The Effects And Possible Mechanisms of Vortioxetine on Pentylenetetrazole-Induced Seizures In Rats

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Research Article

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Abstract

Antidepressants are known to demonstrate various effects on the nervous system. As a new antidepressant, vortioxetine is used for major depression in adult patients, with no clear indication of epileptic seizures. Therefore, the aim here was to examine the impact of vortioxetine on pentylenetetrazole-induced epileptic seizures in rats. The rats were randomly divided into 5 groups, each with 6 rats. Group 1 was control, Group 2 was administered saline (1 mL/kg/day serum physiologic), Group 3 was given (1 mg/kg/day diazepam), and Groups 4 and 5 were administered vortioxetine (2.5 and 5 mg/kg/day). The experimental groups (Groups 2-5) were given the drugs for a total of 7 days. Pentylenetetrazole (45 mg/kg) was administered on day 7 to all but the control group. Behavioral testing was performed using the passive avoidance and open field tasks. Total antioxidant status (TAS), total oxidant status (TOS), tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1 β), neuronal nitric oxide synthase (nNOS), nitric oxide (NO), soluble guanylate cyclase (sGC), cyclic guanosine monophosphate (cGMP) caspase-3, and caspase-9 levels were measured using a commercial kit. The groups receiving vortioxetine (2.5 mg/kg and 5 mg/kg) were found to have delayed epileptic seizure onset times and reduced seizure stages with improved memory impairment after seizures. These groups also had increased TAS levels and decreased TOS levels in the cortex and hippocampus. Additionally, TNF-α, IL-1 β, nNOS, sGC, cGMP, caspase-3, and caspase-9 levels in the cortex and hippocampus were statistically significantly lower for these groups. Vortioxetine was determined to have protective effects on pentylenetetrazole-induced seizures in rats, with alleviated seizures and improved memory impairment, oxidative stress, inflammation, and apoptosis. The mechanisms of vortioxetine may involve the inhibition of oxidative stress, inflammation, and the nNOS/sGC/cGMP signalling pathway.

1. Introduction

Epilepsy is a common neurological disorder that affects more than 50 million people globally (Téllez-Zenteno and Hernández-Ronquillo 2012). Epilepsy is characterized by repetitive seizures, often triggered by genetic predisposition or an underlying chronic pathological condition (Karabulut et al. 2018). A seizure is a temporary dysfunction of the brain due to an abnormal discharge of cortical neurons, with imbalanced excitation and inhibition in cortical and subcortical neuronal circuits (Jenrow and Elisevich 2019).

There have been experimental seizure models carried out to understand their underlying mechanisms. Widely used to induce seizures in rodents and zebrafish, pentylenetetrazole (PTZ) is a selective antagonist of the GABA_A receptor with negative effects on the neuronal membrane. It also affects potassium and calcium channels and releases intracellular calcium ion reserves, decreasing neurotransmitter-induced chloride conductance (Kandratavicius et al. 2014).

Antiepileptic drugs (AEDs) constitute the standard treatment method for epilepsy, although with severe side effects including ischemia, depression, and impaired memory. Almost a third of epileptic patients are
drug-resistant, experiencing refractory seizures regardless of the use of AEDs (Das et al. 2012). This creates a need for more effective and safer AEDs (Brophy et al. 2016).

As a new antidepressant, vortioxetine is used for major depressive disorder (MDD) and has been demonstrated to improve cognitive dysfunction (Koesters et al. 2017). It modulates different subtypes of 5-hydroxytryptamine (5-HT) receptors and acts as a partial agonist to 5-HT1B, an agonist to 5-HT1A, and a receptor antagonist to 5-HT3, 5-HT7, and 5-HT1D, as well as inhibiting 5-HT reuptake (Sanchez et al. 2015). Besides, it indirectly modulates GABA and glutamate receptors in the brain, decreasing GABAergic activity in the prefrontal cortex and increasing region-specific GABAergic activity in the striatum (Riga et al. 2016).

High doses of selective serotonin reuptake inhibitors (SSRIs) have been shown to demonstrate anticonvulsant activity and proconvulsant effects, although with no exact mechanism (Bahremand et al. 2011; Igelström and Heyward 2012). Due to its various modulation effects, vortioxetine might impact seizures differently than SSRIs.

Research has also found 1% of MDD patients using vortioxetine to experience seizures, even though they had no history of epilepsy (McIntyre et al. 2014; Wagner et al. 2018). Vortioxetine is also reported to decrease penicillin-induced epileptiform activity (Ögün et al. 2019). However, its mechanism on seizures is still unclear. Thus, this study aimed to examine the effects and mechanisms of vortioxetine on pentylenetetrazole-induced seizures in rats.

2. Materials And Methods

2.1. Animals

The animals used in this study consisted of 30 male adult Wistar Albino rats with body weights ranging between 230–250 g. The rats were kept in 12 hours of light-dark cycles at a temperature of 22 ± 3°C. Acclimatization to laboratory conditions was ensured, with ad libitum access to food and water. The researcher was blinded to the experiments. All tests were done between 09:00 and 17:00. Approval was obtained from the Animal Ethics Committee at Cumhuriyet University (No:139-65202830-050.04.04-370).

2.2. Drug administration

Vortioxetine, diazepam, and pentylenetetrazole (PTZ) (Sigma-Aldrich Co., St Louis, MO, USA) were dissolved in 1 mL/kg serum physiologic, and each was prepared on the day of the experiment.

2.3. Experimental protocols

The rats were randomly divided into 5 groups, each with 6 rats. Group 1 was control, Group 2 was administered saline (1 mL/kg/day serum physiologic) intraperitoneally (i.p.), Group 3 was given (1 mg/kg/day diazepam) i.p., and Groups 4 and 5 were administered vortioxetine (2.5 and 5 mg/kg/day)
i.p.. The experimental groups (Groups 2–5) were given the drugs for a total of 7 days. 30 minutes after the last doses, Groups 2, 3, 4, and 5 were administered 45 mg/kg pentylenetetrazole (PTZ) i.p. to induce epileptic seizures.

After PTZ administration, the rats were observed for 30 minutes. Modified Racine Scale was used to score seizure severity based on behavioral testing, which was defined in 7 stages, as follows (Lüttjohann et al. 2009):

0 = no convulsion,

1 = twitching of vibrissae and pinnae,

2 = motor arrest, more pronounced twitching,

3 = myoclonic jerks,

4 = tonic-clonic seizure while feeding,

5 = tonic-clonic seizure, loss of righting reflex,

6 = tonic-clonic seizure, wild climbing, and jumping,

7 = lethal seizure.

Following the PTZ infusion, the rats were monitored for behavioral scoring for 30 minutes as indicated by RCS and agreeing on the hour of the first myoclonic jerk (FMJ), the hour of the start of generalized tonic-clonic twitch seizures (oGTCS), and the duration of generalized tonic-clonic jerk seizures (dGTCS). The animals were sacrificed by decapitation 24 hours after PTZ administration. Brain tissues were collected and the cortex and the hippocampus were evaluated.

### 2.4. Behavioral Testing

#### 2.4.1. Passive Avoidance Test

According to negative reinforcement, the passive avoidance (PA) learning test was carried out. The instrument had a grid floor and consisted of two parts: a dark one and a small door with a light connecting the two parts. The research was carried out, recognizing that rats preferred dark environments naturally. The animals were familiar with the instrument for two consecutive days prior to the training session (300 seconds per day). They were positioned in the light section on a subsequent day, and the time latency was recorded to enter the dark section. When facing the walls far away from the door, the animals were placed in the light section and given an electric shock (1 mA, 5 seconds) when they reached the dark section in the training process. The animals were taken to their cages afterward. The rats were located in the light area, and in the retention test process that was carried out one h after the training sessions, time latency was noted for entering the dark site (Karademir et al. 2019).
2.4.2. Open Field Test

Emotional behavior, spontaneous locomotor activity, and autonomic functions were evaluated in the open field arena. The open field apparatus consists of a square area (100 cm×100 cm×30 cm) divided into 16 smaller units. Rats were placed singly in one corner of the open field, allowing them to freely explore the arena. The activity level is evinced as the total number of frames passed, while fear is expressed as the total number of stools and grooming, and exploratory activity is stated as the total number of rearing, over a 5-min test period. The area was cleaned with 70% ethanol and wiped with paper towels following every test.

2.5. Preparation of brain tissue homogenates

Brain tissue samples were mixed using a cold phosphate-buffered saline solution (pH: 7.4). A mechanical homogenizer (Analytic Jena speed mill plus, Jena, Germany) was used to homogenize the tissue samples. The homogenates were centrifuged at 4000 rpm at 4°C for 10 minutes as previously described (Taskiran et al. 2020). The supernatants were obtained from the biochemical analysis and total protein levels were determined using the Bradford protein assay kit (Merck, Germany) (Kruger 2009).

2.6. Measurement of TAS and TOS

The method of measurement of TAS and TOS levels in the cortex and hippocampus was previously described in our study (Akkaya et al. 2019). TAS levels were measured from the supernatants of the cortex and hippocampus using commercial kits (Rel Assay, Antep, Turkey). The experiments were carried out as defined by Erel (Erel 2004). Standards of kit and cell supernatants were premixed with the reaction reagent (reagent I) and added into the mix, followed by the staining reagent (reagent II), and incubated at 37°C for 5 minutes. After incubation, absorbance was read at 660 nm. As hydroxyl radicals are produced in the Fenton reaction, colored dianisidyl radicals are absorbed. This absorbance was quantitated to obtain the reaction rate of free radicals. Since antioxidants in the samples are expected to suppress coloring in proportion to their concentrations, the results are given in micromolar Trolox equivalents per milligram tissue protein (µmol Trolox Eq/mg protein) (Erel 2004).

TOS levels were measured from the supernatants of the cortex and hippocampus using commercial kits (Rel Assay, Antep, Turkey). The experiments were carried out as defined by Erel (Erel, 2005). Standards of kit and cell supernatants were premixed with the reaction reagent (reagent I) and added into the mix, followed by the staining reagent (reagent II), and incubated at 37°C for 5 minutes. After incubation, absorbance was read at 530 nm. As hydroxyl radicals are produced in the Fenton reaction, colored dianisidyl radicals are absorbed. When there are adequate quantities of oxidants in the medium, ferrous ion is oxidized to ferric ion, which was measured to obtain TOS levels using xylenol orange. Since $\text{H}_2\text{O}_2$ was used for calibration, the results are given in micromolar $\text{H}_2\text{O}_2$ equivalents per milligram tissue protein (µmol $\text{H}_2\text{O}_2$ Eq/mg protein) (Erel 2005).

2.7. Measurement of TNF-α, IL-1 β, nNOS, NO, sGC, cGMP, caspase-3, and caspase-9
The method using the present study to measure levels of TNF-α, IL-1 β, nNOS, NO, sGC, cGMP, caspase-3, and caspase-9 in the cortex and hippocampus was described in our previous study (Taskiran et al. 2020). TNF-α, IL-1 β, nNOS, NO, sGC, cGMP, caspase-3, and caspase-9 levels in the cortical and hippocampal supernatants were measured using rat ELISA commercial kits (BT Lab, Shanghai, China) following the manufacturer’s instructions. Standards and tissue samples were added in and incubated at 37°C for 60 minutes, followed by washing and adding the staining solutions, and incubation again at 37°C for 15 minutes. According to the ELISA reader (Thermo Fisher Scientific, Altrincham, UK), the stop solution was read at 450 nm. Standard curves were used for calculations and coefficients of variation between and among the plates were below 10%.

2.8. Statistical analysis

The data are given as mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used for data evaluation. Differences between the experimental groups were determined using Tukey’s posthoc test. Data analysis was done using SPSS Version 23.0 for Windows. $p < 0.05$ was accepted as the statistical significance level for all measurements.

3. Results

3.1. Effects of vortioxetine on epileptic seizure parameters after PTZ-induced seizure in rats

Epileptic parameters were obtained by video recordings after PTZ injection. Racine scale scores differed significantly between the saline + PTZ group and the diazepam + PTZ and vortioxetine + PTZ groups after seizures ($P < 0.05$ to $P < 0.001$; Table 1). The diazepam + PTZ and vortioxetine + PTZ groups had a significantly higher FMJ time compared to the saline + PTZ group after seizures ($P < 0.001$; Table 1). Moreover, vortioxetine + PTZ groups had a significantly higher oGTCS time compared to the saline + PTZ group after seizures ($P < 0.001$; Table 1). There was no significant difference between the groups after seizures in respect of dGTCS time ($P > 0.05$; Table 1).
Table 1
Effect of vortioxetine on RCS, FMJ, oGTCS, and dGTCS after PTZ-induced seizures in rats (n = 6).

| Groups                         | Racine Convulsion Scale (RCS) | Onset of the first myoclonic seizures (FMJ) (sec) | Onset of the generalized tonic-clonic seizures (oGTCS) (sec) | Duration of the generalized tonic-clonic seizures (dGTCS) (sec) |
|--------------------------------|-------------------------------|--------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------|
| Control                        | None                          | None                                             | None                                                        | None                                                          |
| Saline + PTZ                   | 5.16 ± 0.30                   | 51.50 ± 2.29                                     | 64.66 ± 2.07                                                 | 51.66 ± 2.91                                                   |
| Diazepam + PTZ                 | 2.66 ± 0.21***                | 192.50 ± 4.02***                                 | None                                                        | None                                                          |
| Vortioxetine (2.5 mg/kg) + PTZ | 3.83 ± 0.30**                 | 98.00 ± 3.49***                                  | 178.66 ± 7.05***                                             | 50.00 ± 3.19                                                   |
| Vortioxetine (5 mg/kg) + PTZ   | 4.00 ± 0.25*                  | 99.83 ± 2.84***                                 | 179.16 ± 6.27***                                             | 49.50 ± 2.81                                                   |

Values are presented as mean ± SEM (n = 6). *P < 0.05, **P < 0.01, and ***P < 0.001 compared to the saline + PTZ group.

3.2. Effects of vortioxetine on passive avoidance and open field tests after PTZ-induced seizure in rats

According to the passive avoidance test findings, there was no significant difference between any of the groups in terms of training trail (P > 0.05; Table 2). Although, significant differences were noted between the saline + PTZ and control groups in terms of test trial (P < 0.001; Table 2), and between the diazepam + PTZ and vortioxetine + PTZ groups and the saline + PTZ group in terms of test trial times (P < 0.001; Table 2).
### Table 2

Effects of vortioxetine on passive avoidance and open field tests after PTZ-induced seizure in rats (n = 6).

| Groups                  | Passive Avoidance | Open Field |
|-------------------------|-------------------|------------|
|                         | Training Trial    | Test Trial | Crossing (number/5 min) | Rearing (number/5 min) | Grooming (number/5 min) | Focal Boli Count |
| Control                 | 25.33 ± 2.44      | 258.90 ± 14.20 | 17.16 ± 1.07 | 8.66 ± 1.11 | 4.16 ± 0.47 | 5.00 ± 0.57 |
| Saline + PTZ            | 23.66 ± 2.94      | 93.33 ± 5.51*** | 15.16 ± 1.19 | 9.33 ± 1.05 | 4.83 ± 0.60 | 4.33 ± 0.66 |
| Diazepam + PTZ          | 25.83 ± 2.00      | 264.10 ± 9.80*** | 16.50 ± 2.51 | 9.83 ± 1.07 | 4.66 ± 0.66 | 5.33 ± 0.91 |
| Vortioxetine (2.5 mg/kg) + PTZ | 24.00 ± 3.57   | 217.00 ± 11.25*** | 16.5 ± 2.17 | 8.83 ± 0.90 | 5.33 ± 0.61 | 5.00 ± 0.93 |
| Vortioxetine (5 mg/kg) + PTZ | 23.33 ± 3.04   | 222.33 ± 13.94*** | 16.33 ± 1.81 | 9.83 ± 1.35 | 5.00 ± 0.57 | 5.16 ± 0.70 |

Values are presented as mean ± SEM. ###P < 0.001 compared to control; ***P < .001 compared to the saline + PTZ group.

The number of line crossings, grooming, rearing, and defecations were monitored in the open-field test according to the procedure described above. No differences were observed between groups in the open-field test (P > 0.05; Table 2).

### 3.3. Effects of vortioxetine on TAS and TOS levels in the cortex and hippocampus after PTZ-induced seizure in rats

The saline + PTZ group had lower TAS levels compared to the control group (P < 0.001; Fig. 2). Also, the diazepam + PTZ and vortioxetine groups had significantly higher TAS levels than the saline + PTZ group after seizures (P < 0.001; Fig. 2).

The saline + PTZ group had higher TOS levels compared to the control group (P < 0.001; Fig. 2). Also, the diazepam + PTZ and vortioxetine groups had significantly lower TOS levels than the saline + PTZ group after seizures (P < 0.001; Fig. 2).
3.4. Effects of vortioxetine on TNF-α and IL-1 β levels in the cortex and hippocampus after PTZ-induced seizure in rats

TNF-α levels in the cortex did not differ between any of the groups ($P > 0.05$; Fig. 3), while TNF-α levels in the hippocampus were observed to be higher in the saline + PTZ group compared to the control group ($P < 0.001$; Fig. 3). The diazepam + PTZ and vortioxetine + PTZ groups had lower TNF-α levels in the hippocampus than the saline + PTZ group ($P < 0.001$; Fig. 3).

The saline + PTZ group had significantly higher IL-1 β levels in the cortex and hippocampus compared to the control group ($P < 0.001$; Fig. 3). The diazepam + PTZ and vortioxetine + PTZ groups had lower IL-1 β levels in the cortex and hippocampus than the saline + PTZ group ($P < 0.001$; Fig. 3).

3.5. Effects of vortioxetine on nNOS, NO, sGC, and NO levels in the cortex and hippocampus after PTZ-induced seizure in rats

The saline + PTZ group had higher nNOS, NO, sGC, and NO levels than the control group ($P < 0.001$; Fig. 4). The diazepam + PTZ and vortioxetine + PTZ groups had lower nNOS, NO, sGC, and NO levels than the saline + PTZ ($P < 0.001$; Fig. 4).

3.6. Effects of vortioxetine on caspase-3 and caspase-9 levels in the cortex and hippocampus after PTZ-induced seizure in rats

As in the previous findings, the saline + PTZ group had higher caspase-3 and caspase-9 levels than the control group ($P < 0.001$; Fig. 5). The diazepam + PTZ and vortioxetine + PTZ groups had lower caspase-3 and caspase-9 levels than the saline + PTZ group ($P < 0.001$; Fig. 5).

4. Discussion

This study was conducted to assess the effects and mechanisms of vortioxetine on pentylenetetrazole-induced epileptic seizures in rats. Vortioxetine decreased seizure stages, increased the first myoclonic jerk times, alleviated memory impairment, increased TAS levels, and decreased TOS, TNF-α, IL-1β, nNOS, NO, sGC, cGMP, caspase-3, and caspase-9 levels after seizures.

The subtypes of 5-HT receptors, including 5-HT1A, 5-HT2C, 5-HT3, and 5-HT7, are known to be related to epilepsy and to have a role in the occurrence of seizures. Antiepileptic drugs have been shown to increase the activity of these receptors (Panczyk et al. 2015; Zhao et al. 2017). 5-HT receptors have also been shown to be involved in pentylenetetrazole-induced seizures (Li et al. 2014) and to influence neuron
excitability through the modulation of monoamine neurotransmitters, GABA and glutamate (Bagdy et al. 2007). The 5-HT3 subtype is the only ligand-gated ion channel, which might suggest that ionic conduction and concentration may be leading to neuronal depolarization (Zhao et al. 2017). The antagonistic effect of vortioxetine on the 5-HT3 receptor might be related to its anticonvulsive effect (Sanchez et al. 2015).

Oxidative stress occurs due to an imbalance in the oxidant-antioxidant defense system and has been shown to play a key role in seizures (Aguiar et al. 2012). One study found lipid peroxidation to be higher in epileptic patients (Hamed et al. 2004). Another study reported lower levels of antioxidant systems markers, such as glutathione reductase and vitamins C and A, in this patient group (Waldbaum and Patel 2010). PTZ-induced epileptic seizures have been shown to increase free radicals and oxidative damage to proteins, lipids, and cell DNA. Oxidative damage to neurons after seizures might be supported by high levels of mitochondrial superoxide, iron-induced toxicity, and inactivation of iron- and sulfur-dependent enzymes (Sudha et al. 2001). Here, we observed decreased TAS levels and increased TOS levels in the cortex and hippocampus after PTZ-induced seizures, which were improved after the administration of vortioxetine. Previous studies report vortioxetine to decrease the production of superoxide anion in the monocytes, parallel to our findings (Talmon et al. 2018). This effect on oxidant and antioxidant systems could be a possible mechanism in PTZ-induced seizures.

Neuroinflammation is crucial in maintaining homeostasis in the central nervous system (CNS), although pathological for the CNS when prolonged. Research has highlighted neuroinflammation to have contributions to seizures (Rana and Musto 2018). Proinflammatory cytokines, such as TNF-α and IL-1 β, induce neuronal hyperexcitability and enhance glutamatergic transmission, leading to greater susceptibility (Webster et al. 2017; Vezzani et al. 2019). They also contribute to seizure activity and epileptogenesis by modulating neural transmission, although with positive regulation in PTZ-induced seizures at excess levels (Eyo et al. 2017; Webster et al. 2017). Here, it was demonstrated that TNF-α and IL-1 β levels in the brain were increased in PTZ-induced and later alleviated with the administration of vortioxetine. Previous research reports that vortioxetine decreased TNF-α levels, with an anti-inflammatory effect in monocytes and macrophages, similar to our findings (Talmon et al. 2018).

As an essential neuromodulator of neurotransmitters in the CNS, NO is synthesized from the oxidation of the L-arginine amino acid via three types of nitric oxide synthases (endothelial NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS)). Research has shown NO to be involved in the pathophysiology of seizure onset (Bahremand et al. 2010) and the excitatory and inhibitory systems in the neurons (Fuentealba et al. 2008; Steinert et al. 2011). One of the three types of nitric oxide synthases, nNOS is commonly expressed in the neurons (Zhou and Zhu 2009). Its activation leads to increased NO levels in the postsynaptic neurons, initiating soluble guanylate cyclase (sGC) / guanosine monophosphate (cGMP). cGMP increases the release of glutamate in presynaptic neurons, leading to the excitation of postsynaptic neurons. So, the nNOS/sGC/NO/cGMP pathway is key in the excitation between presynaptic and postsynaptic neurons (Tricoire and Vitalis 2012). nNOS has also been found to be involved in seizures that cause excitation in the neurons (Kovacs et al. 2009), with a close association with PTZ-
induced seizures and epileptogenesis (Zhu et al., 2017). Here, similar to previous findings, nNOS, sGC, NO, and cGMP levels in the brain were found to be higher after PTZ-induced seizures, which were later improved by vortioxetine. Research notes a relation between the serotonin receptors and the nNOS/sGC/NO/cGMP pathway in the neurons (Garthwaite 2007; Zhou et al. 2018). Thus, considering the effects of vortioxetine on different subtypes of serotonin receptors, this inhibition effect on the nNOS/sGC/NO/cGMP pathway could be another possible mechanism in PTZ-induced seizures.

Apoptosis is defined as programmed cell death, mainly occurring through intrinsic and extrinsic pathways due to aging in the cell, oxidative stress, and extracellular stimulation (Elmore 2007). The primary markers that are involved in the activation of apoptosis pathways are caspase-3 and caspase-9 (Hengartner 2000). Their activation in the cortex, thalamus, amygdala, or hippocampus leads to apoptosis in neurons (Méndez-Armenta et al. 2014). PTZ-induced seizures have been shown to cause neuronal damage and apoptosis in the cortex and hippocampus (Branco et al. 2013). Hippocampus is well known for its involvement in memory processes, which is why damage to this region can lead to severe memory loss (Whitlock 2006). Besides, damage to the neurons in the hippocampus results in impaired memory and learning. Previous findings highlight impaired passive avoidance memory and significantly decreased latency to enter the dark chamber in the shuttle box in rats with PTZ-induced epilepsy, similar to the findings obtained here (Mehla et al. 2010). Vortioxetine has been shown in a number of studies to modulate synaptic plasticity and to alleviate memory impairment and apoptosis (Dale et al. 2014; McIntyre et al. 2014; Bétry et al. 2015; Ozbeyli et al. 2019). In this research, caspase-3 and caspase-9 levels were found to be increased in the cortex and hippocampus after PTZ-induced epilepsy, although later improved via the administration of vortioxetine, along with a significant improvement in passive avoidance memory.

5. Conclusion

Our findings suggest that when given at appropriate doses, vortioxetine has a protective effect on PTZ-induced seizures and consequent memory impairment. These effects might be associated with the inhibition of oxidative stress, of inflammation, and of the nNOS/NO/sGC/cGMP pathway, suggesting that vortioxetine could be a potential therapeutic and supportive agent in treating epilepsy. Vortioxetine can also be used as an antidepressant in epileptic patients with symptoms of depression. Thus, there is a need for further studies to shed light on the possible mechanisms of vortioxetine.

Declarations

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Authors’ Contributions
AST designed the study, interpreted the data, and had a major contribution in writing and revising the manuscript. AKF performed the experiment, drafted the manuscript and analyzed data. All authors read and approved the final manuscript.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with Ethical Standards

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Conflict of Interest

The authors declare that they have no conflict of interest

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Figures

Figure 1

Experimental protocols (Created by BioRender).
**Figure 2**

Effects of vortioxetine on TAS and TOS levels in the cortex and hippocampus after PTZ-induced seizure in rats (n=6). Values are given as mean ± SEM; ###P < 0.001 compared to the control group; ***P < 0.001 compared to the saline + PTZ group.
Figure 3

Effects of vortioxetine on TNF-α and IL-1 β levels in the cortex and hippocampus after PTZ-induced seizure in rats (n=6). Values are given as mean ± SEM; ###P < 0.001 compared to the control group; ***P < 0.001 compared to the saline + PTZ group.
Figure 4

Effects of vortioxetine on nNOS, NO, sGC, and cGMP levels in the cortex and hippocampus after PTZ-induced seizure in rats (n=6). Values are given as mean ± SEM; ###P < 0.001 compared to the control group; ###P < 0.001 compared to the saline + PTZ group.
Figure 5

Effects of vortioxetine on caspase-3 and caspase-9 levels in the cortex and hippocampus after PTZ-induced seizure in rats (n=6). Values are given as mean ± SEM; ###P < 0.001 compared to the control group; ***P < 0.001 compared to the saline + PTZ group.

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