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Vortioxetine suppresses epileptiform activity and cognition deficits in a chronic PTZ-induced kindling rat model

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ABSTRACT

Objective. This study aimed to examine the effects of vortioxetine, a novel antidepressant, on epileptiform activity in pentylenetetrazole (PTZ)-induced kindling model in rats.

Methods. For this purpose, 20 male Wistar Albino rats were used, and epileptiform activity was induced by injection of PTZ (35 mg/kg, i.p., three times a week). In the vortioxetine groups, vortioxetine (5 mg/kg and 10 mg/kg) was administered before the kindling process. During the kindling process, the Fisher and Kittner seizure scales were used to score seizure severity. After kindling, novel object recognition (NOR) tests were performed to evaluate the cognitive performance of rats. Electrodes were implanted into the fully kindled animals for ECoG recordings.

Results. In the PTZ group, the number of total spikes was 1367±136 spikes/20 minutes. First myoclonic jerks decreased while seizure severity and total spike count increased in the PTZ group. On the other hand, the total spike number and seizure severity significantly decreased and first myoclonic jerks increased in the vortioxetine groups compared to the PTZ group. Based on the NOR test, vortioxetine administration markedly raised the discrimination index compared to the PTZ group.

Significance. Electrophysiological and behavioural data from the present study suggest that vortioxetine, a novel drug, plays a critical role in controlling PTZ-induced epileptiform activity in rats. Vortioxetine may therefore be a valuable candidate to prevent seizure activity and treat cognitive deficits associated with epilepsy.

Key words: vortioxetine, SSRI, PTZ-induced epilepsy, seizure, NOR

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Epilepsy is a complex and devastating neurological disorder with a tendency to produce seizures with abnormal neuronal activity in the brain [1]. The precise mechanism of epileptogenesis is still unclear, although seizures are associated with an imbalance between inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmission [2]. Although advances in antiepileptic drugs have been made, seizures occur in approximately 30% of patients with epilepsy [3]. Moreover, current drugs may have severe side effects that decrease treatment compliance.

About 80 years ago, Bonnycastle *et al*. suggested that there is a close relationship between serotonin neurotransmitters and epilepsy [4]. Drugs increasing synaptic serotonin levels

have beneficial effects on both generalized and focal epileptic seizures, while decreased synaptic serotonin levels lower the epileptic seizure threshold for chemical, electrical, and audiogenic seizures [5, 6]. 5-HT reuptake blockers and 5-HTP suppress generalized and focal seizures [7, 8]. Fluoxetine, a selective serotonin reuptake inhibitor, increases GABA receptor density and protects against lithium-pilocarpine-induced seizures in rats [9]. Similarly, it has been showed that increased brain serotonin levels cause a decrease in seizure susceptibility [10-12].

Molecular studies have shown that 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_7 receptors play essential roles in the pathophysiology of epilepsy. Certain studies have confirmed the role of 5-HT_{1A} receptor antagonism and the potential antiepileptic activity of 5-HT_{1A} receptor agonists in epilepsy even though there are conflicting results [13]. Furthermore, it has been demonstrated that 5-HT_{2C} receptor knockout mice were sensitive to audiogenic convulsions, and agonists of these receptors improved epileptic seizures in penicillin-induced and genetically modified epileptic rodents [14, 15]. Activation of 5-HT_3 receptors causes excitatory postsynaptic potentials via the entry of positive ions into postsynaptic cells. This contributes to excessive postsynaptic discharge which is involved in the pathogenesis of epilepsy [16]. It has been demonstrated that 5-HT_3 receptor antagonists, ondansetron, and granisetron have antiepileptic activities in preclinical models of epilepsy [17, 18]. Studies have shown that stimulation of 5-HT_7 receptors increases the frequency of convulsions while its antagonist has anticonvulsant activity in temporal lobe epilepsy models of rodents [19].

Vortioxetine is one of the novel antidepressant drugs approved by the Food and Drug Administration (FDA), in September 2013. Vortioxetine's mode of action is different from other selective serotonin reuptake inhibitors (SSRI) since it modulates various serotonin receptors [20]. It has been shown that vortioxetine blocks the serotonin reuptake transporter with a high affinity, similar or SSRIs. Moreover, vortioxetine shows agonistic effects on 5-HT_{1A}, is a partial agonist on 5-HT_{1B} receptors, and antagonizing the serotonergic 5-HT_3 and 5-HT_7 receptors [21]. Hence, it seems that vortioxetine might be a valuable antiepileptic drug candidate with a unique pharmacological profile for epilepsy. A limited number of studies have shown that vortioxetine suppressed penicillin-induced epileptiform activity in rodents [22]. This study is the first to investigate the behavioural, electrophysiological, and molecular effects of vortioxetine on a pentylenetetrazole (PTZ)-induced kindling model of rats.

Materials and methods

Animals

Twenty male Wistar Albino rats (180-250 g, eight weeks old) were housed in 12-hour light/dark cycle (22°C) laboratory conditions. The animals were purchased from Erciyes University Experimental Research and Application Center (DEKAM). The Ethics Committee approved this study for animal experiments at Erciyes University (Approval number: 20/098). Animals were divided into the following groups:

Group 1. PTZ group (35 mg/kg, i.p., n=6): PTZ was injected for the kindling process three times a week. Specific conductive electrodes were implanted into the skull of the rats after the kindling process. Neuronal synchronization and firing pattern were recorded by electrocorticography (ECoG) for 20 minutes. In Group 1, saline was administered instead of vortioxetine for Group 2 and 3, in the same volume and at the same time.

Group 2. PTZ + vortioxetine group (5 mg/kg, i.p., n=7): After the kindling process and implantation of specific electrodes, vortioxetine (5 mg/kg) was administered to the rats. Electrophysiological recordings were also performed by ECoG for 20 minutes.

Group 3. PTZ + vortioxetine group (10 mg/kg, i.p., n=7): Vortioxetine was administered at a dose of 10 mg/kg to the rats after the kindling process and implantation of electrodes. ECoG recording was also performed for 20 minutes.

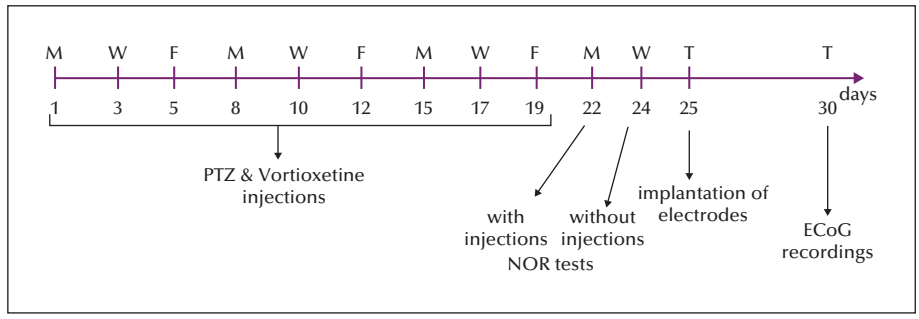
- ***Chemical agents and application***

Pentylentetrazole (Sigma Aldrich, USA) was dissolved in saline at a dose of 35 mg/kg/2 mL daily and administered intraperitoneally (*i.p*) to rats. Vortioxetine (Lundbeck, Denmark) was also prepared in saline at doses of 5 and 10 mg/kg/2 mL and injected *i.p*.

Experimental protocols

- ***Induced seizure activity***

Before implanting electrodes, PTZ was administered for the kindling process three times a week (10 am – 2 pm on Monday, Wednesday, and Friday), and animal behaviour was recorded using a video camera (*figure 1*). The Fisher and Kittner seizure scales were used to score seizure severity [23] (*table 1*). Animals were considered fully kindled after they had at least five Stage 3-5 seizures according to the Fisher and Kittner's scale. The fully kindled animals were then anaesthetized with ketamine/xylazine and fixed in a rat stereotaxic frame. Specific conductive electrodes were implanted into the skull of the rats using a rat brain atlas (positive electrode: 3 mm lateral and 4 mm rostral to bregma; negative electrode: 3 mm lateral and 4 mm caudal to bregma). A five-day washout period was used



■ **Figure 1.** Schematic procedure of experiments.

as post-operative care for the animals. In this model, ECoG activity was recorded by PowerLab 16/SP (AD Instruments, Australia) for 20 minutes for electrophysiological investigation. Electrophysiological recordings were analysed using the software program, LabChart v8. Seizure score, first myoclonic jerks (FMJ), and total spikes/20 minutes were calculated from the video and ECoG recordings.

• ***Novel object recognition (NOR) test***

This test was conducted in a black plexiglass box (50 × 50 × 40 cm) in dimly lit conditions. The NOR test consisted of two different periods performed on two consecutive days. On the first day (habituation), all animals in the same groups were allowed to move freely in the test apparatus for 60 minutes. No object was used in the habituation period. The second day (test day) consisted of two different three-minute trials with a one-hour intertrial interval. In Trial 1 (Familiarization, T1), two identical objects were placed in opposite corners of the chamber (10 cm from each wall). The rats were permitted to move freely and explore this chamber for three minutes. Then, one of the identical objects (A for each) was exchanged with a novel one (B) at a one-hour interval. After that, the same rat was tested in the second trial (Retention, T2). In the retention period, the rats were also allowed to move freely in the test chamber for 3 minutes. All experiments were recorded by a camera, and exploration times were scored by a blind researcher for every object in T2. The test apparatus was cleaned using non-odour disinfectant between each test. The discrimination index (DI) was calculated using the following formula: DI = (EB − EA)/(EB + EA) for each animal [24]. The NOR test was conducted twice to determine both acute and cumulative effects on rats' recognition memory. Therefore, we performed the NOR test to examine the cumulative effects on the 22nd day of experiments. In addition, we conducted the NOR test using different objects on the 24th day of the study to observe the acute effects of vortioxetine (*figure 1*).

Statistical analyses

All statistical analyses were performed using GraphPad Prism 8 software. Electrophysiological data were

▼ **Table 1.** Fischer and Kittner seizure scale.

Stage 0	No evidence of convulsive activity
Stage 1	Weak head nodding
Stage 1,5	Mild forelimb clonic activity
Stage 2	Myoclonic body jerks, clonic forelimb convulsions without rearing
Stage 2,5	Frequent clonic forelimb convulsions, short (incomplete) rearing
Stage 3	Severe bilateral forelimb clonus (>10 s) with full rearing (Kangaroo position)
Stage 3,5	Rearing and falling in addition to severe bilateral forelimb clonus
Stage 4	Generalized clonic convulsions with rearing and falling down episodes or jumps
Stage 4,5	Generalized clonic-tonic seizures with loss of righting reflex (tonic extension of the forelimb)
Stage 5	Generalized clonic-tonic seizures and status epilepticus (>2 min)

analysed using the LabChart program (Version 8). After the injection of drugs, data were calculated in one-minute periods for 20 minutes. The Shapiro-Wilk test was applied to determine the normality of data. In the groups, behavioural and ECoG data were analysed using one-way ANOVA. The Tukey's test was used as a post hoc test for all analyses. Data were presented as mean ± standard error of the mean (SEM), and statistical significance was considered at $p<0.05$.

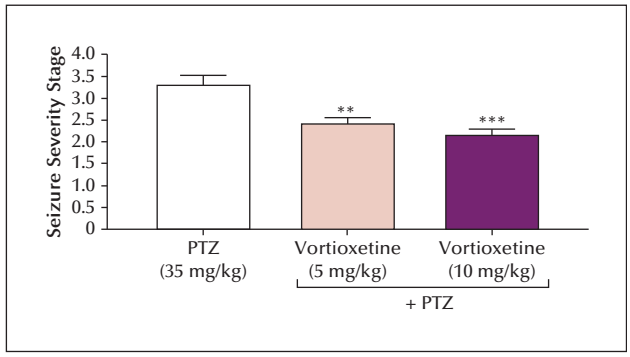
Results

Seizure severity

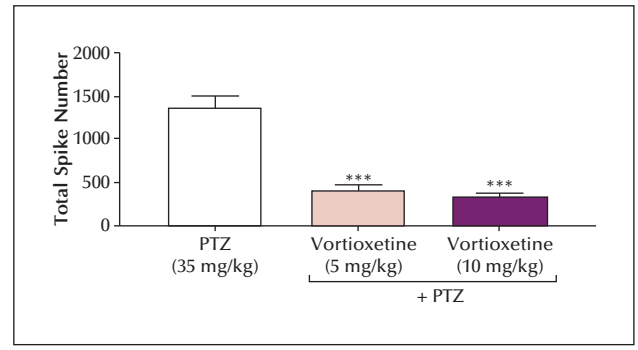
According to the Fischer and Kittner scale, the seizure severity stage was 3.29±0.2 in the PTZ group. Seizure severity scores were significantly lower ($p<0.05$) in the groups with 5 mg/kg vortioxetine (2.42±0.1) and 10 mg/kg vortioxetine (2.16±0.2) compared to the PTZ group (*figure 2*).

Total spike count and first myoclonic jerks

Our results showed that the administration of PTZ alone caused a total spike count of 1367±136 spike/20 minutes. In the vortioxetine 5 and 10-mg/kg groups, total spike counts were 418±41 and 332±33 spike/ 20 minutes, respectively. Treatment with vortioxetine at 5 and 10 mg/kg markedly decreased ($p<0.001$) seizure activity compared to the PTZ group (*figure 3*). The ECoG recording is presented in *figure 4*.



■ **Figure 2.** Seizure severity stages in rats treated with PTZ, 5 mg/kg vortioxetine, and 10 mg/kg vortioxetine according to the Fischer and Kittner scale. Statistical analyses were performed with one-way ANOVA, followed by Tukey's post hoc test. Data are presented as mean ± SEM. $^{**}p<0.01$, $^{***}p<0.001$ compared to the PTZ group ($n=6$ for the PTZ group, $n=7$ for the vortioxetine groups).



■ **Figure 3.** Total spike number in rats treated with PTZ, 5 mg/kg vortioxetine, and 10 mg/kg vortioxetine. Statistical analyses were performed with one-way ANOVA, followed by Tukey's post hoc test. Data are presented as mean ± SEM. $^{***}p<0.001$ compared to the PTZ group ($n=6$ for the PTZ group, $n=7$ for the vortioxetine groups).

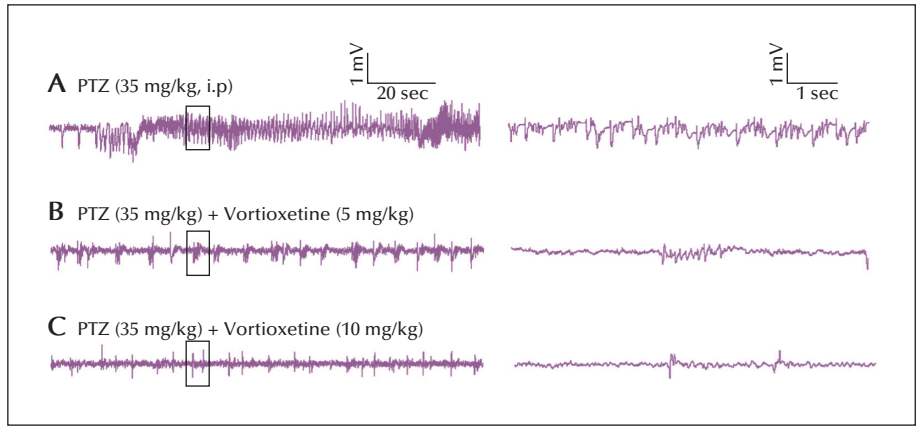
Similar results were seen for the FMJ parameter. In PTZ-administered rats, the duration of FMJ was 134±20 seconds in kindling experiments. In the 10-mg/kg vortioxetine group, the duration of FMJ was significantly elevated (200±15 seconds) compared to rats treated with PTZ ($p<0.05$). However, 5 mg/kg vortioxetine treatment did not statistically alter the duration of FMJ (196±17 seconds), although these tended to decrease ($p=0.0584$) compared to the PTZ group (*figure 5*).

Evaluation of the NOR test

In the first NOR test, 10 mg/kg vortioxetine administration markedly raised ($p<0.05$) the discrimination index compared to the PTZ group. Although 5 mg/kg vortioxetine tended to increase the discrimination index, this was not significant (*figure 6*).
In the second NOR test, there was no injection before the test. This was conducted two days after the last injections. This NOR test showed that the discrimination index in 5 mg/kg vortioxetine-treated rats was higher ($p<0.05$) than that in the PTZ group. However, the discrimination index was not statistically different between the 10-mg/kg vortioxetine group PTZ group (*figure 7*).

Discussion

To the best of our knowledge, the present study is the first in the literature to investigate the chronic effects of vortioxetine on PTZ-induced epilepsy. More precisely, we evaluated the potential beneficial effects of

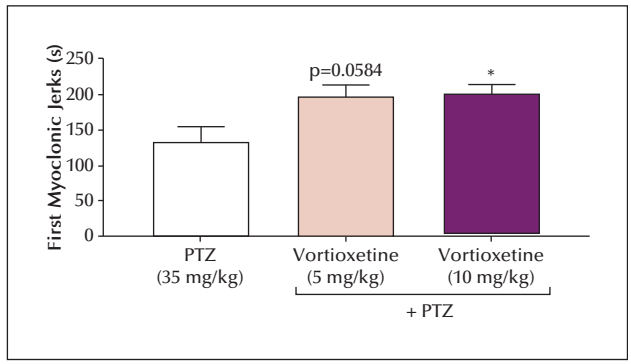


■ **Figure 4.** ECoG recordings for all groups at 15 minutes of PTZ administration. The number and amplitude of the spike provides information about the epileptiform activity. The increase in spike number is considered an indicator of the presence of seizures. To better demonstrate the difference between groups, the traces on the right represent the traces within the respective boxes on the left in greater detail. (A) PTZ (35 mg/kg, i. p): administration of PTZ caused an increase in spike frequency as an indicator of epileptiform activity. (B) PTZ (35 mg/kg) + vortioxetine (5 mg/kg): administration of vortioxetine before PTZ injection caused a decrease in spike frequency. (C) PTZ (35 mg/kg) + vortioxetine (10 mg/kg): administration of vortioxetine before PTZ injection caused a marked decrease in spike frequency (*n*=6 for the PTZ group, *n*=7 for the vortioxetine groups).

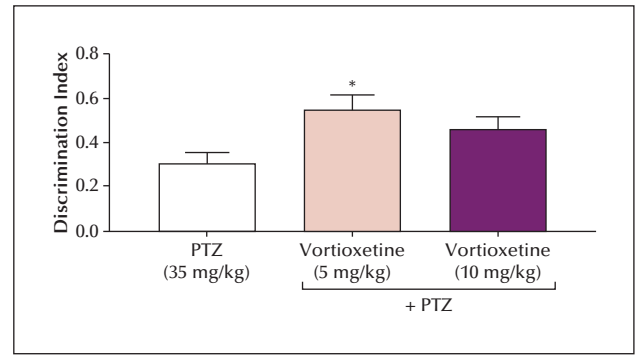
vortioxetine, a new multimodal antidepressant, based on a PTZ model of epilepsy in rats.

Our results show that repeated administration of PTZ (35 mg/kg) induced seizure activity in rats. Injection of PTZ caused increased total spike count and seizure severity and decreased FMJ. These findings are concordant with those from previous studies [25-27]. On the other hand, vortioxetine decreased the effects of PTZ and reduced seizure activity in rats. Studies investigating the effects of vortioxetine on epileptic activity are limited because this was only recently approved by FDA for psychiatric and neurological disorders. In the acute penicillin-induced epilepsy model, Ogun *et al*. found that vortioxetine and diazepam showed similar protective effects against seizure activity. Moreover, they demonstrated that the administration of vortioxetine (10 mg/kg) decreased spike frequency associated with seizure activity in rats [22]. In our study, two different doses of vortioxetine showed similar effects and decreased total spike count associated with seizure activity.

From a broad perspective, various studies have shown effects of antidepressants and selective serotonin reuptake inhibitors (SSRIs) on seizure activity [24, 28]. SSRIs are mostly reported to increase the seizure threshold and have protective effects against seizures [29]. Yan *et al*. showed that fluoxetine (15 mg/kg) decreased the intensity of audiogenic seizures in rats [30]. Similarly, fluoxetine administration caused a decrease in spontaneous seizures in the pilocarpine-induced epilepsy model in rodents [9]. Moreover, other studies with fluoxetine indicated decreased seizure duration and increased seizure threshold, survival, and seizure delay in various epilepsy models [31, 32]. In another study, sertraline exhibited anticonvulsant effects in clinical and experimental studies [33]. However, certain studies showed that SSRI antidepressants might increase the risk of seizure after traumatic brain injuries or strokes in Danish and Taiwanese populations [34, 35]. Considering different pathophysiological and neurobiological mechanisms of post-traumatic brain injury or poststroke epilepsy, SSRI antidepressants are commonly shown to exert beneficial effects on non-comorbid epilepsy. Vortioxetine has been classified as a multimodal antidepressant and is distinguished from SSRIs due to its unique pharmacological profile with an affinity for serotonergic receptors and other neurotransmitter systems. For these reasons, the results of previous studies performed with other antidepressants, such as SSRIs, do not directly mirror the effects of vortioxetine on epilepsy. There are some clinical reports of vortioxetine in epilepsy patients in the literature. In one of these reports, vortioxetine (5 mg/kg/day) caused epileptic seizures in just one of 611 patients [36]. In our study, we found similar results concordant with previous studies. Therefore, in light of this information, we can clearly state that antidepressants



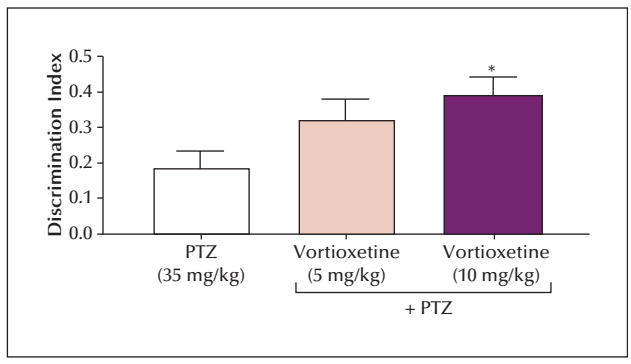
■ **Figure 5.** Duration of FMJ in rats treated with PTZ, 5 mg/kg vortioxetine, and 10 mg/kg vortioxetine. Statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. Data are presented as mean ± SEM. *p<0.05 compared to the PTZ group (n=6 for the PTZ group, n=7 for the vortioxetine groups).



■ **Figure 7.** Discrimination index based on the second NOR test following treatment with PTZ, 5 mg/kg vortioxetine, and 10 mg/kg vortioxetine. Statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. Data are presented as mean ± SEM. *p<0.05 compared to the PTZ group (n=6 for the PTZ group, n=7 for the vortioxetine groups).

and SSRIs have anticonvulsant effects in various epilepsy models.

As mentioned above, molecular and electrophysiological studies have shown that 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_7 subtypes are strongly linked to the pathogenesis of epilepsy [13]. On the other hand, unlike most known antidepressants, vortioxetine simultaneously acts at six pharmacological targets with three modes of action:



■ **Figure 6.** Discrimination index based on the first NOR test in rats treated with PTZ (previously administered), 5 mg/kg vortioxetine, and 10 mg/kg vortioxetine. Statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. Data are presented as mean ± SEM. *p<0.05 compared to the PTZ group (n=6 for the PTZ group, n=7 for the vortioxetine groups).

- inhibition of serotonin transporter or SERT;
- via several G-protein linked receptors (agonist at $5HT_{1A}$ and $5HT_{1B}$ receptors, antagonist at $5HT_{1D}$ and $5HT_7$ receptors)
- and inhibition of a ligand-gated ion channel, the $5HT_3$ receptor [20].

In particular, 5-HT_3 receptor subtype antagonists, ondansetron and granisetron, are reported to have antiepileptic activities in preclinical models of epilepsy [17]. Thus, we suggest that the anticonvulsant effects of vortioxetine result from both inhibition of serotonin transporters and antiepileptic activity via the 5-HT3 receptor.

In addition to these modes of action, vortioxetine alters the downstream release of glutamate and GABA from the prefrontal cortex and hippocampus. 5-HT neurons make connections and terminate directly to glutamatergic pyramidal neurons and indirectly to GABAergic inhibitory interneurons in pyramidal neurons. These connections and the release of these neurotransmitters cause a mixed effect by SSRIs. Thus, the net effect of increased 5-HT would appear to be diverse, with both excitatory and inhibitory effects in the brain. An increase in neuronal output from pyramidal neurons promotes glutamate-dependent neuronal plasticity and long-term potentiation, critical components of cognition, and memory. In another case report, it was asserted that treatment with vortioxetine alleviated visual symptoms in patients with occipital lobe epilepsy. Moreover, in this study, we report a procognitive effect of vortioxetine on visual recognition memory in a chronic PTZ-induced

kindling rat model. Several studies have shown that chemoconvulsants induced recognition and spatial memory deficits in rats [37]. The cognitive enhancer effects of vortioxetine in several neuropsychiatric disorders, such as depression and schizophrenia, have been reported in various studies [36, 38]. However, there is no data about its effect on cognitive deficits in epilepsy. Herein, we report that vortioxetine improved cognitive performance due to an acute effect at high dose or a chronic preventative effect at low dose. We suggest that vortioxetine might be a valuable candidate to prevent seizure activity and treat cognitive deficits of epilepsy.

Conclusion

In this study, we have investigated the effects of vortioxetine on the PTZ-induced epilepsy model in rats. We report that vortioxetine decreases seizure activity and seizure severity, increases FMJ and suppresses the cognitive deficits induced by PTZ in rats. Based on our findings, we suggest that vortioxetine should be studied further in relation to the pathophysiology of epilepsy. Long-term studies with other experimental epilepsy models and different doses of vortioxetine should provide valuable results regarding the use of this novel drug. ■

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References

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Svheffer IE, Shinnar S, *et al*. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56(10): 1515-23.

2. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. *Neuropharmacology* 2013; 69: 16-24.

3. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006; 367(9516): 1087-100.

4. Bonnycastle DD, Giarman NJ, Paasonen MK. Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. *Br J Pharmacol Chemother* 1957; 12(2): 228-31.

5. Prendiville S, Gale K. Anticonvulsant effect of fluoxetine on focally evoked limbic motor seizures in rats. *Epilepsia* 1993; 34(2): 381-4.

6. Statnick MA, Maring-Smith ML, Clough RW, Wang C, Dailey JW, Jobe PC, *et al*. Effect of 5,7-dihydroxytryptamine on audiogenic seizures in genetically epilepsy-prone rats. *Life Sci* 1996; 59(21): 1763-71.

7. Hernandez EJ, Williams PA, Dudek FE. Effects of fluoxetine and TFMPP on spontaneous seizures in rats with pilocarpine-induced epilepsy. *Epilepsia* 2002; 43(11): 1337-45.

8. Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. *J Neurochem* 2007; 100(4): 857-73.

9. Shiha AA, de Cristobal J, Delgado M, de la Rosa RF, Bascunana P, Pozo MA, *et al*. Subacute administration of fluoxetine prevents short-term brain hypometabolism and reduces brain damage markers induced by the lithium-pilocarpine model of epilepsy in rats. *Brain Res Bull* 2015; 111: 36-47.

10. Wenger GR, Stitzel RE, Craig CR. The role of biogenic amines in the reserpine-induced alteration of minimal electroshock seizure thresholds in the mouse. *Neuropharmacology* 1973; 12(7): 693-703.

11. Lazarova M, Bendotti C, Samanin R. Studies on the role of serotonin in different regions of the rat central nervous system of pentylenetetrazol-induced seizures and the effect of di-n-propylacetate. *Naunyn Schmiedebergs Arch Pharmacol* 1983; 322(2): 147-52.

12. Tripathi PP, Di Giovannantonio L, Viegi A, Wurst W, Simeone A, Bozzi Y. Serotonin hyperinnervation abolishes seizure susceptibility in Otx2 conditional mutant mice. *J Neurosci* 2008; 28(37): 9271-6.

13. Taskiran M. Serotonin and role in epilepsy. *J Health Sci* 2019; 28(3): 182-7.

14. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, *et al*. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. *Nature* 1995; 374(6522): 542-6.

15. Taskiran M, Tasdemir A, Ayyildiz N, Ayyildiz M, Agar E. The effect of serotonin on penicillin-induced epileptiform activity. *Int J Neurosci* 2019; 129(7): 687-97.

16. Zhao H, Lin Y, Chen S, Li X, Huo H. 5-HT3receptors: a potential therapeutic target for epilepsy. *Curr Neuropharmacol* 2018; 16(1): 29-36.

17. Aithal S, Balaji V, Geeta S, Swetha ES, Udupa AL. Anticonvulsant activity of Granisetron in Albino mice. *Int J Pharmacol Res* 2015; 5(5): 119-21.

18. Gokul CG, Halemani SS, Acharya A, Santhosh, Adake P. Evaluation of antiepileptic activity of Ondansetron in Albino Rats. *Pharma Innov J* 2017; 6: 112-8.

19. Yang Z, Liu X, Yin Y, Sun S, Deng X. Involvement of 5-HT (7) receptors in the pathogenesis of temporal lobe epilepsy. *Eur J Pharmacol* 2012; 685(1-3): 52-8.

20. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): modifying serotonin's downstream effects on glutamate and GABA (gamma amino butyric acid) release. *CNS Spectr* 2015; 20(4): 331-6.

21. D'Agostino A, English CD, Rey JA. Vortioxetine (brintellix): a new serotonergic antidepressant. *P T* 2015; 40(1): 36-40.

22. Ögün MN, Çetinkaya A, Beyazçiçek E. The effect of vortioxetine on penicillin-induced epileptiform activity in rats. *Arq Neuropsiquiatr* 2019; 77(6): 412-7.

23. Fischer W, Kittner H. Influence of ethanol on the pentylenetetrazol-induced kindling in rats. *J Neural Transm* 1998; 105(10): 1129-42.

24. Gorska N, Slupski J, Cubala WJ. Antipsychotic drugs in epilepsy. *Neurol Neurochir Pol* 2019; 53(6): 408-12.

25. Etemad L, Zamani M, Iranshahi M, Roohbakhsh A. The protective effect of auraptene against oxidative stress and pentylenetetrazol-induced chemical kindling in mice. *Iran J Pharm Res* 2019; 18(3): 1395-402.

26. Tahmasebi S, Oryan S, Mohajerani HR, Akbari N, Palizvan MR. Probiotics and Nigella sativa extract supplementation improved behavioral and electrophysiological effects of PTZ-induced chemical kindling in rats. *Epilepsy Behav* 2020; 104(Pt A): 106897.

27. Günaydîn C, Arslan G, Bilge SS. Proconvulsant effect of trans-cinnamaldehyde in pentylenetetrazole-induced kindling model of epilepsy: the role of TRPA1 channels. *Neurosci Lett* 2020; 721: 134823.

28. Górska N, Słupski J, Cubała WJ, Wiglusz MS, Gałuszko-Węgielnik M. Antidepressants in epilepsy. *Neurol Neurochir Pol* 2018; 52(6): 657-61.

29. Qiu X, Zingano B, He S, Zhu X, Peng A, Duan J, *et al*. Antiepileptic effect of olanzapine in epilepsy patients with atypical depressive comorbidity. *Epileptic Disord* 2018; 20(3): 225-31.

30. Yan QS, Jobe PC, Cheong JH, Ko KH, Dailey JW. Role of serotonin in the anticonvulsant effect of fluoxetine in genetically epilepsy-prone rats. *Naunyn Schmiedebergs Arch Pharmacol* 1994; 350(2): 149-52.

31. Aygun H. The effect of fluoxetine on penicillin-induced epileptiform activity. *Epilepsy Behav* 2019; 95: 79-86.

32. Pottoo FH, Tabassum N, Javed MN, Nigar S, Rasheed R, Khan A, *et al*. The synergistic effect of raloxifene, fluoxetine, and bromocriptine protects against pilocarpine-induced status epilepticus and temporal lobe epilepsy. *Mol Neurobiol* 2019; 56(2): 1233-47.

33. Brennecke A, Weaver DF. Anticonvulsant effects of sertraline: a case report. *Seizure* 2020; 80: 1-2.

34. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) *versus* placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin* 2013; 29(3): 217-26.

35. Pearson JN, Schulz KM, Patel M. Specific alterations in the performance of learning and memory tasks in models of chemoconvulsant-induced status epilepticus. *Epilepsy Res* 2014; 108(6): 1032-40.

36. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 2014; 17(10): 1557-67.

37. Bruno A, Zoccali RA, Troili GM, Scala L, Pandolfo G, Cedro C, *et al*. Vortioxetine on cognition in schizophrenia: a pilot study. *J Clin Psychopharmacol* 2020; 40 (4): 381-5.

38. Unal G, Taskiran M. Vortioxetine improved social and cognitive deficits in acute ketamine model of schizophrenia in rats. *J Res Pharm* 2020; 24(5): 648-55.