IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies, Karabulut İ. et all., 2025; 14(1): 7-16, 14102.

Investigation of the Relationship Between Different Treatment Modalities and Blood Glucose Levels in Epilepsy

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Abstract

Epilepsy is a progressive neurological disorder characterized by recurrent seizures and exists in both acute and chronic forms. Seizures can be classified as focal or generalized. Pentylenetetrazol (PTZ) is a widely used chemical agent for inducing acute and chronic epilepsy. Resveratrol and silymarin are powerful natural compounds produced by plants in response to damage, and both have been reported to reduce epileptic symptoms. Blood glucose levels are known to decrease in epilepsy. In this study, our objective was to investigate the relationship between blood glucose levels and different treatment groups in epileptic rats. A total of 24 rats, aged 8–12 weeks, were divided into four groups. While the control group received no intervention, the other three groups were administered PTZ for 14 days. Following this, resveratrol and silymarin treatments were administered for 14 days to the respective groups. Blood glucose levels were measured and compared during the interventions. A significant difference was observed within all groups except the control group ($p < 0.05$). Intergroup comparisons revealed significant differences in the second and fourth weeks ($p < 0.05$). Notably, all groups showed a significant difference from the control group during the second week ($p < 0.05$). It is known that epilepsy reduces blood glucose levels. In the second week, differences between the control and epileptic groups were observed with the onset of chronic epilepsy. The lack of significant difference between the treatment groups and the control group in the third and fourth weeks indicates the effectiveness of the treatment protocols. It was observed that blood glucose levels decrease in epilepsy and that different treatment modalities positively influence glucose levels.

Keywords: Epilepsy, Resveratrol, Silymarin, Glucose

Introduction

Epilepsy is a neurodegenerative disorder characterized by the spontaneous recurrence of unprovoked seizures (1). Epileptic seizures are recurrent paroxysmal events characterized by stereotypical behavioral changes that reflect the underlying neuronal mechanisms of various diseases (2). Seizures are classified into three types: focal, generalized, and unknown. Focal seizures are typically short-lived, with certain frontal lobe seizures lasting only a few seconds. Generalized tonic-clonic seizures tend to last less than two minutes on average (3). Seizures affect approximately 10% of the global population and result in epilepsy in 1–2% of individuals

worldwide (4).

From a pathophysiological standpoint, epileptic seizures arise from a decreased neuronal excitability threshold, shifting the balance between excitatory and inhibitory systems toward excitation. In epileptic disorders, the coexistence of hyperexcitability—due to reduced GABAergic inhibition or enhanced glutamatergic excitation—and synchronization is widely accepted. Pathological findings typically include loss of specific excitatory and inhibitory neurons, axonal sprouting, synaptic reorganization, glial dysfunction, and structural changes (5).

PTZ can be used to model both acute and chronic epilepsy in animals. For instance, threshold doses (50–100 mg/kg) in rodents lead to myoclonic jerks, clonus, and tonic extension. However, repeated administration of subthreshold doses (20–40 mg/kg) can result in kindling phenomena (6). Many studies use Racine's seizure classification scale to assess PTZ-induced kindling. Racine demonstrated a positive correlation between increased epileptiform activity and motor seizure development in the amygdala kindling model, originally classifying seizure progression into five stages, later modified into six (7).

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural polyphenolic stilbenoid and phytoalexin, first isolated in 1939. It is produced by plants and fruits in response to damage or to combat pathogens such as bacteria and fungi. Grapes, blueberries, raspberries, mulberries, and peanuts are major sources of resveratrol, which exhibits antioxidant properties due to its phenolic nature (8,9). Several studies have shown that resveratrol enhances mechanisms that offer therapeutic benefits in epilepsy (10,11).

Silymarin, one of the main compounds of the milk thistle plant, is a flavonoid with antioxidant properties that allows it to scavenge free radicals within cells. Recent studies have shown that silymarin can treat brain damage through various mechanisms (12–15).

Glucose metabolism is highly regulated due to the energy demand required for cell survival and signaling. Even slight disruptions in metabolic pathways or the inhibition of a single enzyme can result in lactic acidosis and/or energy deficiency. In humans with epilepsy and several rodent models, glucose metabolism is disrupted. Energy deficiency likely contributes to seizure development, as the stabilization of membrane potentials and regulated neural signaling demand high energy (16,17).

This study aims to investigate the relationship between blood glucose levels and treatment with resveratrol and silymarin in epileptic rats.

Materials and Methods

In this study, 24 male Wistar Albino rats aged 8–12 weeks were used. The animals were divided into four groups, each consisting of six rats: Control, Epileptic, Resveratrol, and Silymarin. Animals were housed accordingly, and cages were labeled with group names. Animals were excluded from the experiment if deemed unfit by a veterinarian (for humane reasons), lost more than 15% of body weight, failed to consume adequate food or water, or responded poorly to stimuli. All rats were weighed weekly from the first day of the experiment, and blood glucose levels were measured weekly.

Control group: Received isotonic saline solution for 14 days.

Epileptic group: Administered 1 mL/kg of physiological saline every other day for 14 days, followed 30 minutes later by PTZ (35 mg/kg, i.p.) to induce seizures. Seizure behavior was observed for 30 minutes according to the Racine classification. At the end of 14 days, rats scoring stage 4 or higher were diagnosed with chronic epilepsy (6).

Epilepsy + Resveratrol group: Received the same PTZ protocol as the epileptic group for 14 days. Following epilepsy induction, resveratrol (20 mg/kg, i.p.) was administered daily for 14 days. Seizure activity continued to be monitored during treatment (6).

Epilepsy + Silymarin group: Also subjected to PTZ-induced epilepsy as described above. After confirming chronic epilepsy, silymarin was administered intraperitoneally at 200 mg/kg/day for 14 days. The doses were prepared weekly and stored at -18°C. Seizure activity was monitored during treatment.

All rats were weighed weekly, and blood glucose levels were measured and recorded. Initial and final results were noted and analyzed (6).

Results

In this study, we investigated the relationship between blood glucose levels in epileptic rats and different treatment groups. Blood glucose levels were recorded weekly, starting from the beginning of the experiment.

In the epileptic groups, PTZ was administered every other day for 14 days. Subsequently, the resveratrol and silymarin groups received their respective treatments daily for 14 days. Thus, the experimental period lasted a total of 28 days (4 weeks).

Throughout the experiment, rats were weighed weekly and their blood glucose levels measured. The average glucose levels for each group and time point are detailed in the tables provided in the original study. Overall, a decreasing trend in blood glucose was observed in epileptic rats following the induction of seizures. However, treatment with resveratrol and silymarin resulted in a reversal of this trend by the third and fourth weeks.

The blood glucose levels of the rats included in our study are presented in the tables above. In the control group, the baseline blood glucose levels ranged between 84–113 mg/dl, with a mean value of 103 mg/dl. In the first week, blood glucose levels ranged from 91–120 mg/dl, with a mean value of 100.66 mg/dl. In the second week, the levels ranged between 97–111 mg/dl, with an average of 105.33 mg/dl. In the third week, they ranged from 95–115 mg/dl, with a mean value of 105.33 mg/dl. At the end of the experiment, blood glucose levels were between 98–113 mg/dl, with an average value of 102.66 mg/dl.

The measurements of the control group rats were conducted over a total period of five weeks, with one measurement taken each week, including baseline and final measurements. The reason for the five-week duration was to ensure consistency with the treatment protocols applied to the

other groups, which also lasted five weeks. Accordingly, the control group measurements were aligned with these protocols.

In the epileptic rat group, baseline blood glucose levels ranged from 103 to 127 mg/dl, with a mean value of 110.2 mg/dl. In the first week, blood glucose levels were between 96 and 106 mg/dl (mean: 101.1 mg/dl). In the second week, the levels ranged from 92 to 100 mg/dl, with an average of 96.5 mg/dl. In the third week, glucose levels were between 85 and 109 mg/dl, with a mean value of 93.8 mg/dl. At the end of the experiment, blood glucose levels ranged from 80 to 96 mg/dl, with a mean of 86 mg/dl.

In the epileptic-resveratrol rat group, baseline blood glucose levels ranged from 95 to 113 mg/dl, with a mean value of 104.1 mg/dl. In the first week, levels ranged between 90 and 108 mg/dl (mean: 97.5 mg/dl). In the second week, blood glucose levels were between 83 and 93 mg/dl, with a mean value of 87.3 mg/dl. In the third week, levels ranged from 94 to 106 mg/dl (mean: 101 mg/dl). At the end of the experiment, blood glucose levels ranged from 101 to 125 mg/dl, with a mean of 109 mg/dl.

In the epileptic-silymarin rat group, baseline blood glucose levels ranged from 88 to 112 mg/dl, with a mean value of 99.5 mg/dl. In the first week, glucose levels were between 79 and 109 mg/dl (mean: 93.3 mg/dl). In the second week, levels ranged from 79 to 100 mg/dl, with an average of 91.5 mg/dl. In the third week, blood glucose levels were between 86 and 113 mg/dl (mean: 101 mg/dl). At the end of the experiment, the levels ranged from 90 to 127 mg/dl, with a mean value of 109.8 mg/dl.

As a result of the non-parametric analysis of the findings, the temporal changes within the groups are shown in the tables below.

Table 1. Temporal Changes Within Groups

Group	Test Statistic	p-Value
C	1.47	0.83
E	21.20	0.0003
ER	17.12	0.0018
ES	18.80	0.0009

C: Control group, **E**: Epilepsy group, **ER**: Epileptic Resveratrol group, **ES**: Epileptic Silymarin group

Statistical analysis showed no significant temporal change within the control group ($p > 0.05$). However, significant changes were detected within the Epileptic, Epileptic + Resveratrol, and Epileptic + Silymarin groups ($p < 0.05$), indicating that epilepsy had a notable impact on blood glucose levels.

According to the Kruskal-Wallis analysis, intergroup comparisons showed no significant difference at the beginning (T0) and first week (T1). In contrast, significant differences were found in the second (T2) and fourth (T4) weeks ($p < 0.05$). Notably, the second week marked the emergence of chronic epilepsy, which corresponded with significant reductions in blood glucose levels in the epileptic groups compared to the control group.

Table 2. Changes in Groups Based on Time Points

Time Point	Test Statistic	p-Value
T0 (Baseline)	2.65	0.448
T1	1.49	0.683
T2	14.38	0.0024
T3	5.81	0.121
T4 (Final)	13.46	0.0037

T0: Beginning of experiment, **T1**: Week 1, **T2**: Week 2, **T3**: Week 3, **T4**: Week 4

When we look at this table, the beginning of the experiment was taken as T0. At the beginning of the experiment, no significant difference was found between the groups ($p>0.05$). Week 1 was shown as T1 and the difference between the groups was not found significant in the first week ($p>0.05$). When Week 2 was taken as T2, the difference between the groups was found significant ($p<0.05$). When Week 3 (T3) was examined, there was no significant difference between the groups ($p>0.05$). In Week 4, there was a significant difference between the groups ($p<0.05$).

Table 3. Control and Epilepsy Group

Time	Test Statistic	p-Value

Time	Test Statistic	p-Value
T0	11.0	0.297
T1	12.5	0.423
T2	33.5	0.016
T3	31.5	0.037
T4	36.0	0.005

T0: Beginning of experiment, **T1**: Week 1, **T2**: Week 2, **T3**: Week 3, **T4**: Week 4

When the control and epilepsy groups were compared, no significant difference was found at the beginning of the experiment and in the 1st week ($p>0.05$). However, a significant difference was observed in the 2nd week, 3rd week and 4th week ($p<0.05$).

Table 4. Control and Epileptic Resveratrol Group

Time	Test Statistic	p-Value
T0	17.5	1.000
T1	20.0	0.818
T2	36.0	0.0049
T3	28.5	0.109
T4	10.0	0.228

T0: Beginning of experiment, **T1**: Week 1, **T2**: Week 2, **T3**: Week 3, **T4**: Week 4

When the control and epileptic resveratrol groups were analyzed, a significant difference was observed only in the 2nd week ($p<0.05$).

Table 5. Control and Epileptic Silymarin Group

Time	Test Statistic	p-Value
T0	21.0	0.687
T1	23.0	0.485
T2	33.5	0.016
T3	21.5	0.630
T4	12.0	0.376

T0: Beginning of experiment, **T1**: Week 1, **T2**: Week 2, **T3**: Week 3, **T4**: Week 4

When the control and epileptic silymarin groups were examined, a significant difference was found only in the 2nd week ($p<0.05$). In the analysis of the control and epileptic groups, the control group was significantly differentiated from the other groups in the 3rd and 4th weeks.

Further pairwise comparisons between the control and each treatment group revealed that only the second week showed significant differences ($p < 0.05$), suggesting that resveratrol and silymarin exerted a normalizing effect on glucose levels by the third and fourth weeks.

The Mann-Whitney U test results confirmed that significant differences existed between the control group and all other groups in the second week, reflecting the onset of epilepsy and its impact on glucose metabolism.

Discussion

In this study, we explored the relationship between blood glucose levels and different treatment protocols in epileptic rats. Weekly blood glucose measurements indicated that PTZ-induced chronic epilepsy significantly lowered blood glucose levels, likely due to increased seizure activity and corresponding energy demands.

Glucose metabolism is tightly regulated, as it is essential for cell survival and intracellular communication. Previous studies have demonstrated that glucose metabolism is impaired in both humans with epilepsy and in several rodent models. The resulting energy deficit likely contributes to seizure activity, given that stabilizing membrane potentials and regulating neuronal signaling require high energy input.

Our findings support this mechanism: while the control group did not show any significant

variation in glucose levels over time, the epileptic groups displayed marked reductions, suggesting that epilepsy disrupts glucose metabolism. Notably, the significant drop in blood glucose observed in the second week aligns with the onset of chronic epilepsy and heightened seizure activity.

Additionally, by the third and fourth weeks, blood glucose levels in the resveratrol- and silymarin-treated groups showed a return toward normal values, indicating that both treatments may reduce seizure frequency and severity, and consequently mitigate excessive glucose consumption in the brain.

Statistical analyses further revealed that a significant difference between the control group and all treatment groups was only present during the second week. This suggests that the therapeutic effects of resveratrol and silymarin began to manifest after this time point, alleviating seizure severity and supporting glucose homeostasis.

These findings are consistent with previous research, including the work of ChunCheng Li et al., which identified a relationship between diabetes and epilepsy. Our results reinforce the idea that glucose metabolism plays a central role in seizure dynamics and that interventions targeting this pathway may be therapeutically valuable.

Conclusion

In conclusion, this study demonstrates that chronic epilepsy significantly reduces blood glucose levels. The increase in seizure frequency and excessive cellular activity likely leads to elevated glucose consumption by brain cells.

In groups treated with resveratrol and silymarin over the final 14 days, partial improvement in the chronic epileptic condition and a reduction in seizure frequency were observed. Consequently, blood glucose levels approached normal values by the third and fourth weeks.

A significant difference between the control group and the resveratrol group was only observed during the second week, indicating that the epileptic state was successfully induced by then. However, by the third and fourth weeks, the therapeutic effects of resveratrol appeared to reduce seizures and related symptoms. Similarly, in the silymarin-treated group, significant differences from the control group were also only seen during the second week, suggesting that silymarin helped normalize blood glucose levels by mitigating epileptic symptoms.

Overall, the results suggest that epilepsy significantly lowers blood glucose levels, and that resveratrol and silymarin may provide therapeutic benefits by restoring glucose homeostasis.

Conflict of Interest

The authors declare that there is no conflict of interest.

Support Resources

This TIP.24.015 research was supported by the Scientific Research Projects Coordination Unit of Dicle University.

Ethical Declaration

Prior to the study, ethical approval was obtained from the Animal Experiments Ethics Committee of Dicle University Health Sciences Application and Research Center under protocol number 2023/36.

Acknowledgments

We express our sincere thanks to the Dicle University Experimental Animals Research Center for their support.

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