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Effect of irisin on the epilepsy induced by penicillin G: An electrophysiological study

Yasemin ŞAHİN YILDIZ[1,*], Şerif DEMİR[2], Ersin BEYAZÇİÇEK[2], Ali GÖK[3], Özge BEYAZÇİÇEK[2]

[1]Department of Home Patient Care, Vocational College of Health Services, Bartın University, Bartın, Türkiye
[2]Department of Physiology, Faculty of Medicine, Düzce University, Düzce, Türkiye
[3]Experimental Animals Application and Research Center, Düzce University, Düzce, Türkiye

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Abstract

Epilepsy is a neurological disease characterized by sudden and synchronized seizures caused by abnormal and excessive electrical discharges in brain neurons. The purpose of this study was to electrophysiologically examine the effects of acute administration of irisin, which is thought to be neuroprotective and increase cell proliferation, at different doses (10 and 100 nM) on the penicillin-induced experimental epilepsy in rats. Forty-nine adult male Wistar rats were used in the study. The rats were divided into 7 groups: sham, control group (penicillin), irisin group, the pre- and during-seizure groups of 10 nM and 100 nM irisin. All the substances except penicillin were administered intraperitoneally. The rats were anesthetized using urethane. The bone tissue on the left cerebral cortex was removed and the electrodes were placed in the somatomotor cortex. Thirty minutes before penicillin administration, irisin was administered to the pre-seizure penicillin group at doses of 10 nM and 100 nM. Then, penicillin (500 IU/2 µl) was injected intracortically, and ECoG recording was continued for 120 minutes. On the other hand, 10 nM and 100 nM of irisin were administered to the during-seizure penicillin group after penicillin was injected intracortically and the seizure occurred, and ECoG recording was continued for 120 minutes. The ECoG recordings were analyzed using the PowerLab Chart v.8 software. In conclusion, it was found that irisin prolonged the latency of initial epileptic activity and decreased the number and amplitude of spike-waves in the penicillin-induced experimental epilepsy model. These results suggest that irisin might have an antiepileptic potential.

Keywords: electrocorticography, epilepsy, epileptiform activity, irisin, rat

1. Introduction

Epilepsy is a serious neurological disease characterized by the disruption of the balance between cerebral inhibition and excitation, which affects millions of people around the world (1). Epileptic seizures occur as a result of a decrease in inhibitors such as γ-aminobutyric acid (GABA) or an increase in excitatory neurotransmitters such as glutamate (2). Epileptic seizures induced by abnormal neuronal discharges lead to significant neurobiological, cognitive, psychological and social consequences (3). The incidence of epilepsy is known to be higher in developing countries compared to developed countries (4, 5). Common head trauma, perinatal injury and CNS infections are associated with the risk of epilepsy (4). It very important to find out the underlying biological mechanisms in epilepsy for developing new and more effective drugs in the treatment of patients (6). The use of antiepileptic drugs is the mainstay of treatment in epilepsy (7). Antiepileptic drugs act by increasing the activity of GABA in the brain or by blocking the glutamate receptors (8). Antiepileptic drug therapy is very effective in providing seizure control, however, approximately 30% of patients continue to have seizures (9). Resistance to therapy leads to an increase in mortality and morbidity (10). Despite the increased diversity of antiepileptic drugs, seizures cannot be completely controlled. For these reasons, it is very important to develop new antiepileptic drugs that have less toxicity and are more effective and tolerable. To this end, the antiepileptic properties of different chemicals were investigated in many experimental epilepsy models (11).

Irisin, which was identified by Böstrom et al. in 2012, is a product of fibronectin type III domain 5 (FNDC5), a transmembrane protein. This myokine, which is considered to mediate positive effects on exercise-induced muscle metabolism, was first identified for its role in adipocyte browning and thermogenesis in mice and humans (12). In addition to muscle and adipose tissue, irisin is found in many organs and tissues such as cerebrospinal fluid, cerebellum, thyroid, pineal gland, pancreas, liver, testis, spleen (13). It is considered that irisin may be a molecular mediator of positive effects on different tissues and organs, including brain health (14). It has been reported that the administration of irisin, which has protective effects on central nervous system neurons

*Correspondence: yasemin-omu@hotmail.com

(15–20), at pharmacological doses can prevent neuronal damage in the brain and be effective in neurodegenerative diseases (21). Irisin revealed significant features in memory improvement and synaptic remodeling in the experimental models of neurodegenerative disorders (16, 17 ,22). Furthermore, it was also demonstrated that irisin could mitigate the brain damage and protect the blood-brain barrier (BBB) from disruption after focal cerebral ischemia/reperfusion (23). In parallel, it was concluded that irisin protected against ischemia-induced neuronal injury and reduced the levels of oxidative stress parameters (20). In the study conducted by Elhady et al., serum irisin levels were found to be significantly higher in children with epilepsy, especially in those with uncontrolled seizures, compared to the control groups (24). Inflammation in the brain is known to increase neuronal hyperexcitability and seizures (25). With many recent studies, it has been determined that irisin has an anti-inflammatory effect (26–30). It has been demonstrated that the treatment of irisin reduces inflammation (30) and modulates macrophage activity by reducing the overproduction of reactive oxygen species (ROS) (29).

The increase in irisin levels may occur as a protective mechanism against seizure-induced neuroinflammation by increasing the anti-inflammatory and antioxidant effect (24). The antiepileptic effect of irisin has not been studied much. Erkeç et al. conducted one of the studies with pentylenetetrazole (PTZ). They demonstrated that in seizures induced by PTZ, serum and brain FNDC5/irisin levels were significantly higher compared to the control group (31).

In this study, we investigated the antiepileptic effects of irisin in an experimental model of epilepsy induced by penicillin G. It was aimed to evaluate the effects of acute administration of different doses (10 and 100 nM) of irisin electrophysiologically. Furthermore, in the literature reviews, we observed that the antiepileptic effects of irisin in penicillin model of experimental epilepsy were not investigated. In this respect, our study is the first to demonstrate the antiepileptic effects of irisin in experimental epilepsy.

2. Materials and Methods

2.1. Animals

The study was conducted with the approval of Düzce University Animal Experiments Local Ethics Committee (DÜHADYEK) (2020.11.04). Forty-nine wistar male rats aged 2-3 months and weighing 240±30 g obtained from Düzce University Experimental Animals Application and Research Center were used in this study. The experimental protocols were carried out in accordance with the European Union Directive (2010/63/EU) on the use and care of experimental animals and the ethical rules of Düzce University Animal Experiments Ethics Committee. The rats given free access to food and water were kept under standard laboratory conditions in a 12-hour light–dark cycle, at a humidity of 60± 5% and a room temperature of 23 ºC.

2.2. Experimental Groups, Chemicals and Their Doses

The rats used in the experiments were randomly selected and divided into 7 different groups, each consisting of 7 rats, as sham, control group (penicillin), irisin group, pre-seizure and during-seizure 10 nM and 100 nM irisin groups.

Urethane (Sigma-Aldrich Chemical Co., St. Louis, Missouri, USA) at a dose of 1.25 g/kg was administered as anesthetic, and 500 IU of penicillin G potassium salt (İ.E. Ulagay İlaç Sanayii Türk A.Ş., İstanbul, Istanbul, Turkey) in a volume of 2 µl was administered intracortically to induce epilepsy. Irisin (Phoenix Pharmaceuticals Inc., Burlingame, USA) was prepared at two different concentrations (low dose, 10 nM and high dose, 100 nM) by dissolving in saline. All drugs were prepared daily.

2.3. Surgical procedure and the establishment of epileptiform activity

Each rat in the groups was anesthetized with urethane just before the experiment. The rats that were found to be anesthetized were fixed in a stereotaxic frame after lying down (Harvard Instruments, South Natick, MA, USA). The scalp was incised along the midline from front to back with a scalpel, and the bone structure was reached by opening it sideways. The soft tissue on the bone structure was stripped and it was ensured that the Bregma line was clearly visible. Then, the bone tissue on the left cerebral cortex was removed by thinning with circular movements with a touring motor (FST Rechargeable Microdrill, KF Technology, Rome, Italy). Epileptiform activity was established by administering 500 IU/2 µl of penicillin G potassium intracortically (i.c.) with a Hamilton microinjector to 1.5-2 mm lateral, 1 mm anterior and 1.2 mm depth of the bregma line.

2.4. Electrophysiological recordings

Two Ag-AgCl ball electrodes were placed on the left hemisphere in the somatomotor cortex area opened lateral to the Bregma line. The reference electrode was fixed to the right ear of the rats. After the electrodes were placed, ECoG recordings were taken with the PowerLab/8SP data collection recording system (PowerLab/8SP, ADInstruments Pty Ltd. Castle Hill, NSW, Australia). A five-minute baseline activity recording was taken before the groups were injected with substances. After the baseline activity recording, irisin and saline were administered intraperitoneally the pre-seizure penicillin group and the control (penicillin) group, respectively, and ECoG recording was taken for 30 minutes. After this 30-minute ECoG recording, penicillin was injected intracortically and recording was taken for 120 minutes. The penicillin was injected intracortically after five-minute baseline activity recording to the during-seizure penicillin group, irisin was administered intraperitoneally after the occurrence of seizure, and ECoG recording was taken for 120 minutes. Only in the irisin group, after five-minute baseline activity recording, 100 nM irisin was injected and ECoG recording was taken for 120 minutes. The obtained recordings were analyzed using the PowerLab Chart v.8 software

program. Epileptiform activity occurring in bipolar spike and spike wave complexes was examined. No epileptiform activity was observed in the sham group and the irisin-alone group.

2.5. Statistical Analysis

The analyses of the data were calculated automatically via the software program (Lab Chart 8, ADInstruments Pty Ltd, Castle Hill, NSW, Australia). Epileptiform activity recordings were divided into five-minute periods and analyzed. The differences between the groups in terms of latency and spike-wave frequency and spike-wave amplitude measurements in each period were examined by Kruskal-Wallis test, and different groups were determined by post-hoc Dunn's test. SPSS program was used for the analysis of the data and $p<0.05$ was considered statistically significant.

3. Results

3.1. Latency of the epileptiform activity

There was a statistically significant difference between the groups in terms of mean latency values of epileptiform activity (P=0.005). It was observed that the onset latency of epileptic activity was quite delayed in the pre-seizure 10 nM (722.8 sec) and 100 nM (509.2 sec) irisin groups compared to the control group (282.5 sec). This delay differed according to dose rates, and it was determined that the group that the pre-seizure 10 nM irisin group mostly delayed the onset latency of epileptic activity. There was a statistically significant difference between the pre-seizure 10 nM irisin group and the control group (P=0.013) (Fig. 1).

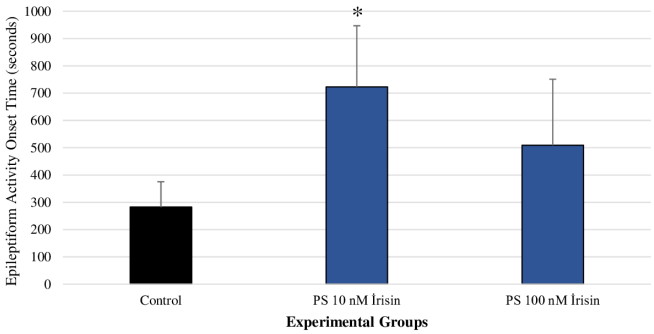

Fig. 1. Onset Latency of epileptiform activity in the control and irisin groups; (*Significant compared to the control group, P<0.05); PS: Pre-Seizure

3.2. Effects of irisin on spike wave frequency

There was a statistically significant difference in terms of mean spike-wave frequency of epileptiform activity between all groups at the 0th-120th minutes (except at the 6th-10th and 81st-85th minutes) after penicillin administration (P<0.05) (Fig. 2).

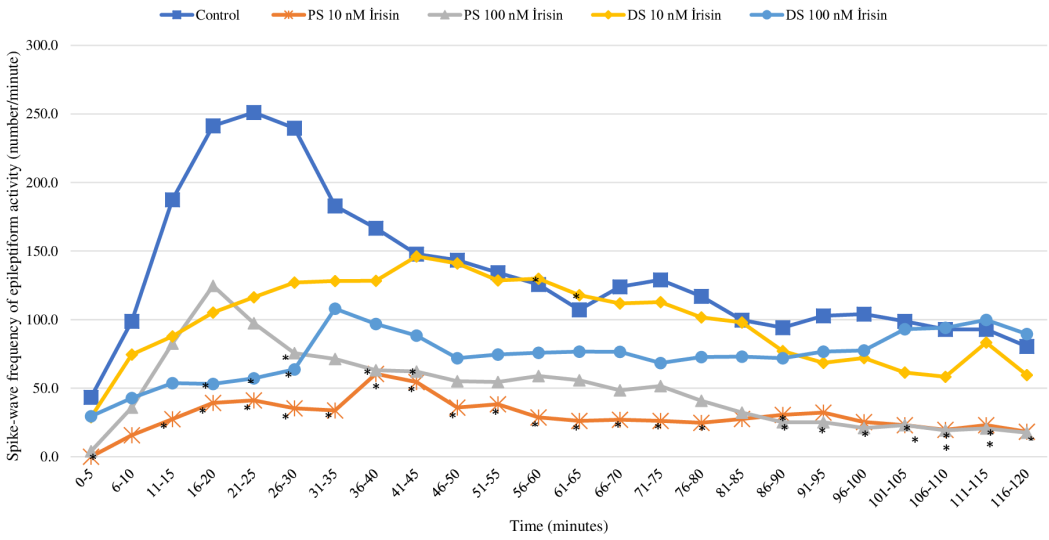

Fig. 2. Mean values of spike-wave frequency (number/minute) observed in the ECoG recording after penicillin G (intracortical) injection; (*Significant compared to the control group, P<0.05); DS: During-Seizure

3.3. Effects of irisin on total spike-wave frequency of epileptiform activity

The total spike wave frequency was significantly reduced in irisin groups, and there was a statistically significant difference between the groups in terms of total mean values of spike-wave frequency (P=0.001) (Fig. 3).

3.4. Effects of irisin on spike-wave amplitude

There was a statistically significant difference in terms of mean spike-wave amplitude of epileptiform activity between all groups at the 0th-120th minutes (except at the 0th-5th minutes) after penicillin administration (P<0.05) (Fig. 4).

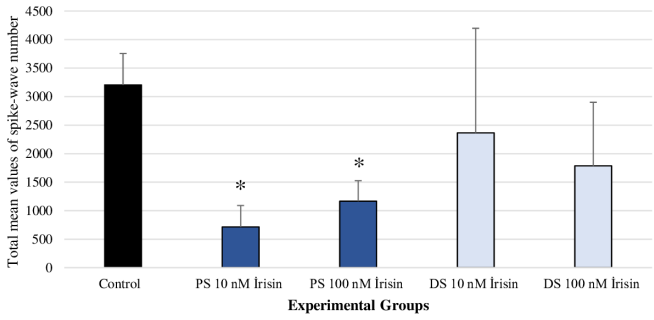

Fig. 3. Total mean values of spike-wave number of all groups; (*Significant compared to the control group, P<0.05)

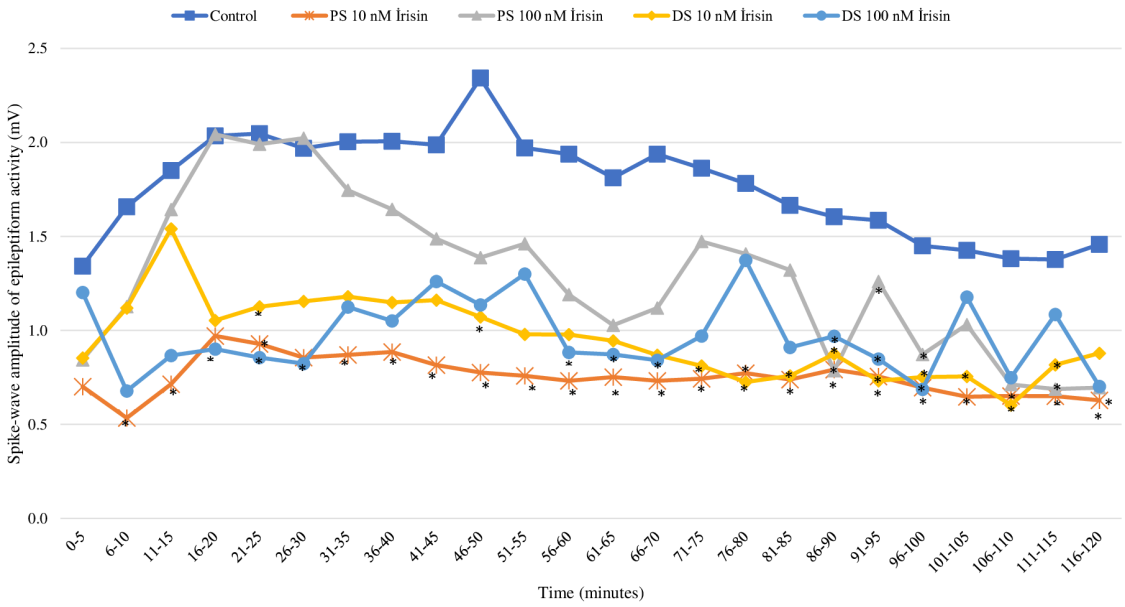

Fig. 4. Mean values of spike-wave amplitude (mV) observed in the ECoG recording after penicillin G (intracortical) injection; (*Significant compared to the control group, P<0.05)

4. Discussion

Irisin was initially identified as a skeletal muscle-derived myokine that increases with exercise to improve energy and glucose homeostasis by supporting the browning of white adipose tissue. In the following studies, it was shown to be secreted by various tissues and organs, including the brain. There are new studies investigating the effects of irisin on brain functions. In addition to its protective role against ischemia-induced neuronal damage, it also plays a role in the regulation of neuronal differentiation, metabolism and energy consumption (24). The gene expression of PGC1α (PPARγ coactivator-1α), a transcriptional coactivator that mediates many biological programs related to energy metabolism, stimulates the increase in FNDC5 gene expression. The formation of irisin, a product of FNDC5, is mainly induced by PGC1α (12).

Irisin, which is considered as a mediator of physical activity, has been extensively studied in recent years. In many studies, it was concluded that irisin levels increased with exercise (32–36). Physical activity has beneficial effects on brain health and cognitive functions. Furthermore, it is known that physical activity has protective effects against neurodegenerative diseases and improves the symptoms (37). Physical exercise is recommended as an alternative treatment to reduce epileptiform discharges and seizure frequency, to increase cardiorespiratory fitness and muscle strength, and to provide better health conditions (38). When these benefits of exercise are taken into account, it can be considered that the increase in the levels of irisin, which is defined as an intermediate in exercise, may contribute to the improvement of epileptic activity.

Mitochondrial dysfunction is considered as one of the potential causes of epileptic seizures (39). The preservation of mitochondrial function is one of the most important therapeutic approaches to prevent the development and progression of neurodegenerative diseases (40). It has been demonstrated that irisin, an exercise-related hormone, can improve the mitochondrial functions and protect against many diseases by reducing the production of reactive oxygen species (ROS) (41). With various studies conducted in parallel with this, it has been confirmed that exogenous irisin treatment improved the mitochondrial dysfunction and significantly reduces the ROS levels (42, 43).

The neuroprotective roles of irisin have been demonstrated with many studies (15–20, 37, 44). Brain-derived neurotrophic factor (BDNF) is one of the most important neurotrophic factors in the regulation of neuronal survival and neurogenesis (45, 46). Physical exercise increases BDNF levels through PGC-1α activation and modulation of FNDC-5 expression (46). With the studies conducted in recent years, it has been confirmed that irisin exerts its neuroprotective effects by increasing the expression of BDNF (43,46). Considering the neuroprotective roles of irisin in accordance with previous studies, it is considered that both exogenous and endogenous irisin may provide protection against epilepsy-induced neuronal damage (43). Neuroinflammation is known to cause neuronal hyperexcitability and an increase in seizures. Inflammation control may provide new strategies to treat seizures and epilepsy (47). In addition to its anti-inflammatory properties (26–30), irisin has protective effects against hypoxia, oxidative stress and apoptosis (48, 49). When it is also considered that inflammation promotes the occurrence of epilepsy (50), irisin level may be increased as a protective mechanism against seizure-induced neuroinflammation (24).

In seizures induced by pentylenetetrazole (PTZ), Erkeç et al. demonstrated that serum and brain FNDC5 / irisin levels of rats were significantly higher compared to the control group (31). In the study conducted by Elhady et al., epileptic children

without seizure control had higher serum irisin levels compared to control groups (24), however, in a study in which Erkeç et al. investigated possible changes in irisin levels between adult epileptic patients and healthy subjects, no significant difference was found in serum irisin levels between the groups (51). These controversial results may be associated with various factors such as patients' age, duration of antiepileptic drug treatment or antiepileptic drug type.

Irisin expression is rich in GABAergic cells that secrete GABA, a major inhibitory neurotransmitter that suppresses neuropathic pain (52-54). Exercise increases circulating GABA (55) and inhibits the reduction in glutamic acid decarboxylase, which catalyzes the decarboxylation of glutamate to GABA in the nervous system (56). Although some studies have reported that exercise supports GABA signaling (57–59), how irisin regulates the GABA pathway remains uncertain and further studies are needed in this regard (60).

Many experimental epilepsy models have been developed to evaluate the pathophysiology of epileptic seizures and to investigated new molecules with antiepileptic effect (61). The penicillin model of epilepsy was used in this study. The reason why we preferred this model was that the effects of irisin on the experimental model of epilepsy induced by penicillin have not been demonstrated previously, and our study is original in this respect. Penicillin leads to rhythmic epileptiform discharges by increasing glutamate release by inhibition of the GABAA receptor (62).

In this study, the effects of irisin administered acutely at different doses (10 nM and 100 nM) in the penicillin model of experimental epilepsy were investigated. The possible mechanism is that PGC1-α increases the circulating GABA concentration and the same substance exerts an anti-glutaminergic effect by decreasing the NMDA (N-Methyl-D-aspartate) receptor activity and increasing glutamate reuptake in astrocytes (55, 63). In the literature, no study in which the effects of irisin on epileptic seizures were investigated electrophysiologically was found, and our study is the first research in this regard.

In our study, it was determined that irisin prolonged the onset latency of epileptic activity and decreased the spike wave number and amplitude in the experimental model of epilepsy induced by penicillin. These results suggest that irisin may have antiepileptic potential. The results presented in our study show that irisin may have an antiepileptic effect. The dose values between 10 nM and 100 nM should be supported by studies in order to determine the efficacy of irisin in epilepsy. There is a need for further studies in which biochemical analyses are performed to show the change at the molecular level.

Conflict of interest

The authors declare there are no conflicts of interest.

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Authors' contributions

Concept: Y.Ş.Y, Ş.D., Design: Y.Ş.Y, Ş.D., E.B, Data Collection or Processing: Y.Ş.Y, Ş.D., E.B, A.G. Analysis or Interpretation: Y.Ş.Y, Ş.D., E.B, Ö.B, Literature Search: Y.Ş.Y, Ş.D., E.B, Writing: Y.Ş.Y, Ş.D.

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