups. A statistically significant decrease was found in the resveratrol + sodium valproate group at 30 minute and after ($P = .043 < .05$) (Multiple comparison tests were used. *$P < .05$, all groups were compared with the first-minute value).

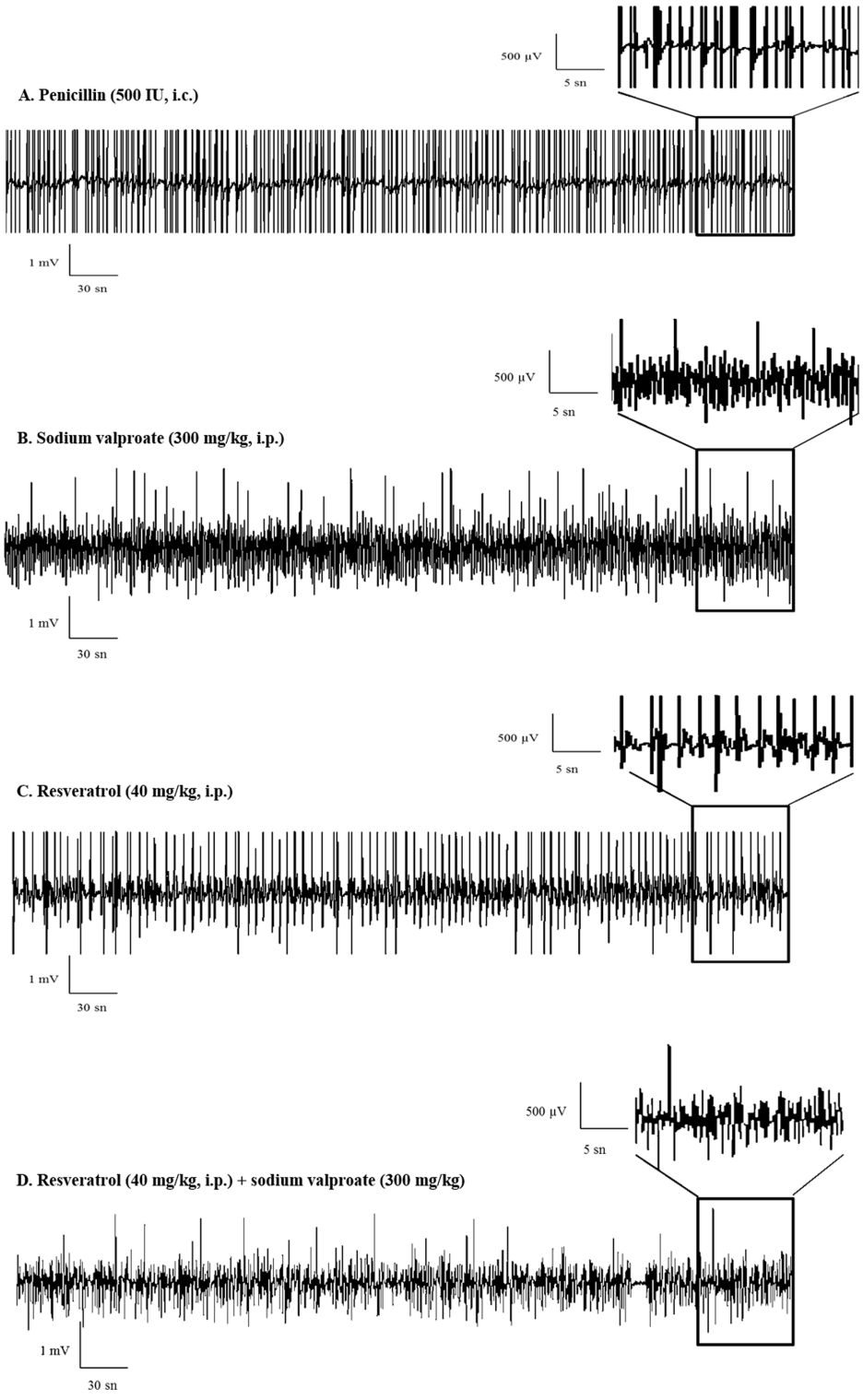

Figure 2 (A) Baseline activity, (B) penicillin, (C) sodium valproate, (D) resveratrol, (E) resveratrol + sodium valproate samples from the 60th and 70th minute of ECoG obtained from epileptiform activity induced by penicillin. ECoG, electrocorticogram. Considering the average frequency of the spike, in the resveratrol + sodium valproate group, resveratrol significantly reduced the frequency of epileptiform activity with sodium valproate.

significant difference. When the amplitudes percentage changes in the resveratrol + sodium valproate group were compared to the 1st minute, a statistically significant decrease was found ($P = .018 < .05$) in the measurements at the 60th-minute and following 30-minute recording intervals. [Figure 3]

DISCUSSION

In this study, in which an experimental epilepsy model was created with penicillin, resveratrol (40 mg/kg) alone did not cause a significant change in epileptiform activity, but when administered with sodium valproate (300 mg/kg), it significantly decreased epileptiform

Table 2. Penicillin-Induced Epileptiform Activity's Mean Spike Amplitude (μV)

Groups	1st	30th	60th	90th	120th
Penicillin	0.170 ± 0.019	0.142 ± 0.025	0.130 ± 0.022	0.131 ± 0.022*	0.104 ± 0.013*
Sodium valproate	0.168 ± 0.014	0.103 ± 0.014*	0.108 ± 0.014*	0.118 ± 0.018	0.121 ± 0.009*
Resveratrol	0.113 ± 0.007	0.115 ± 0.007	0.128 ± 0.014	0.133 ± 0.018	0.129 ± 0.017
Resveratrol + sodium valproate	0.135 ± 0.009	0.108 ± 0.012	0.091 ± 0.007*	0.08 ± 0.009*	0.083 ± 0.012*

Data are presented as mean ± SEM (mean ± standard error).
Multiple comparison tests were used.
All groups compared with the first-minute value.
*$P < .05$

activity. Epilepsy is one of the most common neurological diseases with harmful physical, social, and psychological effects.[25,26] This neurological disorder is characterized by the recurrence of electrical activity discharges in certain brain regions such as the limbic system and cerebral cortex.[27] The mechanism responsible for epilepsy is still not fully understood although several have been suggested.[28] Various types of experimental epilepsy models are used in studies. Among these, models induced by convulsant agents (penicillin, PTZ, bicculline, picrotoxin, KA, etc.) or electrical stimulation in animals genetically predisposed to epilepsy are used frequently.[10] According to Edmonds et al,[33] the advantages of penicillin-induced experimental epilepsy model are as follows: (1) Penicillin causes focal seizures in vertebrates, from fish to man. (2) Seizure induction is rapid and easy, and the recording is uncomplicated and inexpensive. The seizure activity begins in the initial 15 minutes after application and continues at regular intervals for several hours. (3) Penicillin-induced seizures are not resistant to anticonvulsants. (4) The indicated seizure completely disappears 24 hours after the application of penicillin.[6,30] Penicillin causes convulsions when used in high doses or when directly applied to the cerebral cortex in animals[29] by reducing the synaptic activity of GABA, a penicillin inhibitory neurotransmitter.[30] A decrease in the amount of inhibition in a cortical region has a significant effect on neuron groups, and administration of a convulsant drug causes acute focal epilepsy without causing morphological changes in the cell.[10] Neurons in the center of the epileptic focus try to prevent the spread of the seizure, so penicillin initially acts only locally then the epileptiform activity dissipates and turns into generalized epilepsy.[31] Interictal epileptiform discharges, which are displayed as spike and spike waves or sharp waves on Electroencephalography (EEGs), are thought to show the pathophysiological changes in neuronal excitability and synchronization.[32] In our study, penicillin was administered to experimental animals (500 IU, ic) after which epileptic spikes and spike-wave complexes started to be seen within 2-4 minutes. Epileptiform activity stabilized within 30 minutes and lasted more than 2-3 hours.

Sodium valproate is the sodium salt of valproic acid (VPA).[33] The mechanism of action of VPA is not fully known; however, it produces antiepileptic effects in many different ways. Valproic acid increases GABA-mediated inhibition by increasing the level of GABA in the central nervous system and may also increase the postsynaptic GABA response. It prevents voltage-gated sodium channel current and changes calcium current in the thalamus.[34,35] It inhibits the GABA-transaminase enzyme responsible for GABA degradation and to increase the activity of the glutamic acid decarboxylase enzyme involved in GABA synthesis.[36] In addition, VPA inhibits depolarization induced by N-methyl-D-aspartate (NMDA) receptors and blocks NMDA-induced seizures, thereby inhibiting the exacting mechanism.[12] Valproic acid is an effective drug in many types of generalized and partial epilepsy seizures. It has been used successfully especially in the treatment of primary generalized tonic-clonic, myoclonic, and absence seizures, and juvenile myoclonic epilepsy with these seizures, awakening grand mal epilepsy, and photosensitive epilepsy.[37] In our study, VPA significantly reduced epileptic activity by decreasing spike frequency and amplitude values, especially after 60 minutes.

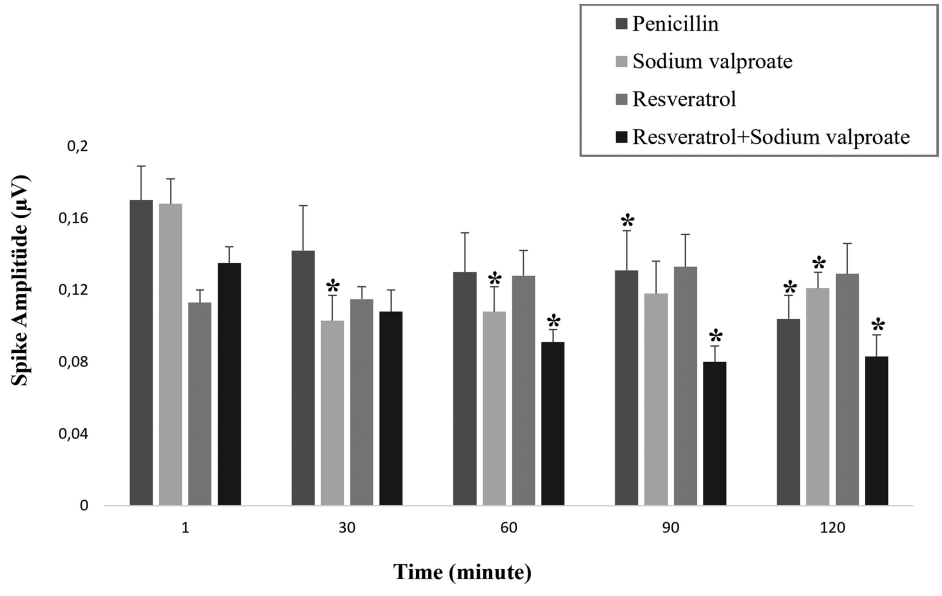

Figure 3 Graph of percentage changes in spike amplitude over time in the penicillin, sodium valproate, resveratrol, and resveratrol + sodium valproate groups. In the resveratrol + sodium valproate, group a statistically significant decrease was found at the 60th minute and after ($P = .018 < .05$) (Multiple comparison tests were used. *$P < .05$, all groups were compared with the first-minute value).

Resveratrol (3,4′,5-trihydroxystilbene) is a phytoalexin formed by spermatophytes against biotic and abiotic stresses in plants and found in *Polygonum cuspidatum* roots, grapes, peanuts, plums, strawberries, and red wine.[38] Pharmacological studies have revealed that resveratrol affects a variety of biological processes, including antioxidant, anti-inflammatory, and anti-aging pathways.[39-41] Resveratrol crosses the blood–brain barrier[20] and has been shown to have antiepileptogenic activity in various preclinical studies.[42] In the PTZ-induced epilepsy model, resveratrol has been shown to dose-dependently reduce the percentage of generalized tonic-clonic convulsions, increase the effect of VPA and diazepam against PTZ-induced seizures, and reduce the incidence of generalized tonic-clonic convulsions when given with adenosine.[23] In another PTZ-induced epilepsy model, resveratrol was shown to suppress seizures in a dose-dependent manner and reverse neuronal damage, oxidative stress, and apoptosis in a dose-dependent manner.[19] Resveratrol significantly reduced PTZ-induced death of neurons in the CA1 and CA3 regions of the hippocampus and significantly reduced S100B protein levels in spinal fluid and serum in a group given resveratrol.[43] A single dose of trans-resveratrol does not inhibit convulsions, while repeated doses reduce the incidence of convulsions and malondialdehyde (MDA) levels in the brain in epilepsy induced by KA.[22] In another KA acid-induced epilepsy model, trans-resveratrol given to infant rats had no effect on growth and did not reduce the seizures caused by KA. Although resveratrol is thought to be effective in preventing epilepsy activity and neurodegeneration in adulthood, it does not have much efficacy in youth.[44] Another KA-induced temporal lobe epilepsy model showed that resveratrol decreases the frequency of spontaneous seizures, inhibits epileptiform discharges, and decreases the expression level of KA receptors in the hippocampus and neurons against neuronal cell death in the CA1 and CA3 regions.[21] Regular exercise and resveratrol inhibit KA-induced seizure activity and oxidative stress.[45] In another study in which a PTZ model, maximal electroshock, and 6 Hz electrical seizure models were used, resveratrol had no protective effect in all 3 models. It was suggested that while acute treatment with resveratrol does not provide protection, it may be protective in chronic treatment models.[46] In the status epilepticus model created with pilocarpine, resveratrol as a single dose does not block convulsions but suppresses the inflammatory response induced in partial seizures by the AMPK/mTOR route.[47] In the post-traumatic epilepsy model created with FC, trans-resveratrol delays the emergence of epileptiform activity on EEG and significantly reduces MDA levels in the brain.[48] There is only 1 study in the literature investigating the effectiveness of resveratrol in an experimental epilepsy model created with penicillin. Ethemoglu et al[50] showed that there was a more significant decrease in spike frequency and amplitude values in the group in which resveratrol was given with liposome compared to other groups. Glutathione S-transferase (GST) and superoxide dismutase (SOD) activity and glutathione (GSH) levels increased compared to the control group, and the MDA level was significantly higher than the resveratrol and control groups. The findings in this study emphasized that the combination of resveratrol and liposome is more effective in controlling epileptiform activity induced by penicillin than resveratrol alone.[49]

In the present study, resveratrol was administered to both a resveratrol group and a resveratrol+sodium valproate group at 40 mg/kg ip. No statistically significant difference was found in the resveratrol group during recordings. In some studies, administration of resveratrol alone reduced epileptiform activity in experimental models, while others showed no change.[19,22,23,46-49] In our study, a single administration of resveratrol did not cause a significant change in epileptiform activity. As mentioned in some studies examining the efficacy of resveratrol, resveratrol administration with repeated doses, not as a single dose, may change epileptiform activity.[16,21,22,43,45] In our resveratrol+sodium valproate group, resveratrol was administered at 40 mg/kg and sodium valproate at 300 mg/kg ip. When comparing the spike frequency to the 1-minute value, a statistically significant decrease ($P = .028 < .05$) was found in the measurements made at the 30th-minute and the following 30-minute recording intervals. When the amplitudes were compared according to the 1-minute value, a statistically significant decrease ($P = .018 < .05$) was found at the 60th- and 30th-minute intervals. There was no previous study showing the effect of resveratrol on epileptiform activity with sodium valproate in an experimental epilepsy model created with penicillin. In our study, in the resveratrol+sodium valproate group, a statistically significant decrease was found in the spike from the 30th minute and the amplitude values from the 60th minute. These findings show that although resveratrol alone does not affect epileptiform activity in the experimental epilepsy model created with penicillin, it significantly reduces epileptiform activity when combined with sodium valproate. This reduction appears to be a stronger effect than the anticonvulsive activity of valproate alone. The efficacy of valproate compared to the control group was found to be significant at the level of $P = .043$ after the 30th minute, while the effectiveness of valproate+resveratrol after the 30th minute was found to be $P = .028$. In addition, when the average number of spikes per minute was examined, 43 ± 9 spikes were seen at 30 minutes in the valproate group, while 33 ± 8 spikes were observed in the valproate+resveratrol group. This difference became more pronounced (10 ± 3 spikes vs. 33 ± 14 spikes at the 120th minute. In a PTZ-induced epilepsy model, Gupta et al showed that co-administration of resveratrol (40 mg/kg) with sodium valproate (150 mg/kg) increases its effect against PTZ-induced seizures. The results of our study are similar to these findings. More studies are needed to determine both the effective dose and frequency of the use of resveratrol to clarify its mechanism of action and to emphasize its antiepileptic efficacy. The available antiepileptic drugs could achieve the prevention of only 60%-70% of seizures. Resveratrol could be used as a co-agent with sodium valproate to suppress epileptiform activity in humans. Based on the results from the literature, the use of resveratrol in therapy with repeated doses and other antiepileptic drugs increase its antiepileptic effectiveness. The addition of resveratrol may be an option to increase the effectiveness of current antiepileptic drugs without increasing their dose. The results of our study should be confirmed by further studies.

Ethics Committee Approval: Atatürk University Animal Experiments Local Ethics Committee (Date: November 28, 2014, Decision no: 8-134).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.KA, T.N.; Design - Z.KA, T.N.; Supervision - Z.KA, T.N.; Funding - Z.KA, T.N.; Materials - Z.KA, T.N.; Data Collectionand/or Processing - Z.KA; Analaysis and/or Interpretation - Z.KA; Literature Review - Z.KA; Writing - Z.KA; Critical Rewiew - Z.KA, T.N.

Declaration of Interests: The authors declare that they have no competing interest.

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