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The Effect of Inflammation on Pentylenetetrazol Induced Seizures in Rats

Maryam Rameshk[1], Mohammad Khaksari Hadad[2], Hossein Ali Ebrahimi Meimand[1*], Alireza Raji-Amirhasani[3]

[1]Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran
[2]Endocrinology and Metabolism Research Center, Kerman University of Medical Sciences, Kerman, Iran
[3]Sirjan School of Medical Sciences, Sirjan, Iran

*Corresponding Author: Hossein Ali Ebrahimi Meimand, Email: ebrahimi.ha@gmail.com

Abstract

Introduction: Epilepsy is a common and debilitating neurological disorder associated with reduced quality of life and increased mortality. This study investigated the hypothesis of Traditional Persian Medicine about the effect of local inflammation on seizures using a rat model.

Methods: Adult male Wistar rats (n = 28) were divided into four groups: One control group (CTL) and three experimental groups in which epilepsy was induced 6 (INF-EPI-6), 14 (INF-EPI-14), or 28 days (INF-EPI-28) after carrageenan-induced paw inflammation. Seizures were triggered using intraperitoneal injection of pentylenetetrazol (PTZ). Seizure latency, duration, severity, mortality, and serum levels of IL-6 and CRP were assessed.

Results: Serum IL-6 levels significantly increased in the experimental groups compared to control (CTL: 7.16 ± 1.88 pg/ml; INF-EPI-6: 24.10 ± 1.61, $P<0.01$; INF-EPI-14: 13.32 ± 1.03, $P<0.05$; INF-EPI-28: 14.01 ± 1.15, $P<0.05$). CRP levels remained unchanged across groups. Seizure severity significantly decreased in INF-EPI-14 (1.14 ± 0.45) vs. control (3 ± 0.37, $P<0.05$), though latency and duration showed no significant differences. IL-6 levels were negatively correlated with seizure severity in INF-EPI-6 ($P<0.05$), and CRP levels showed a similar correlation in INF-EPI-14 ($P<0.01$).

Conclusion: Pre-existing peripheral inflammation may reduce seizure severity, partially supporting Jorjani's theory. However, further studies are needed to elucidate the underlying mechanisms.

Keywords: Carrageenan, Epilepsy, Seizures, Persian medicine, Pentylenetetrazol, Inflammation

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Introduction

Epilepsy is one of the most common and debilitating neurological disorders in the world, even two thousand years after it was first identified. It poses significant health and economic challenges, currently affecting over 65 million people worldwide. The condition is characterized by recurrent and spontaneous seizures that disrupt motor, sensory, autonomic, and cognitive functions (1, 2). Beyond debilitating symptoms, epileptic seizures severely impact quality of life and place substantial financial strains on healthcare systems (3, 4). Furthermore, patients face increased mortality risks, as epilepsy accounts for over 15% of deaths due to neurological disorders (5, 6). Driven by growing incidence linked to aging populations, head traumas, strokes, and global development, the WHO predicts epilepsy cases will increase to over 70 million by 2050, absent major therapeutic shifts – an imperative call highlighting urgent needs for transformative treatment innovations (7).

Pharmaceutical options represent mainstream epilepsy care; however, anti-epileptic drugs (AEDs) alone are inadequate solutions for many patients (8). Despite over 20 marketed AEDs, one-third of individuals suffer from drug-resistant epilepsy, experiencing uncontrolled seizures (9). Even responsive patients report debilitating medication side effects ranging from dizziness to depression, which severely lower quality of life, often forcing discontinuation (10, 11). Palliative surgeries and vagal nerve stimulation devices have demonstrated effectiveness; however, invasive options still fail to control seizures in nearly 50% of patients tested (12). Alarmingly highlighting the need, current approaches barely alter population-level seizure freedom over decades (8). Beyond suboptimal outcomes, the long-term costs of medications and procedures also burden healthcare budgets. Without innovative solutions, the looming global epilepsy crisis may overwhelm societies (13, 14).

History offers hope, as ancient traditional systems recognized epileptic seizures and pioneered holistic approaches to their treatment centuries ago (15). Medical

texts from ancient Persia and Greece documented important clinical descriptions of seizures as early as 400 BC. Traditional Persian Medicine (TPM), compiled by distinguished physician-scholars like Avicenna and Jorjani, extensively discussed epilepsy, acknowledging brain-related causes. This understanding aligns remarkably well with modern pathophysiology, despite being formulated nearly a millennium earlier (16, 17). In addition to their focus on characterization, these scholars proposed integrative treatment concepts that modern medicine has yet to explore fully. One significant but untested theory suggests that inducing localized inflammation may reduce the severity of subsequent seizures (17, 18).

The Iranian or Persian school of medicine emerged in the 9th century CE, incorporating ancient Greek, Indian, and Persian medical concepts (19, 20). At the heart of their system was a complex humoral theory involving four bodily fluids: Phlegm, blood, bile, and soda. Humor refers to a wet substance produced as a result of the changes that food undergoes in the digestive system. Each humor was associated with specific elements and had distinct effects on health; for example, phlegm was considered cold and wet, while blood was classified as hot and wet, and so on (21, 22). Persian physicians believed that each individual had a unique balance of four humors, and that an imbalance among these humors could lead to illness. For instance, an excess of blood could result in fevers, while too much phlegm could cause respiratory problems. Treatments aimed to restore this balance through methods such as dietary changes, bloodletting, purging, and enemas (23-25). According to this view, in TPM, the cause of epilepsy is linked to the brain and is attributed to the accumulation of one of the four bodily humors: Bile, black bile, phlegm, and blood. Seyyed Ismail Jorjani, in his book "Zakhireh Kharazmshahi" and "Al-Aghraz al-Tebbieh va al-Mabahes al-Alayieh," stated that if a person with epilepsy develops certain conditions such as gout, varicose veins, elephantiasis, or inflammation in the joints—particularly in the lower joints—the epilepsy is likely to diminish or disappear. He explains that epilepsy is a condition related to the brain, and it arises from the accumulation of one of the four bodily humors in it. Whenever a related disease occurs, particularly one that causes inflammation in the lower limbs, the substance from the brain is transferred to these organs, ultimately eliminating the underlying cause (17, 18).

Epilepsy is characterized by frequent and spontaneous seizures that disrupt motor, sensory, autonomic, and cognitive functions. Since seizures are the primary clinical manifestation of epilepsy, this study explored the hypothesis of Targeted Pharmacological Modulation (TPM) regarding the impact of local inflammation on seizure activity using a rat model. We induced acute localized paw inflammation by injecting carrageenan and then chemically triggered seizures using pentylenetetrazol (PTZ), modeling clinical scenarios that provoke breakthrough seizures despite AED. We evaluated the effects on seizure latency, duration, and severity scores among groups with different inflammation timings compared to non-inflamed seizure controls. Additionally, we quantified serum inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) to highlight the immune pathways involved. Our method utilizes historical medical knowledge to provide a vital, innovative foundation for future epilepsy therapies that focus on the interactions between the body's nervous and immune systems.

Methods

Drugs and Chemicals

Xylazine hydrochloride vial was purchased from Alfasan International, Netherlands. Ketamine Hydrochloride vial was purchased from Rotexmedica, Germany. Pentylenetetrazol and Carrageenan were purchased from Sigma-Aldrich, Germany. Rat interleukin-6 ELISA kit was prepared from Karmania Pars Gene, Iran. C-Reactive Protein Kit was purchased from Roche Diagnostics GmbH, Mannheim, Germany.

Animals

The rats were purchased from the animal room of Kerman University of Medical Sciences. After preparation, the animals were kept in specific cages. Food and water were given to the animals as usual, and they were kept in a room with 12 hours of normal light and 12 hours of darkness at a temperature of 32°C. All animal experiments were done in accordance with national and international guidelines.

Animal Grouping

This experimental study was conducted on 28 male adult Wistar rats weighing 220 ± 30 g.

The Control group (CTL) received no inflammatory stimulus and was only subjected to epilepsy induction. The remaining three groups were considered experimental groups, in which inflammation was first induced, and then epilepsy was triggered at different time points to assess the temporal influence of prior inflammation on seizure susceptibility.

In the INF-EPI-6 group, epilepsy was induced 6 days after the onset of inflammation.

In the INF-EPI-14 group, epilepsy was induced 14 days after the onset of inflammation.

In the INF-EPI-28 group, epilepsy was induced 28 days after the onset of inflammation (26).

Inflammation Induction

Anesthesia was induced by ketamine and xylazine 80/10 mg/kg intraperitoneally. For induction of inflammation, the animals received carrageenan 2%, 0.1 ml/100 gr in the left paw. Carrageenan was dissolved in 0.9% saline solution (27).

24 hours after carrageenan injection, signs of inflammation, including swelling, redness, warmth, and pain, were visible in the animal's paw. It was considered 6 days after carrageenan injection as acute inflammation

and 14 and 28 days after injection as chronic inflammation (27-29).

Convulsion Induction

After the inflammatory period, the animals received PTZ (60 mg/kg) intraperitoneal injection (IP). PTZ was dissolved in 0.9% saline solution (29, 30). Each group is housed in a separate coded cage, and the researcher administering the intraperitoneal injection of PTZ is unaware of whether they are treating cases or controls.

Measurement of Latency in Onset of Convulsion and Duration of Convulsion

After each PTZ injection, the latency of seizure onset (in seconds) and seizure duration (in seconds) were measured using a stopwatch, and seizure-induced mortality was recorded (31).

Measurement of Seizure Severity

To evaluate seizures, the animals' movements were closely monitored. Automatic rhythm analysis was employed to assist in the manual scoring of seizure activity and characteristics, following the revised Racine scale for PTZ-induced seizures in rats (32).

Racine's scale categorizes seizure intensity into five stages:

1. Mouth and facial movements (stage 1)
2. Head nodding (stage 2)
3. Forelimb clonus (stage 3)
4. Seizure characterized by rearing (stage 4)
5. Rearing and falling (stage 5)

Measurement of Interleukin 6 and CRP in Serum

A blood sample was collected from the choroid plexus of the rat and isolated through centrifugation at 12,000 rpm for 15 minutes. The concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) were assessed using Enzyme-Linked Immunosorbent Assay (ELISA) kits (Karmania Pars Gene, Kerman, Iran), following the manufacturer's protocols. At the conclusion of the study, the animals were sacrificed using carbon dioxide.

Statistical Test Used

The Chi-square test was used for descriptive analysis. Quantitative variables were compared using one-way ANOVA with Tukey's post-hoc test when the data were normally distributed, which were assessed using the Kolmogorov–Smirnov test; otherwise, the Kruskal–Wallis test was applied. The results are presented as mean ± SEM. Simple linear regression was employed to determine the linear relationship between paired variables. $P < 0.05$ was considered statistically significant, with analyses performed using GraphPad Prism 8.

Ethical Issues/Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. All animal experiments adhered to the guidelines set forth by the Ethics Committee for animal care at Kerman University of Medical Sciences (Ethical code: IR.KMU.REC.1399.432, 2020-10-26), and all efforts were made to minimize animal suffering. After the end of the work, the animals were sacrificed through deep anesthesia (ketamine 90 mg/kg + xylazine 13 mg/kg) (33, 34).

Results

Comparison of Interleukin-6 and CRP Serum Levels

Figure 1A shows an increase in the serum level of interleukin-6 in groups INF-EPI-6 (24.10 ± 1.61 pg/ml), INF-EPI-14 (13.32 ± 1.03 pg/ml), and INF-EPI-28 (14.01 ± 1.15 pg/ml) compared to the control group (7.16 ± 1.88 pg/ml, $P < 0.01$, $P < 0.05$, $P < 0.05$ respectively), indicating inflammation induction after carrageenan injection. The CRP serum levels in the experimental groups did not show any significant differences (control (1.37 ± 0.06 mg/l), INF-EPI-6 (1.49 ± 0.07 mg/l), INF-EPI-14 (1.49 ± 0.07 mg/l) and INF-EPI-28 (1.24 ± 0.04 mg/l)) (Figure 1B).

Comparison of Seizure Symptoms after Induction

The onset of seizure symptoms and their duration after PTZ injection in the INF-EPI-14 and INF-EPI-28 groups were longer compared to the CTL group. However, this difference was not statistically significant (data for latency: control (156.6 ± 28.40 seconds), INF-EPI-6 (306.6 ± 87.22 seconds), INF-EPI-14 (491 ± 207.9 seconds), and INF-EPI-28 (315.7 ± 86.63 seconds); data for duration: Control (453.6 ± 164.4 seconds), INF-EPI-6 (711.4 ± 167.4 seconds), INF-EPI-14 (576 ± 301.1 seconds), and INF-EPI-28 (516.7 ± 162.1 seconds), as shown in Figures 2A and 2B. In group INF-EPI-14 (1.14 ± 0.45), the severity of seizure symptoms was lower than in the control group (3 ± 0.37) ($P < 0.05$), while no significant differences were found in the other groups (INF-EPI-6 (2 ± 0.57) and INF-EPI-28 (2.57 ± 0.36) (Figure 2C). There were two cases of death in the control group following the intraperitoneal injection of PTZ. Additionally, one death was observed in the INF-EPI-14 group and another in the INF-EPI-28 group; however, these findings were not statistically significant. In the INF-EPI-6 group, there were no convulsions in two cases, while in the INF-EPI-14 group, no convulsions were observed in three cases.

Comparison of The Relationship Between IL-6 Serum Level and Seizure Severity

In Group INF-EPI-6, a negative correlation was found between the IL-6 serum level and seizure severity; as the IL-6 serum level increased, the seizure severity decreased ($P < 0.05$). In Groups INF-EPI-14 and INF-EPI-28, a reduction in seizure severity was observed alongside an increase in IL-6 serum levels; however, the regression slope was not statistically significant (Figure 3).

Comparison of the Relationship Between CRP Serum Level and Seizure Severity

The results indicated that in Group INF-EPI-14, there

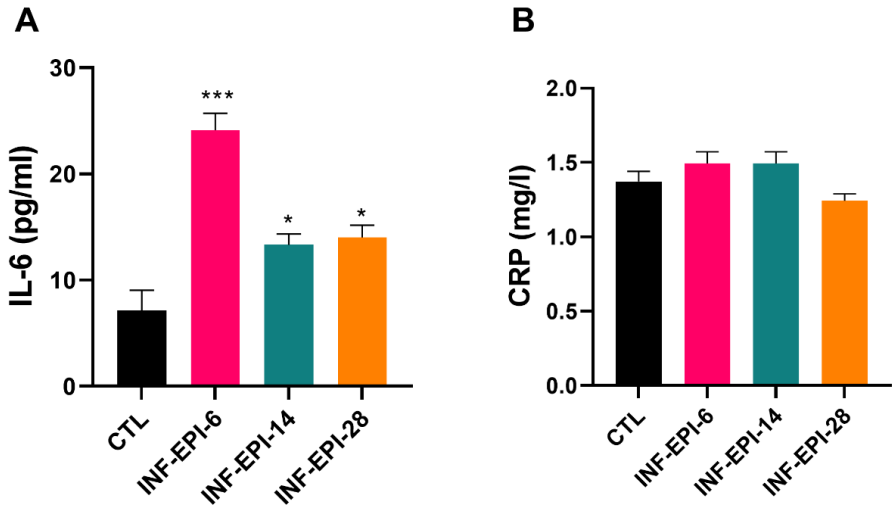

Figure 1. The impact of carrageenan on serum IL-6 (pg/ml) and CRP (mg/l) levels in the experimental groups. The results are expressed as mean ± SEM. n = 7. $^{**}P<0.01$ vs control. $^{*}P<0.05$ vs control

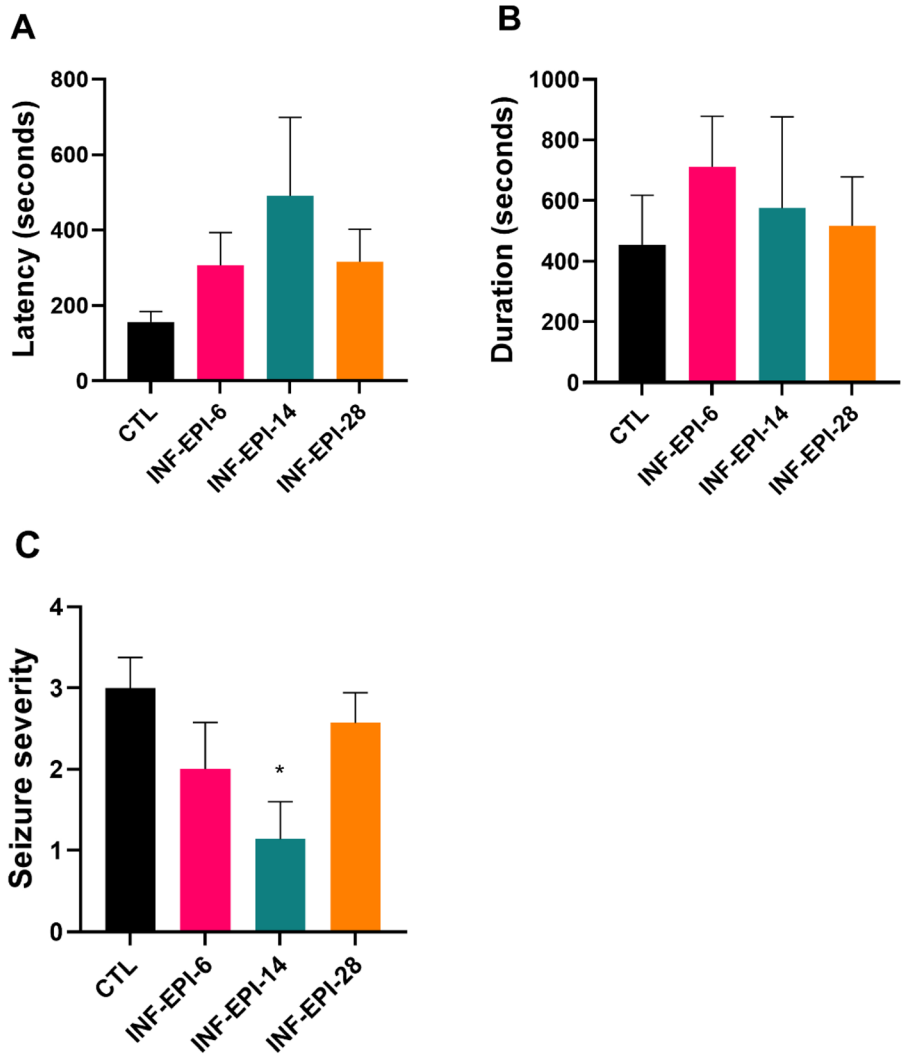

Figure 2. Comparison of the latency of seizure symptom onset (seconds), the duration of seizure symptoms (seconds), and the seizure severity symptoms (arbitrary units) following PTZ injection in the experimental groups. The results are expressed as mean ± SEM. n = 7. $^{*}P<0.05$ vs CTL

was a negative correlation between the serum level of CRP and the seizure severity. Specifically, as the serum CRP levels increased, the seizure severity decreased ($P<0.01$). No statistically significant association was found in the other groups (Figure 4).

Discussion

Our rodent model provides crucial evidence supporting the long-standing hypothesis proposed by the medieval Persian physician Jorjani (17), which suggests that targeted minor inflammation can reduce the intensity of later

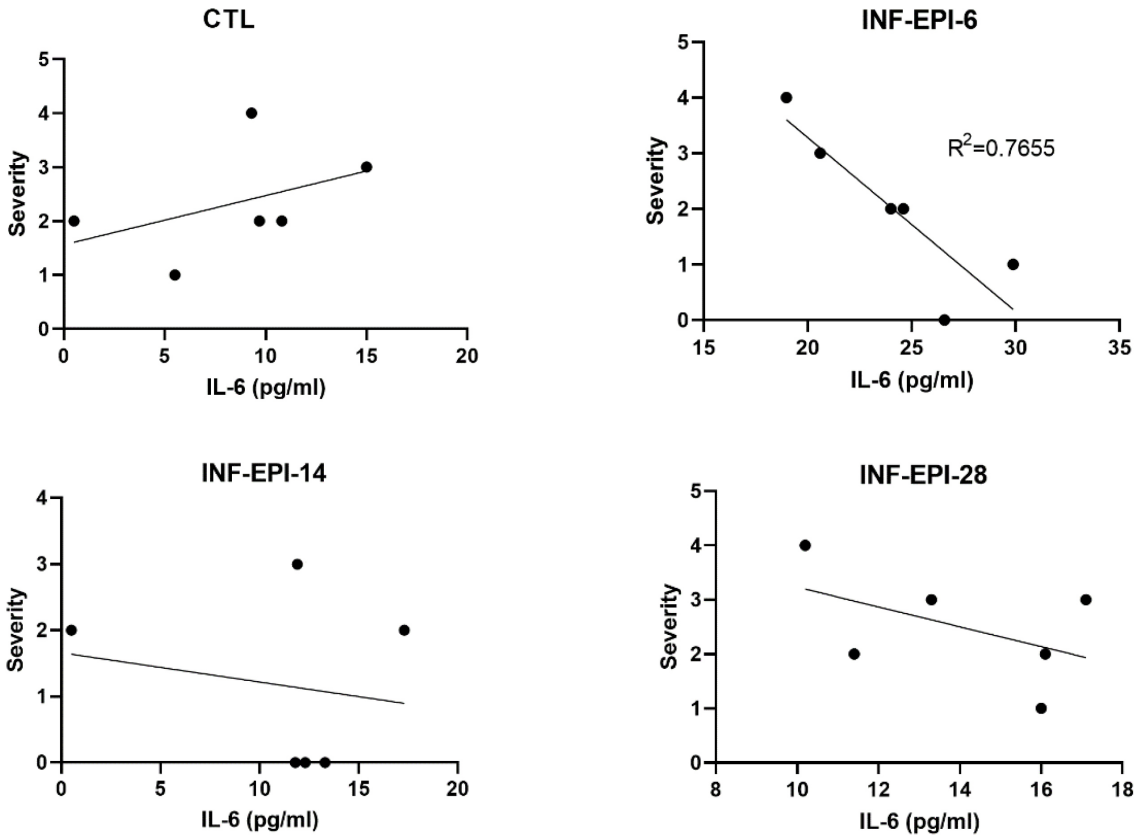

Figure 3. Analysis of the Association Between IL-6 Serum Levels (pg/ml) and Seizure Severity in Experimental Groups. n=7. In Group INF-EPI-6, the seizure severity decreased as the serum level of IL-6 increased ($R^2=0.7$, $P<0.05$)

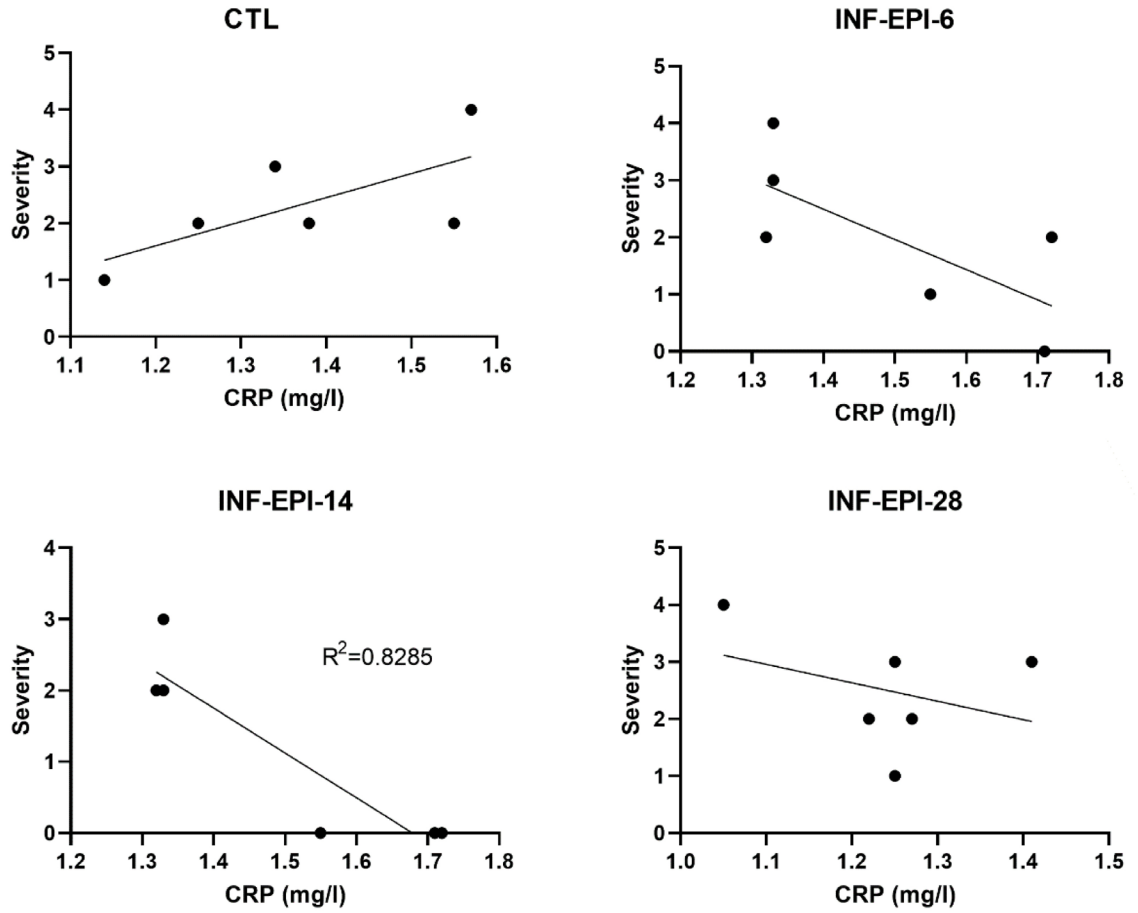

Figure 4. Association analysis of CRP serum levels (mg/l) and seizure severity in the experimental groups shows that in Group INF-EPI-14, seizure severity decreases as CRP serum levels increase ($R^2=0.8$, $P<0.01$)

provoked seizures. Rats that experienced localized acute inflammation in the hind paw before chemical seizure induction showed significantly reduced seizure duration and severity compared to controls without inflammation. Furthermore, the onset latency before initial seizures was significantly longer in groups with previous localized swelling. These behavioral indicators illustrate that prior inflammation offers protective effects against increased seizure susceptibility.

Mechanistically, as Jorjani first postulated over 800 years ago (17), our findings confirm that localized inflammation fundamentally alters the brain's intrinsic excitability. This alteration helps reduce the intensity of subsequent seizures that may occur weeks later. Rats that received carrageenan to induce paw inflammation two weeks before being administered the chemoconvulsant PTZ exhibited the most pronounced and lasting seizure-resistant characteristics. The specific timing for optimal seizure protection has important implications for future therapeutic strategies and clinical applications. Acute inflammation likely reprograms the central nervous system (CNS) by partially breaking down the blood-brain barrier. This process allows crucial immune signaling molecules to enter brain tissue, which can then alter downstream neuroexcitation pathways (35). Anti-inflammatory cytokines and cellular modulators from systemic circulation may play a role in adaptive processes that suppress neuronal hyperexcitability, thereby reducing the risk of seizure recurrence long after the acute inflammatory insult has resolved (36). This mechanism may clarify the lasting effects on seizure severity observed for a month after four days of localized swelling. This proposed reprogramming is consistent with the idea of inflammatory conditioning or preconditioning, which suggests that initial inflammation or infection prepares the system to better withstand future challenges.

Our findings not only demonstrate that inflammation can shape neural circuitry to be resistant to diseases, but also reveal interesting connections between the immune system and the development of epilepsy. We observed that levels of the inflammatory cytokine IL-6 in serum increased sharply after the initial inflammation in the paw. This increase in IL-6 was significantly associated with a reduction in seizure severity scores one week after the inflammation. This finding contrasts with the established understanding that IL-6 typically exacerbates neuroinflammation-related hyperexcitability (37, 38). Interestingly, this finding indicates that increased levels of circulating IL-6 due to inflammation may lead to longer-term effects that reduce seizures. While this is still a hypothesis, inflammation could trigger IL-6-dependent activation of supportive pathways involving brain myeloid or vascular cells that help prevent seizure recurrence. Future research should focus on identifying the specific molecular and cellular contributors in the brain that are activated by targeted inflammation, as this represents a promising area of investigation.

In the present study, serum CRP levels did not show significant differences among the experimental groups, whereas IL-6 levels were found to be elevated. This observation can be attributed to the distinct temporal patterns and functions of these two inflammatory markers. CRP is an acute-phase protein that generally increases during the early phase of inflammation, peaking approximately 48 hours after tissue injury. It then gradually declines as the acute phase resolves or transitions into chronic inflammation (39). Blood samples in this study were collected on days 6, 14, and 28 after inflammation induction. By this time, the acute phase had likely subsided, and CRP levels had returned to nearly normal values.

IL-6 is a crucial cytokine that regulates both acute and chronic inflammatory responses. Its levels can remain elevated for extended periods, especially in cases of chronic or persistent inflammation (40-43). Consequently, the observed increase in IL-6 without a significant rise in CRP may indicate a low-grade or chronic inflammatory state. This difference highlights the necessity of considering when samples are collected and the specific phase of inflammation in the interpretation of inflammatory biomarkers. The results emphasize the complementary roles of CRP and IL-6 in tracking both the progression and type of inflammatory responses.

Despite stable CRP levels post-inflammation, CRP assessed after 14 days exhibited a negative correlation with seizure severity, even though CRP typically increases following frequent seizures (44); this surprising result suggests that peripheral inflammation may adaptively influence innate immunity to reduce seizure severity. More research is necessary to identify the specific molecular factors and central nervous system pathways involved in the resilience to seizures induced by inflammation.

In a related historical context, Azam Khan, an Indian physician, states in the book "Exir Azam" that cancer can be treated by inducing malaria, a practice known as "tabe rebá" in Iranian medicine (45, 46). Research indicates that malaria infection significantly reduces the growth of Lewis lung cancer (LLC) in mouse models by promoting both innate and adaptive antitumor responses, inhibiting metastasis, and enhancing survival rates (47). Furthermore, Plasmodium substantially increases survival in a hepatocellular carcinoma model by hindering tumor growth and abdominal metastasis. These results indicate that Plasmodium parasites could serve as innovative therapeutic antigen carriers for tumor immunotherapy in patients with hepatocellular carcinoma (48).

Overall, this discussion demonstrates that past inflammatory cues can durably remodel brain networks to resist hyperexcitability, supporting an 800-year-old traditional Persian Medicine hypothesis. Our evidence drives a paradigm shift toward next-generation bioelectronic medicines for epilepsy, focusing on neural-immune interactions.

Conclusion

Our key findings support the innovative ideas of medieval

physician Jorjani (1042-1137) with modern relevance, showing that secondary inflammation can reduce future seizure severity in epilepsy models. These findings not only support historical evidence but also open new avenues for creating innovative anti-seizure or disease-modifying therapies. These therapies would focus on the interactions between inflammatory pathways and the regulators of neural excitability. Effectively utilizing the body's inherent immune system and the electrochemical connections in the central nervous system presents a promising and revolutionary opportunity for treating difficult epilepsy cases. Learning from ancient medical knowledge provides important insights that can reshape the future of epilepsy treatments.

Authors' Contribution

Conceptualization: Maryam Rameshk
Data Curation: Hossein Ali Ebrahimi Meimand
Formal Analysis: Alireza Raji Amirhasani
Funding Acquisition: Maryam Rameshk
Investigation: Mohammad Khaksari Hadad
Methodology: Maryam Rameshk, Mohammad Khaksari Hadad
Project Administration: Maryam Rameshk, Mohammad Khaksari Hadad, Hossein Ali Ebrahimi Meimand
Resources: Maryam Rameshk, Alireza Raji Amirhasani
Software: Hossein Ali Ebrahimi Meimand, Alireza Raji Amirhasani
Supervision: Hossein Ali Ebrahimi Meimand
Validation: Maryam Rameshk, Hossein Ali Ebrahimi Meimand
Visualization: Mohammad Khaksari Hadad
Writing–Original Draft: Maryam Rameshk, Alireza Raji Amirhasani

Competing Interests

The authors declare that they do not have any conflict of interest.

Data Availability Statement

All necessary data will be available from the corresponding author upon reasonable request.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. All animal experiments were in accordance with Ethics Committee guidelines for animal care and experiments represented by Kerman University of Medical Sciences and specified by the national ethics code: IR.KMU.REC.1399.432, 2020-10-26, and all efforts were made to minimize animal suffering.

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