Original Article

Exploring the Impact of Persistent Morphine Exposure on Kindling Susceptibility in Rat Models

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How to Cite This Article Panahi, Y., & Abdollahzade, M. (2025). Exploring the Impact of Persistent Morphine Exposure on Kindling Susceptibility in Rat Models. *Iranian Journal of Veterinary Medicine, 19*(4), 655-664. http://dx.doi.org/10.32598/ijvm.19.4.1005586

http://dx.doi.org/10.32598/ijvm.19.4.1005586

ABSTRACT

Background: Epilepsy is a complex neurological disorder. The relationship between this condition and morphine is intricate and not yet fully understood.

Objectives: This study aims to explore the complex relationship between epilepsy and morphine to shed light on their interactions. The main goal is to better understand how morphine can affect seizure thresholds and how a history of epilepsy may alter a patient's response to morphine.

Methods: Forty male Wistar rats were divided into four groups: Control (normal saline [1 mL/kg, intraperitoneally]+pentylenetetrazol [PTZ] [35 mg/kg, intraperitoneally]), morphine 2 (morphine [2 mg/kg, intraperitoneally]+PTZ [35 mg/kg, intraperitoneally]) and morphine 10 (morphine [10 mg/kg, intraperitoneally]+PTZ [35 mg/kg, intraperitoneally]) and diazepam (diazepam [10 mg/kg, intraperitoneally]+PTZ [35 mg/kg, intraperitoneally]). PTZ (35 mg/kg, intraperitoneally, 10 weeks) was administered to induce kindling, and local field potentials were recorded for 10 minutes. Diazepam was administered to terminate the PTZ-induced epileptiform activity.

Results: Seizures commenced within less than 100 s and morphine administration did not affect the onset time. The groups that received doses of 2 and 10 mg/kg morphine experienced a significant increase in mean spike counts ($P>0.05$); in contrast, the mean amplitude remained unaffected compared to the control group.

Conclusion: The study found that while morphine may increase the frequency of epileptiform activity induced by the chemical agent PTZ, it does not alter the strength of the electrical activity, which can be a crucial consideration when evaluating the potential use of morphine in the management of seizures.

Keywords: CA1 region, Drug-resistant, Epilepsy, Hippocampal, Tonic-clonic

Article info:
Received: 10 Dec 2024
Accepted: 01 Mar 2025
Publish: 01 Oct 2025

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Introduction

Epilepsy is a neurological disorder that affects the central nervous system, leading to recurrent and unprovoked seizures. When managing pain during or after epilepsy, healthcare providers must exercise caution when considering the use of morphine, a powerful opioid analgesic. This is due to several crucial factors that intertwine epilepsy and morphine administration, including potential impacts on seizure threshold, interactions with antiepileptic drugs, and the need for careful monitoring to ensure the safety and well-being of individuals experiencing both seizures and acute pain. The relationship between morphine and epilepsy is complex and not fully understood (Burtscher & Schwarzer, 2017). This relationship unfolds with intricate dynamics because the therapeutic benefits of opioids in managing pain must be balanced against potential risks, such as seizure control and the overall well-being of individuals living with epilepsy. Studies have shown that morphine can have both proconvulsing and anticonvulsing effects depending on the dose and specific circumstances (Panahi et al., 2017). To reconcile conflicting findings regarding the pro- and anti-convulsant effects of morphine, it is essential to consider several factors. First, the dosage of morphine is critical; lower doses may exhibit anticonvulsant effects, while higher doses can increase seizure susceptibility. This suggests that morphine's effects are dose-dependent and require careful titration (Panahi et al., 2017). Second, the timing of administration relative to seizure induction can influence outcomes, with morphine potentially having different effects when administered before and after seizures. Third, variations in animal models and experimental conditions can lead to different results, as genetic background and health status may affect responses to morphine. Additionally, the mechanisms of action are complex; morphine interacts with both excitatory and inhibitory neurotransmitter systems, which can lead to increased seizure activity in some contexts while providing protective effects in others (Charles & Hales, 2004). Future research should systematically explore these variables to clarify morphine's role in seizure management and to optimize therapeutic strategies for patients with epilepsy. The use of opioid medications, such as morphine, for pain management has been a common practice for many years. However, the chronic use of these drugs has been associated with the development of tolerance and dependence, leading to the need for higher doses to achieve the same therapeutic effects (Rosenblum et al., 2008). Additionally, long-term opioid use has been linked to an increased risk of seizures and epilepsy (Lankhuijzen & Ridler, 2024). A potential factor that may contribute to these neurological effects is kindling.

Kindling plays a pivotal role in epilepsy studies due to its ability to replicate and control seizure activity within experimental settings. This model provides researchers with a dependable platform to investigate the multifaceted facets of epilepsy, offering insights into the neurological and molecular mechanisms underpinning this disorder. Its reproducibility enables consistent experiments, while its temporal control permits the study of epilepsy's evolution over time, from onset to progression. Through kindling, researchers can assess the efficacy of potential anti-epileptic drugs, probe the intricacies of epileptogenesis, and explore different types of seizures while adhering to ethical considerations that put the welfare of laboratory animals first. Kindling is a cornerstone of epilepsy research, contributing invaluable insights that improve our understanding of this complex neurological condition and support the development of novel therapeutic strategies (Post & Weiss, 1998). In laboratory animals, repeated exposure to sub-convulsive doses of pentylenetetrazol (PTZ) or other convulsing drugs leads to the development of more severe and frequent seizures over time. PTZ is a chemical compound that is commonly used in scientific research to induce seizures. Kindling with PTZ can cause changes in the body, including alterations in the release of neurotransmitters, which transmit signals between nerve cells in the brain. It may also lead to changes in receptor function, which refers to how neurotransmitters bind to specific receptors on nerve cells, and gene expression, which refers to the process by which genes are turned on or off in response to various stimuli. As kindling progresses, animals become more susceptible to seizures, even in the absence of PTZ or other convulsive drugs. This increased susceptibility may be related to changes in brain function, as well as changes in the threshold for seizure initiation. Animals that have undergone kindling with PTZ may exhibit a range of behavioral changes, including hyperactivity, aggression, and anxiety. PTZ has also been shown to impair memory function in laboratory animals, particularly in tasks that require spatial learning and memory (Shimada & Yamagata, 2018).

Chronic morphine use and kindling with PTZ are two separate concepts related to drug addiction and seizure susceptibility (Zamanian et al., 2020). While chronic use of morphine and kindling with PTZ are not directly related, some evidence suggests that chronic use of morphine may increase the risk of seizure activity and kindling in certain individuals (Panahi et al., 2019). This may be

because opioids can affect the excitability of neurons in the brain, leading to increased seizure susceptibility. In this context, we aim to explore how persistent morphine exposure influences susceptibility to kindling, focusing on PTZ-induced chemical kindling in rats. Through the investigation of potential interactions between chronic morphine administration and kindling, this study aims to enhance the understanding of the neurological consequences of long-term opioid use and provide valuable information for the development of clinical approaches to pain management.

Materials and Methods

Animals

In this experiment, 40 male Wistar rats weighing 200-250 g were obtained from the Animal Breeding and Maintenance Center of Urmia University of Medical Sciences, Faculty of Pharmacy. They were housed at the pharmacology laboratory animal house of the Faculty of Veterinary Medicine of the University of Tabriz City, Iran. The rats were kept in polypropylene cages with a maximum of five animals per cage. They were maintained under standard conditions with free access to food and water, following a 12-hour cycle of darkness and light.

Chemicals

The drugs used were PTZ (Sigma Aldrich P6500-25G PTZ), morphine sulfate (MORPHINE SULFATE DP 10MG/1ML AMP, Tabriz University of Medical Sciences, Tabriz City), and diazepam (DIAZEPAM CHEMIDAROU 10MG/2ML AMP. Tehran, Iran). The rats were divided into four experimental groups (control, morphine 2, morphine10, and diazepam), each of which was used only once, and each treatment group consisted of 10 animals. The first group was treated with normal saline (1 mL/kg, i.p.) plus PTZ (35 mg/kg, i.p.); the second and third groups received morphine at doses of 2 and 10 mg/kg, respectively plus PTZ (35 mg/kg) and, the fourth group received diazepam at a dose of 10 mg/kg plus PTZ (35 mg/kg) (Gharehaghaji et al., 2023). Animals were injected intraperitoneally with their respective daily treatments (Saturday, Monday and Wednesday every week) for 10 weeks.

Procedure

To induce kindling, a chronic model of seizures, PTZ was administered at a dose of 35 mg/kg body weight on Saturdays, Mondays and Wednesdays. After 10 weeks of treatment, the animals were anesthetized with a ketamine-xylazine (80+8 mg/kg) combination, and the scalp was prepared for recording. The animals were secured in a Stereotaxic apparatus, and a scalp incision of 1.5-2 cm was performed to access the recording area, which had coordinates of (AP: -2.76 mm, ML: -1.4 mm, DV: 3 mm) (Gharehaghaji et al., 2023). A tungsten bipolar microelectrode was placed (histological evidence was used to ensure the correct placement of the electrodes) in the CA1 area of the hippocampus. After recording basal brain activity for 5 minutes, seizure activity was induced by intraperitoneal administration of PTZ at a dose of 80 mg/kg. Local field potential recordings were performed from the hippocampal CA1 pyramidal neurons. The data were digitized using the eLab instrument and eTrace Analyzer software (Science Beam, Tehran, Iran) and stored on a computer hard drive for offline analysis. Single-site recordings of seizure-like events (SLEs) were obtained from the CA1 pyramidal cell layer using 1-Hz low-pass and 1000-Hz high-pass filters. The onset of convulsive activities, number of spikes, and amplitude were compared among the different groups using eTrace software. The experiment concluded with the administration of diazepam (10 mg/kg) to terminate PTZ-induced epileptiform activity.

Data analysis

Statistical differences were determined by a one-way analysis of variance followed by Tukey's post hoc test using IBM® SPSS® software, version 27 (IBM Company, USA). All values are expressed as Mean±SE of the mean (SEM). A value of $P<0.05$ was considered statistically significant.

Results

In this experimental study, in which epileptiform activity was induced by PTZ, the onset time of seizures remained consistent across all groups, occurring in less than 100 s. The results revealed that the administration of 2 and 10 mg/kg morphine led to an increase in the mean spike counts, indicating a higher frequency of epileptiform activity compared to the control group (Figures 1A, 2B and 2C) ($P<0.05$). Importantly, this increase in frequency was not accompanied by any significant alteration in the mean amplitude of electrical activity (Figure 1B) ($P>0.05$). Furthermore, when diazepam was administered at 10 mg/kg, a significant reduction ($P<0.05$) in the number of spikes (Figures 1A and 2D) was observed compared to the control group. However, the amplitudes of these epileptiform activities (Figure 1B) were not significantly different from the control group ($P>0.05$).

In summary, these results suggest that morphine can elevate the frequency of epileptiform activity induced by PTZ while leaving the strength or intensity of these electrical events largely unaffected. Additionally, diazepam exhibited an antiepileptic effect by reducing the number of spikes without altering their amplitude, providing crucial insights into the specific effects of these substances on seizure-related electrical activity.

Discussion

This study investigated the effects of morphine on epileptiform activity induced by the chemical agent PTZ. The results showed that the onset time of seizure activity induced by PTZ did not change in any group and was less than 100 s. This suggests that PTZ is a potent inducer of seizures and that the onset time is not affected by morphine administration. The results related to diazepam show that the number of spikes was significantly reduced compared to the control group (Figures 1A and 2D). At the same time, the amplitude of these activities was not affected by diazepam. Diazepam's mechanism of action is primarily focused on reducing the number of individual spikes during a seizure by enhancing the inhibitory effects of gamma-aminobutyric acid (GABA) in the brain. However, it does not necessarily modulate or diminish the overall amplitude or intensity of the seizure activity. When compared to other anticonvulsants, diazepam's effects differ; for instance, phenytoin not only reduces spike counts but also lowers the amplitude of seizure activity, making it particularly effective for generalized tonic-clonic seizures (Shorvon et al., 2018). Similarly, valproate reduces spike frequency and amplitude, providing a broader spectrum of efficacy against various seizure types (Romoli et al., 2019). Therefore, diazepam is typically used as a rescue medication to manage acute seizures and is often part of a broader treatment plan that may include other anticonvulsant medications to address the underlying causes of seizures and reduce their overall intensity (Czapinski et al., 2005).

The results also revealed that the administration of 2 and 10 mg/kg morphine increased the mean spike counts but did not alter the mean amplitude compared to the control group (Figures 1A, 2B and 2C). This suggests that morphine increases the frequency of epileptiform activity without affecting the strength of the electrical activity. These results have crucial implications for the use of morphine for the treatment of seizures. Although morphine is known to have analgesic and sedative effects, its use in treating seizures is controversial due to its potential to increase the frequency of epileptiform activity. The results of this study suggest that while morphine may increase the frequency of epileptiform activity, it does not alter the strength of electrical activity, which could be a crucial consideration when evaluating the potential use of morphine in the management of seizures. This experiment was conducted using specific doses of PTZ and morphine in a specific animal model. Further studies using different doses of PTZ and morphine are needed to confirm these results in different animal models.

Studies have shown that morphine can have both proconvulsant and anti-convulsant effects depending on the dose and specific circumstances (Panahi et al., 2017). In some cases, morphine has been shown to lower seizure thresholds and increase the risk of seizure activity (Kumar et al., 2022). However, other studies have shown that morphine can also exert anticonvulsant effects and reduce seizure activity (Frenk, 1983). Regarding the relationship between morphine and kindling with PTZ, some studies have suggested that morphine can have a kindling effect and can increase susceptibility to PTZ-induced seizures. One study found that repeated administration of morphine can lead to increased susceptibility to PTZ-induced seizures in rats (Atapour et al., 2000), while another study found that pretreatment with morphine can prevent kindling development in PTZ-induced seizures (Mansour et al., 1981). Morphine can increase the risk of convulsive activity, particularly in individuals with epilepsy or predisposed to seizures (Buchanan, 2001). One study conducted in rats found that chronic administration of morphine led to an increase in seizure susceptibility and reduced seizure threshold in response to PTZ-induced seizures (Jafarzadeh et al., 2009). This effect was observed even after a washout period of morphine administration, suggesting long-lasting changes in brain circuitry (Jafarzadeh et al., 2009). Chronic administration of morphine can lead to changes in the brain's reward system, which may contribute to the development of addiction. These changes include alterations in the expression and function of neurotransmitters and their receptors, and gene expression and protein synthesis (Ammon-Treiber & Höllt, 2005). Studies have also shown that chronic morphine use can lead to changes in the brain's stress response system, which may contribute to the development of withdrawal symptoms and other negative effects associated with opioid use. These changes in brain circuitry can have long-lasting effects on an individual's behavior and physiology. They may contribute to the development of opioid addiction and other negative consequences associated with chronic opioid use (Kosten & George, 2002). This study also found that morphine administration led to increased expression of glutamate receptors in the brain, which may contribute to increased seizure susceptibility. Glu-

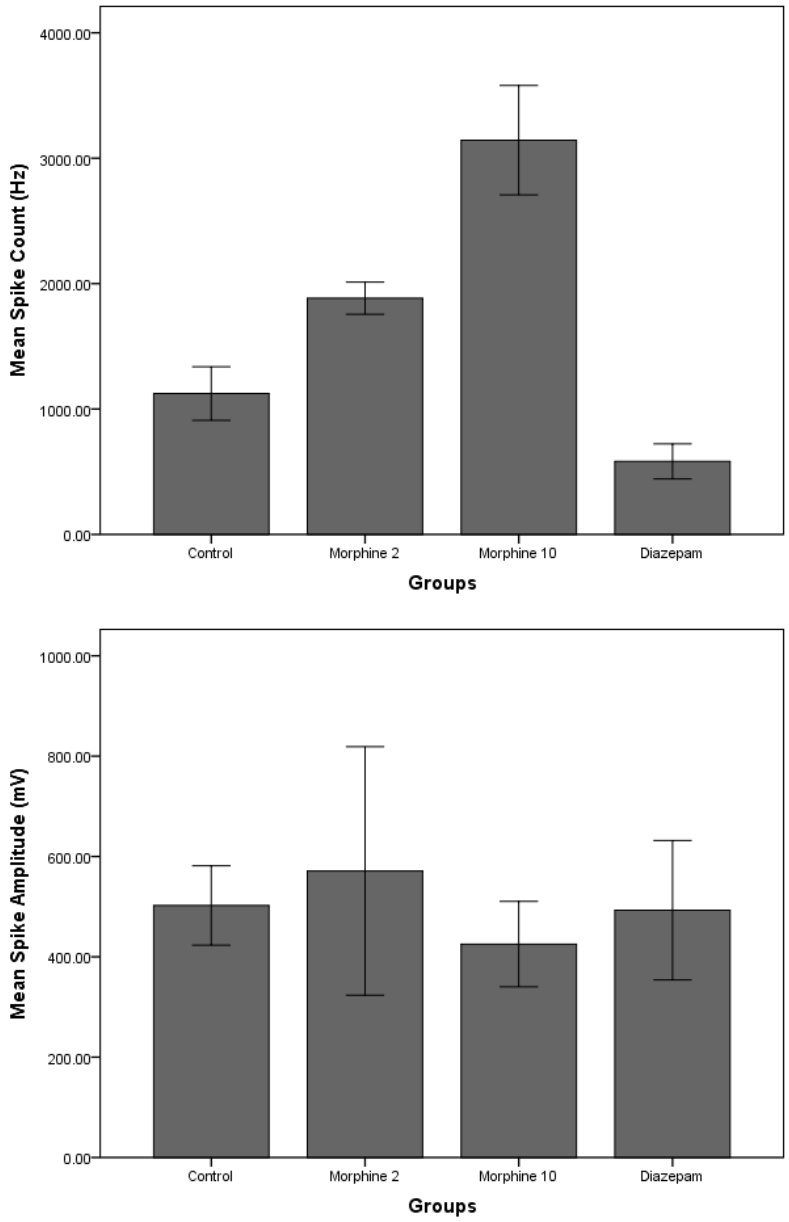

Figure 1. Effect of acute administration of morphine (2 and 10 mg/kg) and diazepam (10 mg/kg) on A) spike counts (Hz) and B) amplitudes (mv) of PTZ-kindling model of epileptiform activities

Note: Each column represents the Mean±SEM of 10 rat databases. The asterisk (*) indicates a significant difference between the study and control groups. P<0.05 is considered significant.

tamate is the most abundant excitatory neurotransmitter in the brain and is involved in many crucial physiological processes, including learning and memory, synaptic plasticity and regulation of neuronal excitability. Several studies have shown that chronic morphine administration can increase the expression of both ionotropic and metabotropic glutamate receptors in the brain. These changes may contribute to the increased susceptibility to seizures observed in animal models following chronic morphine use because glutamate receptors play a key role in regulating neuronal excitability and seizure activity (Hearing et al., 2018; Saeedi et al., 2021).

Another study in mice found similar results, with chronic morphine administration leading to increased seizure susceptibility and a decreased seizure threshold in response to PTZ-induced seizures. A study also found that chronic morphine use led to changes in the expression of several genes involved in the regulation of synaptic plasticity, which may contribute to the development

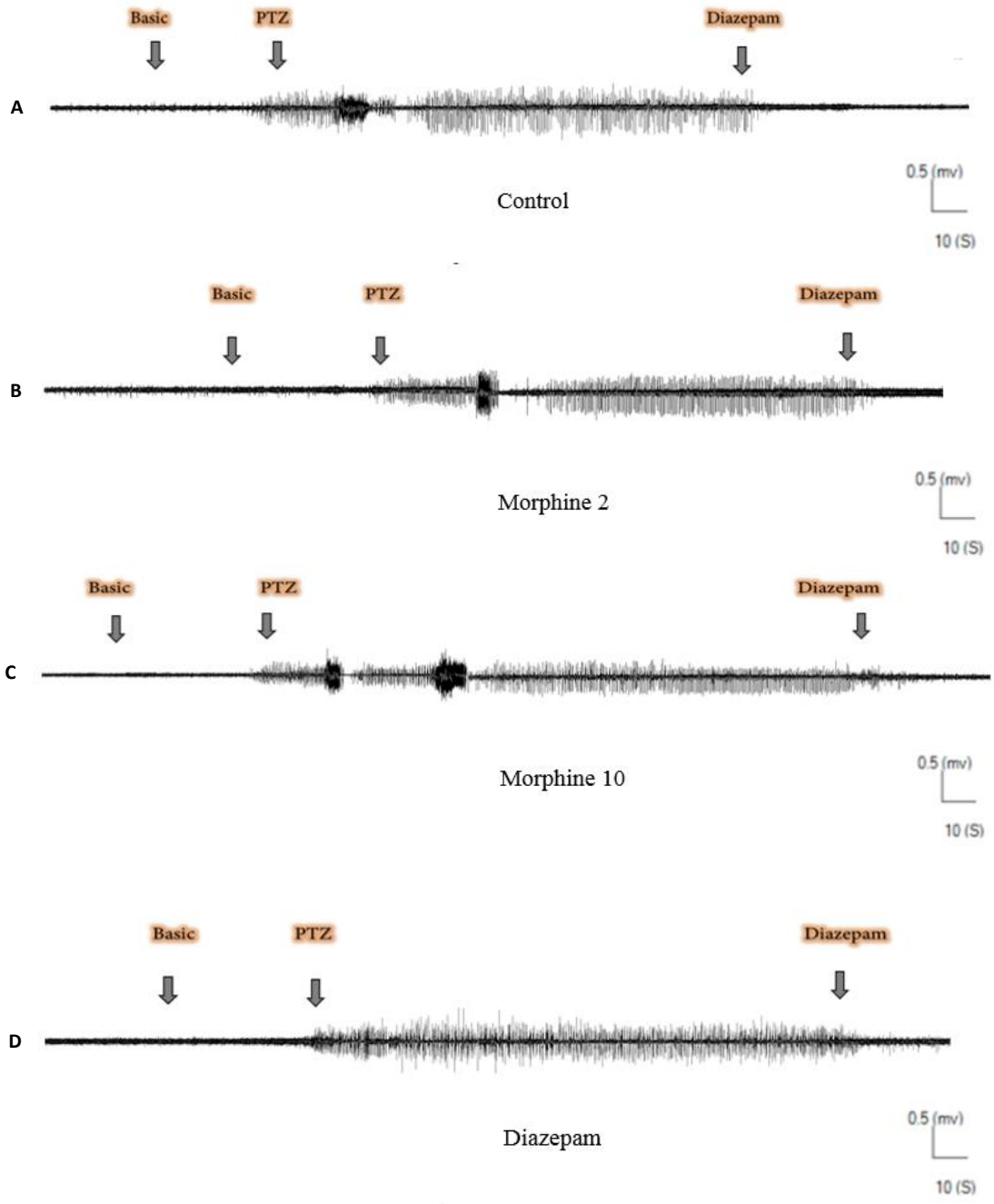

Figure 2. Trace samples recorded from the CA1 region of the hippocampus in A) control, B) morphine 2, C) Morphine 10 and D) Diazepam groups after administration of normal saline (1 ml/kg), morphine (2 and 10 mg/kg) and diazepam (10 mg/kg) obtained from ptz-kindled rats

Note: Each sample is recorded for one animal. Basic: Indicates brain-based activities without any drug interference, PTZ: Representing local field potentials following intraperitoneal injection of PTZ (80 mg/kg) and diazepam: Indicates inhibition of local field potentials by diazepam (10 mg/kg).

of seizures (Zamanian et al., 2020). Synaptic plasticity is how the strength of connections between neurons can be modified in response to environmental stimuli and experiences (Stampanoni Bassi et al., 2019). Several studies have found that chronic morphine use can lead to changes in the expression of genes involved in long-term potentiation and depression, including genes encoding glutamate receptors, ion channels, and intracellular signaling molecules. These changes may contribute to the development of seizures by altering the balance between excitatory and inhibitory synaptic transmission in the brain (Traynelis et al., 2010; Chen et al., 2022). For ex-

ample, one study found that chronic morphine use led to a decrease in the expression of the gene encoding the AMPA glutamate receptor subunit *GluR2*, which is involved in regulating the strength of excitatory synapses. This decrease in *GluR2* expression was associated with increased seizure susceptibility in animal models (Zhang et al., 2023). These results suggest that chronic morphine use can lead to changes in gene expression that alter synaptic plasticity and contribute to seizure development. However, further research is needed to fully understand the mechanisms underlying these effects and their clinical relevance in humans.

Morphine is not a first-line treatment for epilepsy and has been shown to affect epileptiform activity (Velíšek et al., 2000). However, the mechanisms underlying these effects are not fully understood, and further investigation is needed.

One possible mechanism by which morphine may affect epileptiform activity is its interaction with the endogenous opioid system in the brain. The endogenous opioid system comprises a group of neurotransmitters, receptors, and peptides that are involved in pain modulation, reward, and addiction. Morphine is an exogenous opioid that binds to these receptors and produces analgesia, euphoria, and other effects. Some studies have suggested that the endogenous opioid system may also play a role in the seizure regulation. For example, it has been shown that activation of opioid receptors can reduce seizure activity in animal models of epilepsy. Therefore, morphine may have anticonvulsant effects by activating opioid receptors (Mu, kappa and delta) in the brain (Al-Hasani & Bruchas, 2011). Another possible mechanism by which morphine may affect epileptiform activity is its interaction with other neurotransmitter systems. For example, it has been suggested that morphine may enhance the activity of GABA, an inhibitory neurotransmitter that can suppress epileptiform activity. Morphine may also affect the release of glutamate, an excitatory neurotransmitter that promotes epileptiform activity (Rashan et al., 2021). Thus, the mechanisms underlying the effects of morphine on epileptiform activity are complex and multifactorial. Further research is needed to fully understand these mechanisms and determine the potential benefits and risks of using morphine as a treatment for epilepsy. The relationship between morphine and kindling with PTZ is complex and depends on several factors. It is essential to note that these results are based on animal studies and may not necessarily translate to humans; morphine should only be used under the guidance of a healthcare professional and prescribed dosage instructions.

Conclusion

This study provides valuable insights into the effects of morphine on epileptiform activity induced by PTZ. These results indicated that while morphine administration significantly increased the frequency of SLEs, it did not alter the amplitude of these electrical activities. This suggests a potential pro-convulsant effect of morphine, raising concerns about its use in patients with epilepsy. Conversely, diazepam demonstrated a notable antiepileptic effect by reducing the number of spikes without affecting their amplitude, thereby highlighting its efficacy in managing seizure activity. These results underscore the need for caution when considering morphine as a treatment option for seizure disorders because its impact on seizure frequency could complicate patient management. Further research is warranted to explore the underlying mechanisms of morphine's effects on seizures and to evaluate its safety and efficacy in clinical settings. Ultimately, these results contribute to a deeper understanding of the complex interplay between opioids and seizure activity, paving the way for more informed therapeutic decisions.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of University of Tabriz, Tabriz, Iran (Code: IR.TABRIZU.REC.1401.080).

Funding

This study was financially supported by the University of Tabriz, Tabriz, Iran (Grant No.: 4305969678).

Authors' contributions

Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization, supervision, project administration, and funding acquisition: Yousef Panahi; Investigation: Marjan Abdollahzadeh.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to express their sincere gratitude to Gholamreza Vafaei for providing the facilities of the Physiology Laboratory, which were essential for this research.

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