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Research Article

Anticonvulsant and Neuroprotective Effects of Felodipine in a PTZ-Induced Epileptic Seizure Model

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Abstract

Aim: This research sought to evaluate the anticonvulsant properties of Felodipine in a rat model of pentylenetetrazol (PTZ)-induced seizures, with a particular focus on its modulatory effects on neuroinflammatory responses and oxidative stress biomarkers.
Material and Method: The entirety of 48 male Wistar rats were separated into two main groups for behavioral and electrophysiological assessments. The anticonvulsant properties of Felodipine at dosages of 10 mg/kg and 20 mg/kg were evaluated according to seizure severity, using Racine's Convulsion Scale and the latency to the First Myoclonic Jerk (FMJ). Electroencephalographic (EEG) recordings were analyzed to measure epileptiform activity by assessing the proportion of spike-wave discharges. Neuroinflammatory and oxidative stress markers, namely tumor necrosis factor-alpha (TNF-α) and malondialdehyde (MDA), were quantified in brain tissue using Enzyme-linked immunosorbent assay (ELISA) and Thiobarbituric Acid Reactive Substances (TBARS) tests, respectively. A p-value of less than 0.05 was deemed statistically significant.
Results: Felodipine significantly decreased seizure intensity and prolonged FMJ start time relative to the PTZ and saline-treated cohorts ($p<0.05$). EEG recordings revealed a marked decrease in spike percentages in the Felodipine-treated groups. Furthermore, biochemical analyses demonstrated that Felodipine significantly reduced TNF-α and MDA levels, indicating its neuroprotective effects by mitigating neuroinflammation and oxidative stress.
Conclusion: The PTZ-induced seizure model showed that felodipine significantly reduced seizure activity, neuroinflammation, and oxidative stress, indicating robust anticonvulsant and neuroprotective benefits. Its favorable safety profile and dual-action mechanism targeting calcium channels and inflammatory pathways position it as a promising candidate for epilepsy management. Further studies are warranted to explore its long-term efficacy and potential in chronic epilepsy models.

Keywords: Epilepsy, felodipine, calcium channel blockers, neuroinflammation, oxidative stress, anticonvulsant therapy

INTRODUCTION

Recurrent and spontaneous seizures are the hallmarks of epilepsy, a chronic neurological illness affecting over 50 million people globally. The necessity for new treatment options is underscored by the fact that, despite the availability of numerous antiepileptic medicines (AEDs), over 30 % of patients have drug-resistant epilepsy (1,2). This unmet medical need has encouraged the exploration of alternative approaches with novel mechanisms and the repurposing of existing drugs for different indications.

In this context, calcium channel blockers (CCBs) have emerged as promising candidates for the treatment of epilepsy. Neuronal excitability, synaptic transmission, and intracellular signaling are all significantly impacted by L-type voltage-gated calcium channels (VGCCs), which CCBs aim to block. Felodipine, a dihydropyridine CCB widely used in the treatment of hypertension, has demonstrated anticonvulsant potential in several preclinical studies (3-5). Its ability to modulate calcium influx and reduce excitatory neurotransmission provides dual benefits in seizure control and neuroprotection.

Calcium ions play a central role in neuronal physiology, including action potential generation, neurotransmitter release, and intracellular signaling cascades. However, excessive calcium influx through VGCCs, particularly L-type channels, contributes significantly to the pathophysiology of epilepsy. Prolonged calcium entry triggers excitotoxicity, leading to neuronal damage and hyperexcitability, which contribute to the initiation and propagation of seizures (6,7). Felodipine's action on

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these channels reduces intracellular calcium levels, alleviating these pathological processes and stabilizing hyperexcitable neural networks.

The efficacy of felodipine as an antihypertensive agent is attributed to its high vascular selectivity and potent inhibition of L-type calcium channels in smooth muscle. This property minimizes systemic side effects and makes it a suitable candidate for repurposing in neurological conditions. Preclinical studies have shown that felodipine exhibits significant anticonvulsant effects in PTZ- and maximal electroshock (MES)-induced seizure models (2,5,6). These effects are thought to result from its ability to increase seizure thresholds, reduce seizure severity, and mitigate neuroinflammation and oxidative stress.

For example, studies have shown that felodipine reduces the duration and frequency of seizures in rodent models, with minimal sedative effects. The neuroprotective advantages of this compound are further shown by its ability to reduce inflammatory markers like TNF-α and oxidative stress indicators like MDA (4,6,7).

Additionally, nimodipine and diltiazem, two additional calcium channel blockers, have been studied for their anticonvulsant effects. For instance, nimodipine has been found effective in reducing seizure severity in animal models; however, dose-dependent cardiovascular side effects limit its clinical application (3,5,6). Felodipine's higher vascular selectivity and lipophilicity allow it to cross the blood-brain barrier more effectively and reduce peripheral side effects (7,8).

The pathophysiology of epilepsy is influenced by neuroinflammation and oxidative stress, according to recent studies. In the epileptic brain, proinflammatory cytokines like TNF-α and interleukin-1β are increased, which worsens neuronal hyperexcitability and aids in the advancement of the condition. Likewise, oxidative stress caused by the overproduction of reactive oxygen species (ROS) results in lipid peroxidation, protein oxidation, and DNA damage, which further diminishes neuronal function (6,7). Felodipine's ability to mitigate these processes adds a neuroprotective dimension to its anticonvulsant effects. By reducing TNF-α levels and MDA concentrations, it not only controls seizure activity but also prevents secondary neuronal damage, positioning it as a promising candidate for long-term epilepsy management (7,8).

The mechanisms underlying the anticonvulsant and neuroprotective effects of felodipine remain insufficiently explored despite promising preclinical evidence. Most studies have focused on its impact on seizure activity, with limited data on its role in modulating neuroinflammatory and oxidative stress pathways.

The purpose of this research is to fill these knowledge gaps by studying felodipine's impact on a model of PTZ-induced seizures. Specifically, it investigates the drug's impact on seizure severity, onset latency, and biochemical markers of neuroinflammation and oxidative stress. By integrating behavioral, electrophysiological, and biochemical analyses, this research seeks to provide a comprehensive understanding of felodipine's therapeutic potential in the treatment of epilepsy.

MATERIAL AND METHOD

Animal and Laboratory

The research process for this work received approval from the Animal Ethics Board of Science University (Approval Number: 0123113305). Following the guidelines set forth by the National Institutes of Health (U.S.), all procedures involving the use of laboratory animals were carried out.

The research used 48 male Wistar rats, each weighed between 200 and 250 grams. Of these, 24 rats were allocated for EEG recordings, whilst the other 24 were earmarked for behavioral evaluations. A peaceful habitat with an ambient temperature of 22-24°C was provided for the animals, and they were maintained on a 12-hour light-dark cycle (lights on from 07:00 to 19:00). All participants were allowed unlimited access to tap water and standard laboratory diet.

Methods for Conducting Experiments

Forty-eight rats were randomly assigned to one of two groups: Group A, which was used to record the EEG, and Group B, which was used for behavioral assessment. Group A rats were stereotactically drilled with a small hole in their heads after a powerful anesthetic was administered to them. The left frontal cortex dura mater was implanted with stainless steel electrodes that were covered with polyamide. The electrodes had a diameter of 0.1 mm and an electrical resistance of less than 1 Ω/10 mm. The midline reference electrode was positioned 1.5 mm behind the lambda on the cerebellum (9). Dental acrylic, a material often used in tooth restoration procedures, was employed to attach the electrodes. Ketamine (80 mg/kg) and xylazine (4 mg/kg) were administered intraperitoneally to begin anesthesia.

The PTZ dosage of 35 mg/kg was used, as previously applied in our earlier study, since it reliably creates identifiable EEG spike activity without consistently eliciting obvious behavioral alterations, while 70 mg/kg results in significant behavioral changes but compromises the EEG signal-to-noise ratio for dose-dependent studies (10).Twelve days post-electrode implantation, the 24 rats in Group A were randomly allocated into four subgroups (n=6 each): A1, A2, A3, and A4.

- **Group A1 (Control):** No therapy provided,
- **Group A2 (Saline):** Rats were administered saline intraperitoneally,
- **Group A3 (Felodipine 10 mg/kg):** Rats received an intraperitoneal injection of 10 mg/kg Felodipine,
- **Group A4 (Felodipine 20 mg/kg):** Rats received an intraperitoneal administration of 20 mg/kg Felodipine.

Felodipine doses of 10 mg/kg and 20 mg/kg were selected based on previous studies demonstrating their efficacy in seizure models (3,4). All pharmacological interventions were administered 30 minutes prior to PTZ administration (35 mg/kg, intraperitoneally). EEG recordings were performed five minutes post-PTZ treatment in conscious rats situated in a dedicated enclosure.

The EEG signals were captured for 60 minutes using the BIOPAC MP150 Data Acquisition System (Biopac Systems Inc., Santa Barbara, CA, USA), amplified by a factor of 10,000, and filtered within a frequency range of 1–60 Hz. The spike percentage, indicative of epileptiform activity, was measured as the ratio of 1-second periods containing at least one spike-wave event ("spike-wave percentage") (10). This measurement was evaluated by two clinical neurophysiologists. The initiation and cessation of spike-wave complexes were determined by amplitudes exceeding twice the baseline values. Cumulative spike-wave lengths were assessed at 2-minute intervals.

In Group B, a distinct cohort of 24 rats was randomly allocated into four subgroups (n=6 each): B1, B2, B3, and B4.

- **Group B1 (Control):** No therapy provided,
- **Group B2 (Saline):** Rats were administered saline by intraperitoneal injection,
- **Group B3 (Felodipine 10 mg/kg):** Rats received an intraperitoneal administration of 10 mg/kg Felodipine,
- **Group B4 (Felodipine 20 mg/kg):** Rats received an intraperitoneal administration of 20 mg/kg Felodipine.

Pharmacological interventions were delivered 30 minutes before to the PTZ administration (70 mg/kg, intraperitoneally). Using the latency to the "FMJ" and Racine's Convulsion Scale (RCS) seizures were assessed (10). The severity of the seizures was assessed as follows, and the FMJ latency was measured in seconds:

0=Absence of seizure,

1=Twitching of vibrissae and pinnae,

2=Motor arrest accompanied by significant twitching,

3=Generalized myoclonic jerks (FMJ onset time documented),

4=Tonic-clonic seizure with preserved posture,

5=Tonic-clonic seizure with loss of righting reflex,

6=Fatal seizure.

There was a 30-minute restriction on the observation duration for PTZ-induced seizures. Following anesthesia (100 mg/kg ketamine, Richterpharma AG, Austria, and 50 mg/kg xylazine, Bayer, Germany), all rats were cervically dislocated and put to death at the end of the trial. The brains were subsequently taken for biochemical assessments and further tests.

Assessment of Cerebral Lipid Peroxidation

Malondialdehyde (MDA) levels were measured using the thiobarbituric acid reactive substances (TBARS) technique to evaluate lipid peroxidation as described before (11). Samples were treated with trichloroacetic acid and TBARS reagent, followed by mixing and incubation at 100°C for 60 minutes. Following refrigeration on ice, the samples were subjected to centrifugation at 3000 rpm for a duration of 20 minutes. The absorbance of the supernatant was measured at 535 nm. MDA concentrations were quantified using a standard calibration curve utilizing tetraethoxypropane and expressed as nmol/g protein.

Quantification of Cerebral Protein Concentrations

Total protein concentrations in brain homogenates were measured using the Bradford assay, following the method described before (12). Bovine serum albumin was used as the standard in the Bradford test to measure the amount of total protein in brain samples.

Examination of Brain TNF-α

Upon extraction, brain tissues were promptly preserved at -20°C for biochemical examination. Using a glass homogenizer, the brain tissues were mixed in five liters of phosphate-buffered saline (PBS, pH 7.4) for tissue preparation. They were then centrifuged for 15 minutes at 5000 g. After collecting the supernatant, the Bradford test was used to measure the amount of protein present in the brain homogenate overall.

The levels of tumor necrosis factor-α in the brain tissue supernatants were assessed using ELISA kits that are commercially available for rats. Following the instructions provided by the manufacturer (eBioscience, Inc, San Diego, CA), each sample was examined twice. A MultiscanGo microplate reader (Thermo Fisher Scientific, NH, USA) was used to measure absorbance.

Statistical Evaluation

Every outcome is shown as the mean plus or minus the standard error of the mean (SEM). We used SPSS 15.0 for Windows to conduct the statistical analyses. We used the Shapiro-Wilk test to make sure the data was normally distributed. The FMJ delay was analyzed using a one-way analysis of variance (ANOVA), whereas Racine's convulsion scores were analyzed using the Kruskal-Wallis test. Mann-Whitney U tests and post hoc Bonferroni analyses were used to compare the two experimental groups. We regarded $p<0.05$ as having statistical significance.

RESULTS

This research thoroughly assessed the impact of Felodipine on the PTZ-induced seizure model by behavioral, electrophysiological, and biochemical metrics. The findings are detailed below.

1. Behavioral Assessments

Convulsion Stage (Racine Scale)

We used the Racine Convulsion Scale to measure the impact of Felodipine on seizure severity. While the control group (Stage 0) showed no seizure activity, the PTZ and saline-treated group (Group 2) had an average convulsion stage of 5.4±0.5 (Table 1). However, the convulsion stage significantly decreased to 3.6±0.2 (*p<0.05) in the group treated with 10 mg/kg Felodipine (Group 3). In the group receiving 20 mg/kg Felodipine (Group 4), this value was further reduced to 2.8±0.5 (**p<0.001). These results demonstrate that Felodipine effectively reduces seizure severity.

Onset Time of the First Myoclonic Jerk (FMJ)

The FMJ onset time of 68.2±7.7 seconds was recorded in the group that was treated with PTZ and saline. The duration was notably extended to 105.4±12.3 seconds (*p<0.05) in the cohort administered 10 mg/kg Felodipine compared with 162.1±16.5 seconds (**p<0.001) in the cohort receiving 20 mg/kg Felodipine (Table 1). The data demonstrate that Felodipine postpones seizure onset, underscoring its anticonvulsant properties.

Table 1. Behavioral assessments: Convulsion stage and FMJ onset time

Groups	Convulsion stage (Racine)	FMJ onset time (sec)
1-Control	0	0
2-PTZ (70 mg/kg) and saline	5.4±0.5	68.2±7.7
3-PTZ (70 mg/kg) and 10 mg/kg felodipine	3.6±0.2*	105.4±12.3*
4-PTZ (70 mg/kg) and 20 mg/kg felodipine	2.8±0.5**	162.1±16.5**

Data were expressed as mean±SEM; Statistical analyses were performed by one-way ANOVA test; *p<0.05, ** p<0.001 (different from saline-treated PTZ group)

2. Electrophysiological Assessments

EEG Spike Activity

The electrical activity of seizures was evaluated through EEG recordings, and spike percentages were calculated (Table 2). The control group had no spike activity, but the PTZ plus saline-treated group demonstrated a spike percentage of 73.6±8.3. Treatment with 10 mg/kg Felodipine resulted in a considerable reduction in the spike % to 55.2±10.6 (**p<0.01), while administration of 20 mg/kg Felodipine further lowered it to 41.8±9.1 (**p<0.01). Examples of EEG recordings are shown in Figure 1. Figure 1A shows a normal EEG pattern in the control group without PTZ or Felodipine administration. In contrast, Figure 1B illustrates pronounced epileptiform spikes in the PTZ (35 mg/kg) and saline group. Figure 1C and Figure 1D demonstrate a noticeable reduction in spike activity in the groups treated with 10 mg/kg and 20 mg/kg of Felodipine, respectively, indicating its dose-dependent protective effect.

Table 2. EEG spike activity

Groups	Spike percentage
1-Control	0
2-PTZ (70 mg/kg) and saline	73.6±8.3*
3-PTZ (70 mg/kg) and 10 mg/kg felodipine	55.2±10.6**
4-PTZ (70 mg/kg) and 20 mg/kg felodipine	41.8±9.1**

Data were expressed as mean±SEM; Statistical analyses were performed by one-way ANOVA test; *p<0.05, **p<0.01 (different from saline-treated PTZ group)

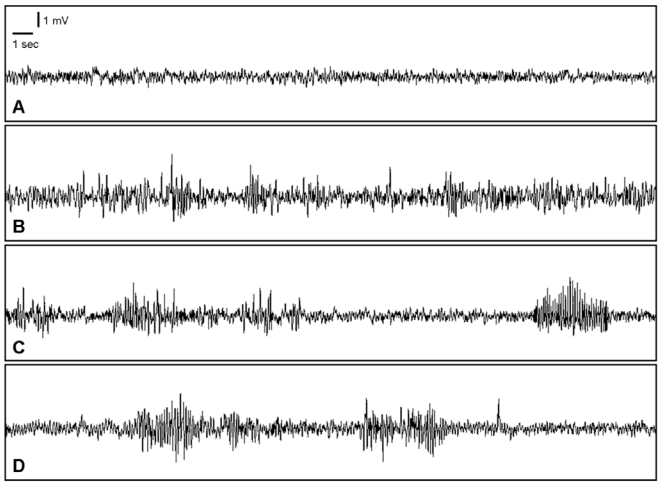

Figure 1. Representative EEG recordings: (**A**) Control Group; (**B**) PTZ (35 mg/kg) and saline group; (**C**) PTZ (35 mg/kg) and 10 mg/kg Felodipine group; (**D**) PTZ (35 mg/kg) and 20 mg/kg Felodipine group

3. Biochemical Assessments

Lipid Peroxidation Indicator (MDA)

Malondialdehyde (MDA) levels were measured to assess Felodipine's impact on oxidative stress (Table 3). There was a substantial rise in MDA levels to 23.7±3.02 nmol/g protein in the PTZ and saline-treated groups (*p<0.05). In contrast, the MDA levels decreased to 11.2±1.6 nmol/g protein (#p<0.05) in the group treated with 10 mg/kg Felodipine and to 9.5±0.8 nmol/g protein (##p<0.01) in the group treated with 20 mg/kg Felodipine. These findings demonstrate that Felodipine reduces oxidative stress markers.

Neuroinflammation Indicator (TNF-α)

Levels of TNF-α were assessed to determine the anti-inflammatory capabilities of Felodipine (Table 3). In the PTZ and saline-treated group, TNF-α levels were measured at 133.4±7.5 pg/mg protein (**p<0.001). TNF-α levels dramatically dropped to 93.8±5.6 pg/mg protein in the 10 mg/kg Felodipine group (#p<0.05), and they dropped even lower to 64.6±4.3 pg/mg protein in the 20 mg/kg Felodipine group (##p<0.01). These findings underscore the substantial anti-inflammatory properties of Felodipine.

Table 3. Biochemical parameters: MDA and TNF-α levels

	Control	PTZ (70 mg/kg) and saline	PTZ (70 mg/kg) and 10 mg/kg felodipine	PTZ (70 mg/kg) and 20 mg/kg felodipine
Brain MDA level (nmol/gr protein)	2.8±0.3	23.7±3.02*	11.2±1.6#	9.5±0.8##
Brain TNF-alpha (pg/mg protein)	21.5±2.4	133.4±7.5**	93.8±5.6#	64.6±4.3##

Data were expressed as mean±SEM. Statistical analyses were performed by one-way ANOVA test. *p<0.05, ** p<0.001 (different from control group), # p<0.05, ## p<0.01 (different from PTZ and saline group)

DISCUSSION

This research thoroughly assessed the anticonvulsant effects caused by Felodipine in the pentylentetrazol (PTZ)-induced epileptic seizure paradigm, along with its impact on neuroinflammation and oxidative stress. Our findings demonstrate that Felodipine significantly improves seizure severity and onset time while also reducing neuroinflammatory and oxidative processes. When evaluating the consistency of our results with other studies in the literature, the significance of these findings in epilepsy treatment is discussed.

Felodipine was shown to reduce the seizure stage on the Racine Convulsion Scale and significantly extend the start time of FMJ. This data suggests that felodipine may reduce the frequency and severity of seizures caused by PTZ. These findings parallel those of Yiu and Knaus (1996), who reported that Felodipine reduced seizure severity in the MES model (5). Saniya et al. (2019) correlated Felodipine's capacity to diminish seizure severity with its function as an inhibitor of calcium channels of the L-type (4). A study demonstrated that felodipine outperformed other CCBs in PTZ- and pilocarpine-induced seizure models. Felodipine showed superior efficacy in reducing seizure frequency and protecting against neuronal damage, offering a favorable therapeutic profile (5,6).

Felodipine's effectiveness in seizure management is attributed to its capacity to block L-type voltage-dependent calcium channels, hence diminishing intracellular calcium influx. This plays a critical role in mitigating neuronal hyperactivity and suppressing epileptogenesis processes (2). Considering the central role of calcium in seizure pathophysiology, Felodipine is thought to achieve seizure control through this mechanism (7).

Felodipine's anticonvulsant effect involves not only the inhibition of L-type calcium channels but also indirect effects on N-methyl-D-aspartate (NMDA) receptors and sodium channels. Given the role of NMDA receptors in epileptogenesis, Felodipine's potential to block these channels could be significant in reducing epileptic brain activity (1,2). This mechanism has also been demonstrated in pilocarpine-induced seizure models, where Felodipine delayed seizure onset and reduced severity (13). Therefore, these findings are consistent with our results and suggest that Felodipine exerts its effects through various molecular pathways.

Following Felodipine administration, a significant reduction in spike activity was observed in EEG recordings. The reduction in spike percentage indicates that Felodipine can suppress the electrical activity of PTZ-induced seizures. Erbaş et al. (2015) published similar results in PTZ models, showing that antiepileptic medications greatly decreased PTZ-induced spike activity (7). These reductions in EEG activity support the ability of Felodipine to control the electrical propagation of seizures (8).

The effect of Felodipine on neuroinflammation was confirmed by a significant reduction in TNF-α levels. Neuroinflammation is a crucial factor in epileptic brains that enhances neuronal hyperactivity and epileptogenesis processes. These findings are consistent with those of Vezzani and Baram (2007), who highlighted the effects of proinflammatory cytokines on the epileptic brain (14). Our study demonstrates that Felodipine has the potential to mitigate neuroinflammation by reducing TNF-α levels.

Additionally, Felodipine's effect on oxidative stress was evaluated through a reduction in MDA levels. Oxidative stress is a major cause of cellular damage during epilepsy and plays a critical role in chronic epileptogenesis (15). The role of oxidative stress in epileptogenesis was highlighted by Rogawski and Löscher (2004), who also discussed the possibility of medications that lessen oxidative stress in the treatment of epilepsy (8). In our study, Felodipine was found to mitigate oxidative stress-related damage by lowering MDA levels (14).

Targeting these processes with pharmaceutical therapies is crucial because of the significant role that oxidative stress plays in the pathogenesis of epilepsy. Felodipine's ability to reduce lipid peroxidation and MDA levels is

notable in this context. The findings reported in our study align with other studies examining the effects of calcium channel blockers like flunarizine on oxidative stress. Clinical trials with flunarizine have shown a decrease in oxidative stress indicators in individuals with migraines, for instance (16). Similarly, Felodipine's effects expand its potential use in neurological conditions such as epilepsy and migraine.

Regarding neuroinflammation, the reduction in TNF-α levels demonstrates Felodipine's ability to alleviate seizure-induced inflammatory processes. These findings are consistent with theories suggesting that Felodipine, known as a P-glycoprotein (P-gp) inhibitor, can enhance the efficacy of antiepileptic drugs in the brain (14,17,18).

There have been comparisons between felodipine and other calcium channel blockers, including nimodipine and diltiazem, in terms of their effectiveness in controlling seizures. While nimodipine has shown promise in MES and PTZ models, its potential for adverse effects on the cardiovascular system has restricted its use in clinical practice (1). Felodipine's higher vascular selectivity and anti-inflammatory effects make it a more advantageous option for epilepsy treatment. Kamal et al. (1990) reported that calcium channel blockers are effective in seizure control and noted that Felodipine demonstrates superior efficacy in this regard (2).

Felodipine is considered to have greater vascular selectivity and a favorable safety profile compared to other calcium channel blockers, based on previous reports. Our findings support its efficacy and neuroprotective properties in the PTZ-induced seizure model. While other drugs like nimodipine are known to be effective in seizure control, their cardiovascular side effects limit their clinical applications (1,19). Felodipine's higher vascular selectivity is a critical advantage in minimizing cardiovascular side effects. Furthermore, the ability of calcium channel blockers to reduce oxidative stress and provide neuroprotective effects enhances their importance in epilepsy treatment (20).

In addition to its anticonvulsant effects, Felodipine's potential to mitigate post-seizure cognitive impairments is significant. Jansone et al. (2015) demonstrated that a novel 1,4-dihydropyridine derivative improved spatial learning and memory in animal models and highlighted the therapeutic potential of calcium channel blockers in reducing cognitive deficits during neurodegenerative processes (21). Similarly, earlier studies have reported that Felodipine reduced cognitive losses in passive avoidance learning tests under hypoxic conditions, supporting its evaluation as a potential agent for managing post-epileptic neurodegenerative outcomes (1). Although cognitive performance was not directly assessed in our study, the observed neuroprotective effects of Felodipine—such as reduced TNF-α and MDA levels—may provide a rationale for future studies to investigate its potential in mitigating post-epileptic cognitive deficits.

One of the distinguishing features of this study is its comprehensive evaluation of Felodipine's effects not only on seizure activity but also on neuroinflammatory and oxidative stress markers within the same acute PTZ-induced seizure model. While previous studies have primarily focused on Felodipine's anticonvulsant effects using behavioral or electrophysiological measures alone, our study integrates behavioral scoring (Racine scale and FMJ latency), EEG-based spike analysis, and biochemical quantification of TNF-α and MDA levels. This multimodal approach allows for a more holistic understanding of Felodipine's dual action—both seizure-suppressing and neuroprotective—within a single experimental framework. Furthermore, unlike earlier reports that often compare Felodipine with other calcium channel blockers without simultaneously measuring markers of inflammation or oxidative stress, our study directly assesses these neurobiological processes, providing stronger mechanistic insights.

Our study presents a comprehensive approach by evaluating the anticonvulsant and neuroprotective effects of Felodipine at both behavioral and biochemical levels. However, this study is limited to an acute seizure model, and the efficacy of Felodipine in chronic epilepsy models remains unexplored. Additionally, whether its neuroprotective effects persist with long-term use warrants further investigation. This study was conducted using an acute PTZ-induced seizure model in rats, which may not fully mimic the complex and chronic nature of human epilepsy. Additionally, the long-term effects and safety of Felodipine in chronic seizure models or clinical settings were not assessed. Future studies should explore its sustained efficacy, optimal dosage, and potential interactions with other antiepileptic medications in both chronic models and clinical trials.

This study concludes by demonstrating Felodipine's potential as a potent neuroprotective and anticonvulsant drug in the PTZ-induced seizure model. By reducing seizure severity, delaying seizure onset, and mitigating neuroinflammatory and oxidative stress processes, Felodipine demonstrates its ability to address multiple pathological mechanisms underlying epilepsy. Its dual-action mechanism, targeting both L-type calcium channels and other molecular pathways, provides a promising foundation for its therapeutic application. Furthermore, the significant reductions in TNF-α and MDA levels emphasize its role in minimizing secondary neuronal damage and improving long-term outcomes. These findings, supported by Felodipine's previously reported vascular selectivity and lower side effect profile compared to other calcium channel blockers, suggest its potential utility as a safer and more versatile option for epilepsy management (19). Nonetheless, additional research is required to assess its effectiveness in chronic epilepsy models and its enduring neuroprotective advantages to comprehensively determine its clinical significance in epilepsy management.

CONCLUSION

In conclusion, this study provides robust evidence supporting the anticonvulsant and neuroprotective potential of Felodipine in a PTZ-induced acute seizure model. Through comprehensive behavioral, electrophysiological, and biochemical analyses, Felodipine was shown to significantly reduce seizure severity, delay seizure onset, and attenuate both neuroinflammation and oxidative stress. These findings suggest that Felodipine exerts a dual mechanism of action by modulating calcium influx via L-type calcium channels and suppressing pathophysiological processes underlying epileptogenesis. Given its favorable safety profile, vascular selectivity, and ability to cross the blood-brain barrier, Felodipine emerges as a promising candidate for repositioning in epilepsy management. Nonetheless, further studies in chronic epilepsy models and clinical trials are warranted to evaluate its long-term efficacy, cognitive outcomes, and potential synergistic effects with existing antiepileptic drugs.

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