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Modulation of Cypermethrin and PTZ-induced Astrogliosis and GABAergic Interneuron Loss in the Septal Nucleus by Vitamin E and Valproic Acid Co-Therapy

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ABSTRACT

Exposure to environmental neurotoxicants is linked to neurological effects of epilepsy, impacting not only seizure severity but also neuroglial integrity across different brain regions. This study investigated the effects of Vitamin E and Valproic Acid on neuronal and glial changes in the septal nucleus of rats exposed to pentylenetetrazol-induced seizures and cypermethrin. Fifty-six male Wistar rats were divided into control and experimental groups in a two-phase design, receiving various combinations of pentylenetetrazol, cypermethrin, Vitamin E, and valproic acid. Septal sections underwent Hematoxylin and Eosin staining, along with immunohistochemical markers for astrogliosis (GFAP) and Gamma-Aminobutyric Acidergic interneurons (Parvalbumin). Cypermethrin or Pentylenetetrazol significantly decreased parvalbumin-positive interneurons and GFAP+ astrocyte expression in the septal nucleus, with observable degenerative features in the septal neuronal cytoarchitecture. Conversely, VPA and Vitamin E, whether alone or combined, partially restored PV-positive interneurons and GFAP+ astrocytic expressions, indicating partial preservation of astrocytes, with the combination showing the greatest improvement. There was also a cumulative structural recovery in the overall cytoarchitecture with combined treatment. These findings suggest that cypermethrin contributes to septal neuropathology in seizure models, and that combined antioxidant and antiepileptic therapy may partly reduce astrocytic and neuronal loss.

Keywords: cypermethrin, epilepsy, astrogliosis, GABAergic interneuron, septal nuclei

INTRODUCTION

Epilepsy is a widespread neurological condition characterized by a persistent predisposition to generate spontaneous, recurrent seizures[1]. It affects an estimated 50 million people globally, with a disproportionate burden, nearly 80%, in low- and middle-income countries[2]. In Africa alone, approximately 25 million individuals are diagnosed with epilepsy, accounting for a significant portion of the global prevalence[3,4]. The etiology of epilepsy is complex and multifactorial, encompassing structural, genetic, metabolic, and immune-related causes[5,6]. Among environmental risk factors, exposure to pesticides has garnered increasing attention for its potential role in enhancing seizure susceptibility[7]. Pyrethroids, a widely used class of synthetic insecticides, are of particular concern. Derived from natural pyrethrins, they are extensively applied in agriculture, public health (e.g., malaria and Zika virus control), and veterinary medicine[8].

The primary neurotoxic mechanism of pyrethroids involves prolonged activation of voltage-gated sodium channels (VGSCs), leading to sustained neuronal depolarization and hyperexcitability[9]. This mechanism is directly relevant to epilepsy, where similar hyperexcitability underlies seizure generation. Furthermore, pyrethroids can induce oxidative stress, neuroinflammation, and mitochondrial dysfunction, exacerbating their neurotoxic potential[8,10]. Cypermethrin, a common Type II pyrethroid, is used to control a broad spectrum of pests. Its neurotoxicity, primarily from delaying VGSC closure, is well-documented[11,12]. The pathological pathways it activates, especially oxidative stress and neuroinflammation, overlap significantly with those implicated in epileptogenesis, suggesting that CPM exposure could worsen or trigger seizure disorders [13,14].

The septal nucleus, a key subcortical structure, is integral to the septo-hippocampal pathway, regulating hippocampal theta rhythms, memory, and emotional

behaviors. It is densely populated with GABAergic interneurons, particularly parvalbumin-positive (PV+) subtypes, which are essential for maintaining local inhibitory balance. Disruption or loss of these interneurons can lead to septal disinhibition, contributing to hippocampal hyperexcitability and seizure propagation [14].

While anti-seizure medications (ASMs) like Valproic Acid effectively manage seizures in approximately 70% of patients, gaps in treatment and drug-resistant epilepsy remain significant challenges[3,15]. Valproic Acid's anticonvulsant effects are mediated through multiple mechanisms, including VGSC blockade, enhanced GABAergic transmission, and histone deacetylase (HDAC) inhibition[16–18]. Adjunctive therapies with antioxidant properties, such as Vitamin E, have shown promise in preclinical models by mitigating oxidative stress and neuroinflammation, which are key drivers of seizure-induced damage[19–21]. This study was designed to evaluate the neuropathological impact of cypermethrin exposure in a pentylenetetrazole-induced epileptic rat model, specifically within the septal nucleus. We further investigated the potential synergistic protective effects of combined Vitamin E and Valproic Acid therapy on astroglial reactivity (GFAP) and GABAergic interneuron (PV) integrity.

MATERIALS AND METHODS

Ethical approval

All experimental procedures received approval from the Departmental Research and Ethical Review Committee, College of Health Sciences, University of Ilorin, and were conducted in strict compliance with the guidelines of the Institutional Animal Care and Use Committee (IACUC).

Experimental animals

Adult male Wistar rats were obtained from the University of Ilorin Central Research Laboratory breeding facility. They were housed in the animal holding facility in wire-gauze plastic cages with sawdust bedding, under a natural light/dark cycle. The animals had ad libitum access to a standard laboratory diet and water. A minimum one-week acclimatization period was observed before the experiment commenced.

Experimental design and treatment protocol

The study was conducted in two phases to first establish the model and then test the interventions.

Phase 1: Model Establishment

Thirty-six rats were randomly divided into four groups (n=9 per group):

Group 1 - Control: Received 1 ml/kg/day of corn oil (vehicle) orally.

Group 2 - Cypermethrin (CPM): Received 4.4 mg/kg body weight of CPM orally, once daily.

Group 3 - pentylenetetrazol (PTZ): Received 35 mg/kg body weight of PTZ intraperitoneally every 48 hours.

Group 4 (CPM+PTZ): Received both CPM (4.4 mg/kg orally, daily) and PTZ (35 mg/kg intraperitoneally, every 48 hours).

Phase 2: Therapeutic Intervention

Based on Phase 1 results, a new cohort of thirty-six rats was divided into four groups (n=9 per group), all receiving the combined CPM+PTZ treatment as described above, plus the following interventions:

Group 1 (CPM+PTZ): Control for this phase, received only the combined CPM+PTZ treatment.

Group 2 (VPA+CPM+PTZ): Received 100 mg/kg Valproic Acid 30 minutes before CPM/PTZ administration.

Group 3 (VitE+CPM+PTZ): Received 100 mg/kg Vitamin E 30 minutes before CPM/PTZ administration.

Group 4 (VPA+VitE+CPM+PTZ): Received both 100 mg/kg Valproic Acid and 100 mg/kg Vitamin E 30 minutes before CPM/PTZ administration.

In both phases, treatments were administered for 10 consecutive days. PTZ was injected on days 1, 3, 5, 7, and 9. Seizure severity was monitored and scored according to a modified Racine scale during the 60 minutes following each PTZ injection[22].

Animal euthanasia and tissue processing

At the end of the treatment period, three rats from each group were randomly selected and deeply anesthetized with ketamine (20 mg/kg, intramuscular). Transcardial perfusion was performed with normal saline, followed by 10% neutral buffered formalin for whole-body fixation. The brains were carefully dissected and post-fixed in 10% formalin.

Following 10% formalin fixative, brains were processed through graded alcohols, cleared in xylene, and embedded in paraffin wax. Coronal sections (5.8 µm thick) through the septal nuclei were cut using a semi-automatic rotary microtome.

Histological and immunohistochemical staining

Hematoxylin and Eosin (H&E) Staining: Sections were stained with H&E following standard protocols to assess general neuronal cytoarchitecture[23].

Immunohistochemistry (IHC): Sections were deparaffinized, rehydrated, and subjected to heat-mediated antigen retrieval in citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 0.3% H_2O_2, and non-specific protein binding was blocked with 2.5% normal horse serum. Sections were then incubated overnight at 4°C with primary

antibodies: goat polyclonal anti-GFAP (1:250, Abcam, ab5076) or rabbit polyclonal anti-Parvalbumin (1:1000, Novus Biologicals, NB120-11427). Following washes, sections were incubated with appropriate ImmPRESS™ HRP Polymer Reagents (Vector Labs). Immunoreactivity was visualized using a DAB Peroxidase Substrate Kit (Vector Labs), and sections were counterstained with hematoxylin.

Microscopy, photomicrography and stereology

Stained sections were examined and photographed using an AmScope compound microscope equipped with a 5.0 MP digital camera (iSCOPE Corp., USA). Images were captured at 400x magnification. Quantitative analysis of cellular density was performed using unbiased stereological methods using ImageJ software (NIH, USA), integrated with the cell counter and color deconvolution plugins.

High-resolution digital images of the septal region were imported into ImageJ. The analysis focused on: GFAP-positive astrocytes: quantified by counting brown DAB-stained cell bodies with characteristic astrocytic morphology; PV-positive interneurons: counted based on strong cytoplasmic immunostaining and distinct multipolar shapes. To reduce bias, all image quantification was conducted blind to the treatment group. The data collected were compiled and statistically analyzed using one-way ANOVA followed by post hoc Tukey's test to determine significant differences across groups. This stereological analysis provided reliable and reproducible quantitative data on neuronal loss, glial reactivity, and therapeutic outcomes.

RESULTS

GABAergic interneuron loss in the striatum of cypermethrin-exposed PTZ-challenged rats

Immunohistochemical analysis of parvalbumin (PV) expression, a marker for a key subset of GABAergic interneurons, revealed distinct differences among the experimental groups (Figure 1). In the septal region, the control group exhibited the highest expression of parvalbumin-positive (PV+) GABAergic interneurons, indicating a healthy and preserved population of inhibitory neurons. Compared to the control, the PTZ group showed a reduction in PV+ interneuron expression, reflecting neuronal damage. The CPM group also displayed a decrease in PV+ cell expression, which was statistically significant, suggesting that cypermethrin exposure leads to notable impairment of GABAergic interneurons in this region. Similarly, the combined CPM+PTZ group demonstrated reduced PV+ expression when compared to the control. Statistical analysis revealed significant differences across all groups relative to the control. However, no statistically significant difference was observed between the CPM group and the CPM+PTZ group, indicating that the addition of PTZ to CPM exposure did not exacerbate GABAergic interneuron loss beyond the effect of CPM alone as shown in (Figure 1).

Astrogliosis in the striatum of cypermethrin-exposed PTZ-challenged rat

GFAP immunohistochemistry was used to assess astrocytic reactivity (Figure 2). The control group exhibited baseline GFAP expression, reflecting a quiescent astrocyte population. In contrast, the PTZ group showed a reduction in GFAP expression, suggesting the onset of reactive astrogliosis and glial dysfunction. The CPM group demonstrated a further decrease in GFAP expression, which was statistically significant when compared to the control, indicating that cypermethrin exposure induces notable astrocytic activation and potential neuroinflammation. Similarly, the combined CPM+PTZ group also showed lower GFAP expression compared to the control. Statistical analysis revealed significant differences across all groups when compared to the control, confirming the impact of PTZ, CPM, and their combination on astrocytic integrity. However, no statistically significant difference was observed between the CPM group and the CPM+PTZ group, indicating that the addition of PTZ to CPM did not significantly intensify astrogliosis beyond the effect of CPM alone (Figure 2).

Striatal histological integrities in cypermethrin-exposed PTZ-challenged rat

H&E-stained sections of the septal nucleus (Figure 3) revealed normal neuronal architecture with well-defined cellular outlines in the control group. The PTZ group exhibited noticeable histopathological alterations, including neuronal shrinkage and reduced cell density. The CPM group showed more pronounced neuronal damage, characterized by increased cell loss and disrupted cytoarchitecture, which was statistically significant when compared to the control. Similarly, the combined CPM+PTZ group demonstrated neuronal degeneration and tissue disorganization, with reduced neuronal density relative to the control group. Statistical analysis revealed significant differences across all treatment groups when compared to the control, confirming the deleterious effects of PTZ, CPM, and their combination on septal neuronal integrity. However, no statistically significant difference was observed between the CPM group and the CPM+PTZ group, indicating that the combination of both agents did not exacerbate the histological damage beyond the effect of CPM alone (Figure 3).

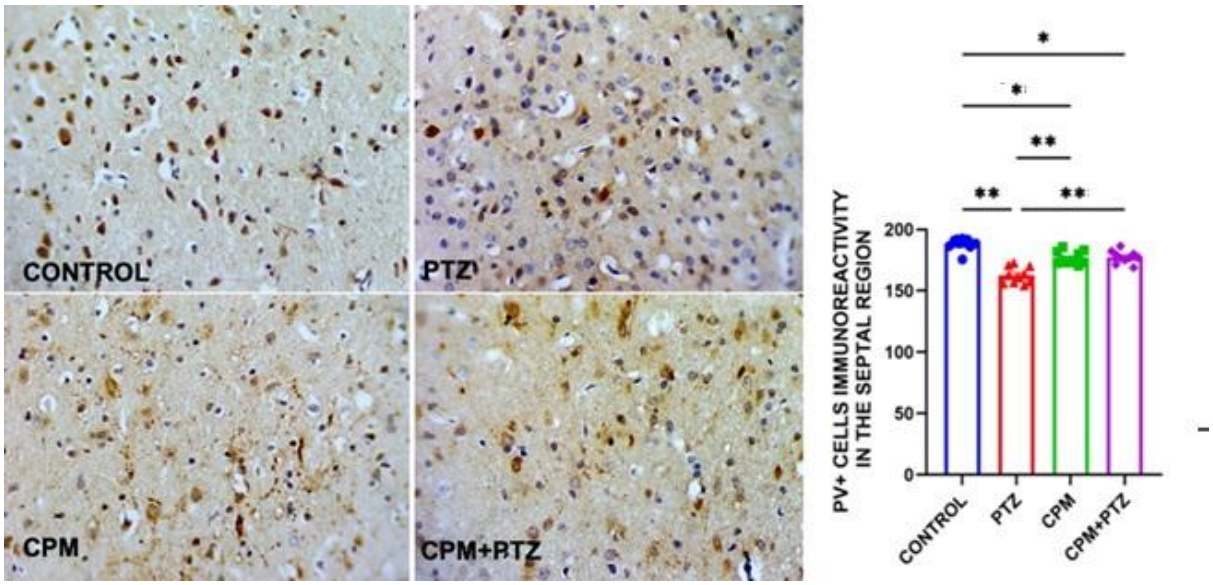

Figure 1: Representative photomicrographs of Parvalbumin (PV)-stained cells in the septal nuclei of rats exposed to corn oil (Control), Pentylenetetrazol (PTZ), Cypermethrin (CPM), and PTZ plus CPM, respectively showing a decrease in the PV+ stained cells in PTZ, CPM, and CPM+PTZ groups when compared with the Control. Reduced distributions of the PV expressing GABAergic interneurons was observed across exposures, but more in the co-morbid brains. Anti-PV, 400X, Scale bar: 35 µm. one-way ANOVA, mean ± SEM. Asterisks (*,**) indicate significant differences.

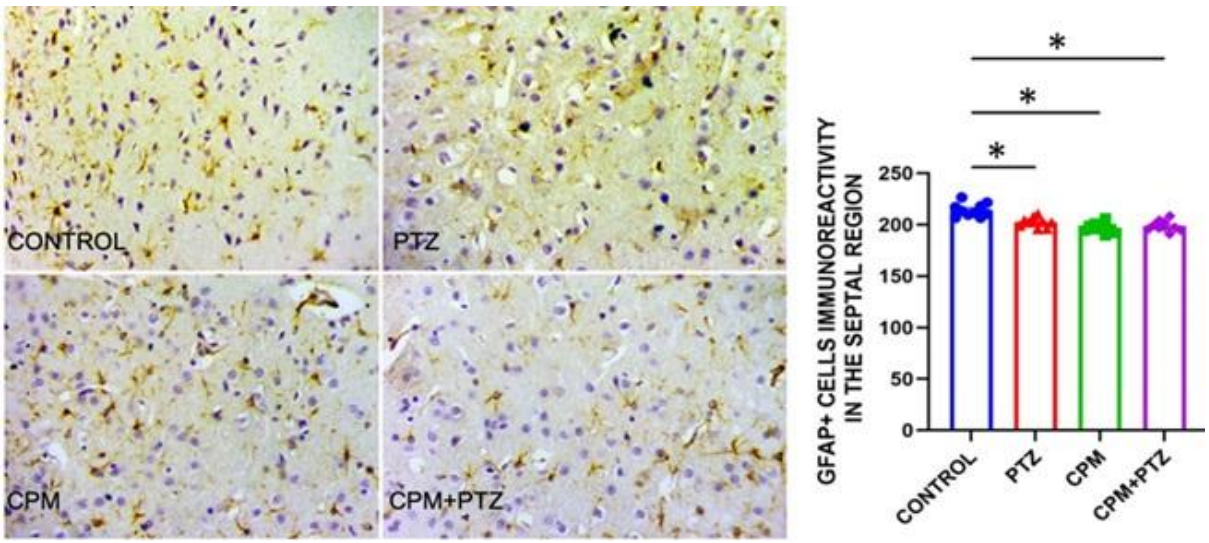

Figure 2: Representative photomicrographs of Glial Fibrillary Acidic Protein (GFAP) immunohistochemistry in the septal nuclei of rats exposed to corn oil (Control), Pentylenetetrazol (PTZ), Cypermethrin (CPM), and PTZ+CPM, respectively showing a reduction in GFAP positive stain in PTZ, CPM, and CPM+PTZ groups when compared with the control group. Anti-GFAP, 400X, Scale bar: 35 µm. one-way ANOVA, mean ± SEM. Asterisks (*) indicate significant differences.

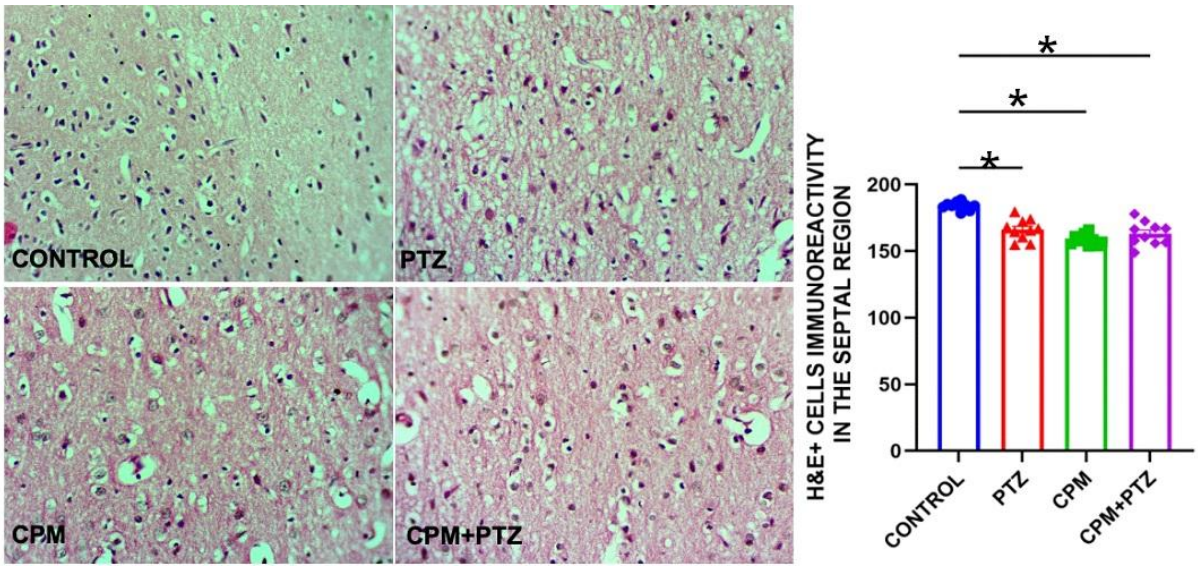

Figure 3: Representative photomicrographs of H&E-stained cells in the septal nuclei of rats exposed to corn oil (Control), Pentylenetetrazol (PTZ), Cypermethrin (CPM), and PTZ+CPM, respectively showing a notable neuronal loss and disrupted cytoarchitecture in the PTZ, CPM, and CPM+PTZ groups when compared with the control. H&E, 400X, Scale bar: 35 µm. one-way ANOVA, mean ± SEM. Asterisks (*) indicate significant differences.

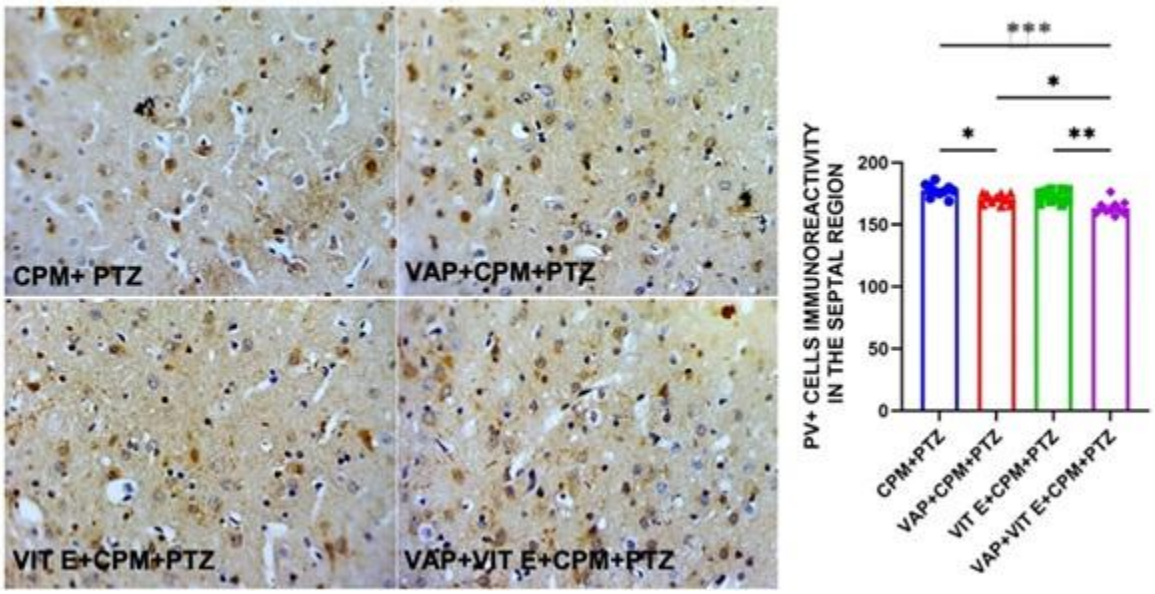

Figure 4: Representative photomicrographs of Parvalbumin immunohistochemistry in the septal nuclei in rats exposed to Pentylenetetrazol and Cypermethrin without intervention (CPM+PTZ), and with interventions, Valproic Acid (VAP), Vitamin E (Vit E), and the combination, showing notable expression of enormous parvalbumin positive cells in the intervention groups when compared with the CPM+PTZ group. Anti-PV, 400X, Scale bar: 35 µm. One-way ANOVA, mean ± SEM. Asterisks (*,**,***) indicate significant difference

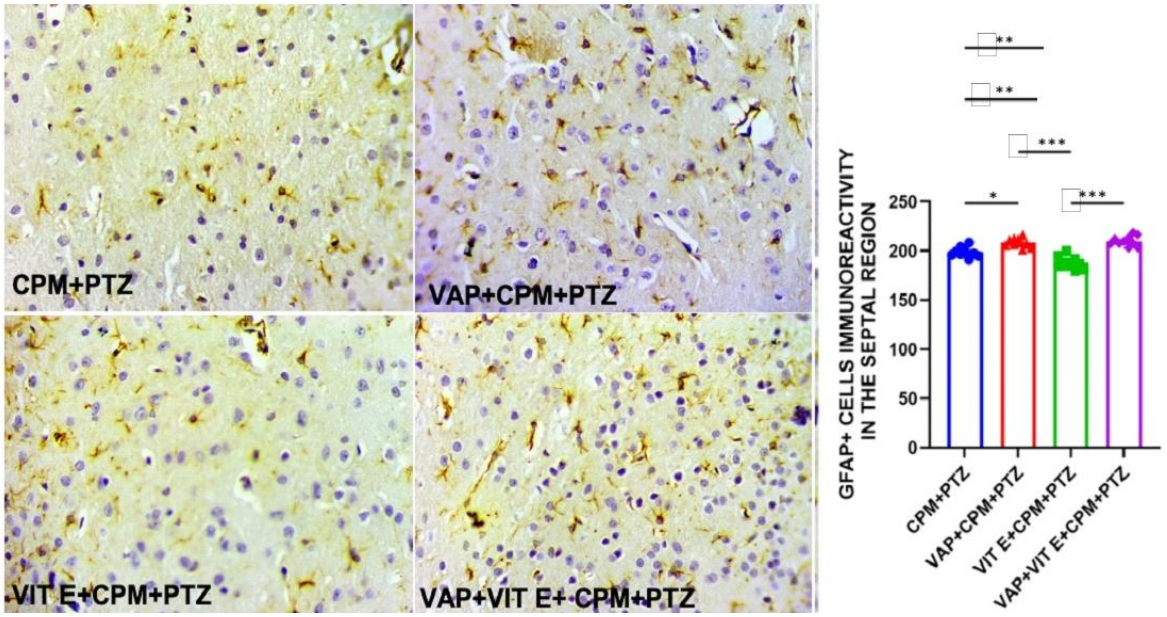

Figure 5: Representative photomicrographs of Glial Fibrillary Acidic Protein (GFAP) immunohistochemistry in the septal nuclei in rats exposed to Pentylenetetrazol and Cypermethrin without intervention (CPM+PTZ), and with interventions (Valproic Acid (VAP), Vitamin E (Vit E), and the combination) showing reduced GFAP-positive cells in the intervention groups when compared with CPM+PTZ group . Anti-GFAP, 400X, Scale bar: 35 µm. One-way ANOVA, mean ± SEM. Asterisks (*,**,***) indicate significant difference.

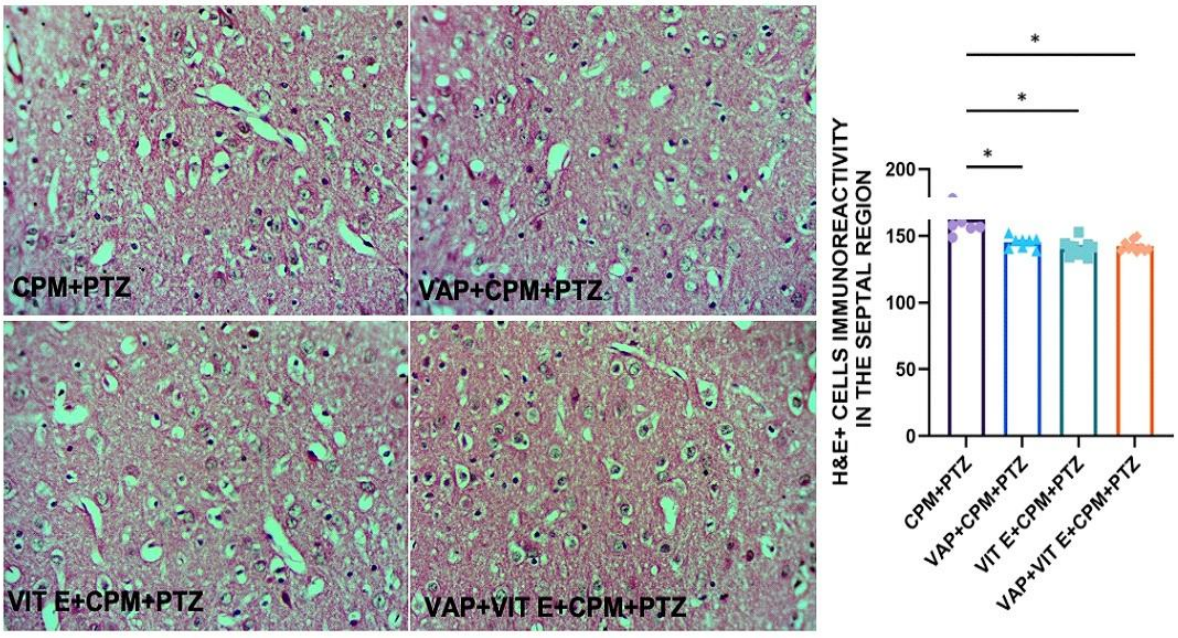

Figure 6: Representative photomicrographs of H&E-stained cells in the septal nuclei of rats exposed to Pentylenetetrazol and Cypermethrin without intervention (CPM+PTZ), and with interventions, Valproic Acid (VAP), Vitamin E (Vit E) expressing a notable restoration of the neuronal integrity and architecture in the intervention groups when compared to the CPM+PTZ group, and the combination. H&E, 400X, Scale bar: 35 µm. One-way ANOVA, mean ± SEM. Asterisks (*) indicate significant difference.

Preservation of parvalbumin positive GABAergic interneuron by vitamin E and valproic acid in the septal nucleus of cypermethrin-exposed PTZ-challenged rats

In the septal region, animals exposed to the combined CPM+PTZ treatment exhibited reduced expression of parvalbumin-positive (PV+) GABAergic interneurons, indicating neuronal damage and loss of inhibitory interneurons. The group receiving Valproic Acid (VAP)+CPM+PTZ showed a further decrease in PV+ expression compared to the CPM+PTZ group, suggesting that Valproic Acid alone offered limited neuroprotection in this context. Similarly, the Vitamin E+CPM+PTZ group demonstrated reduced PV+ expression, though slightly higher than the VAP group, indicating partial preservation of interneurons. The group treated with the combination of Valproic Acid+Vitamin E+CPM+PTZ exhibited the lowest PV+ expression among all groups, reflecting the most pronounced reduction in parvalbumin-positive interneurons. Statistical analysis revealed significant differences across all groups, confirming the impact of the various treatments on GABAergic interneuron integrity. However, no statistically significant difference was observed between the CPM+PTZ group and the Valproic Acid+CPM+PTZ or Vitamin E+CPM+PTZ groups, indicating that neither intervention alone was sufficient to restore PV+ expression. The combined use of both Valproic Acid and Vitamin E also failed to significantly improve PV+ levels when compared to the dual exposure group.

Modulation of astrogliosis (GFAP) by vitamin E and valproic acid in the septal nucleus of cypermethrin-exposed PTZ-challenged rats

In the septal region, GFAP staining revealed that animals exposed to CPM+PTZ exhibited reduced astrocytic expression, indicating astrocyte loss or dysfunction following combined neurotoxic exposure. Treatment with Valproic Acid (VAP)+CPM+PTZ resulted in an increase in GFAP expression compared to the CPM+PTZ group, suggesting that Valproic Acid may offer some protective effect by preserving astrocyte integrity. Similarly, animals receiving Vitamin E+CPM+PTZ demonstrated a reduction in GFAP expression, lower than both the CPM+PTZ and VAP+CPM+PTZ groups, indicating limited protection or possible vulnerability of astrocytes despite antioxidant support. Notably, the group treated with the combination of Valproic Acid+Vitamin E+CPM+PTZ showed the highest GFAP expression among all groups, suggesting a potential synergistic effect in preserving astrocytic populations. Statistical analysis revealed significant differences across all groups when compared to the CPM+PTZ group, confirming the influence of Valproic Acid, Vitamin E, and their combination on astrocyte response. However, no statistically significant difference was observed between the CPM+PTZ group and the Vitamin E+CPM+PTZ group, indicating that Vitamin E alone did not significantly modify GFAP expression in this context (Figure 5).

Preservation of septal nuclei histology by vitamin E and valproic acid in cypermethrin exposed PTZ-challenged rats

Histological examination with Haematoxylin and Eosin (H&E) staining revealed noticeable neuronal damage in the CPM+PTZ group, with features such as reduced cell density, pyknotic nuclei, and disrupted cytoarchitecture, reflecting significant neurodegeneration. Animals treated with Valproic Acid+ CPM+PTZ exhibited further reductions in neuronal preservation, with more marked histopathological alterations compared to the CPM+PTZ group as shown in the figure 6. Similarly, the Vitamin E+CPM+PTZ group demonstrated decreased neuronal integrity, showing the lowest neuronal density among the groups, indicative of ongoing cellular degeneration despite antioxidant intervention. Interestingly, the group receiving the combination of Valproic Acid+Vitamin E+CPM+PTZ also displayed substantial histological damage, with neuronal density slightly improved compared to Vitamin E alone but still lower than the PTZ+CPM group. Statistical analysis revealed significant differences across all groups when compared to the CPM+PTZ group , highlighting the variable effects of Valproic Acid, Vitamin E, and their combination on neuronal preservation. However, no statistically significant difference was observed between the CPM+PTZ group and the Vitamin E+CPM+PTZ group, suggesting that Vitamin E alone did not offer significant histological protection (Figure 6).

DISCUSSION

This study provides compelling evidence of the synergistic neurotoxic effects of the convulsant PTZ and the pyrethroid insecticide cypermethrin on the septal nucleus, a brain region critical for regulating hippocampal excitability. Our findings demonstrate that this co-exposure exacerbates seizure severity[22] and induces significant pathological changes,

including reactive astrogliosis, loss of GABAergic interneurons, and general neuronal damage. Crucially, we show that co-treatment with Vitamin E and Valproic Acid can partially mitigate these effects.

The marked downregulation of glial fibrillary acidic protein observed with (GFAP) in the cypermethrin and pentylenetetrazole ingestions indicates degenerative-like reactive astrogliosis[24]. Astrocytes play a dual role in epilepsy; while they can form glial scars to contain seizure foci, their persistent activation can also perpetuate neuroinflammation and impair glutamate and ion homeostasis, contributing to a pro-epileptogenic environment[25,26]. The pronounced astrogliosis observed, aligns with the known ability of pyrethroids to induce oxidative stress and neuroinflammation, which are potent triggers for astrocytic reactivity[27]. This suggests that cypermethrin exposure significantly amplifies the neuroinflammatory burden in an already compromised epileptic brain.

The selective loss of PV+ GABAergic interneurons in the septum is a critical finding. These fast-spiking interneurons are essential for generating inhibitory output to the hippocampus and maintaining network synchrony[28]. Their degeneration, prominently driven by cypermethrin in our model, would lead to septal disinhibition, a mechanism strongly implicated in the generation and propagation of seizures[18,29]. The vulnerability of these neurons may stem from their high metabolic rate, making them particularly susceptible to the oxidative stress and mitochondrial dysfunction induced by both PTZ and cypermethrin.

The partial neuroprotection conferred by Vitamin E and VPA, especially in combination, highlights the potential of therapies targeting multiple pathological pathways [20,21]. The antioxidant properties of Vitamin E are well-suited to counter the oxidative stress component of the injury[30]. VPA, beyond its well-known GABAergic and ion channel effects, also possesses anti-inflammatory and neuroprotective properties, potentially through HDAC inhibition and modulation of glial activity[31,32]. The combined therapy's superior efficacy in reducing GFAP expression and improving histological outcomes suggests a synergistic action: Vitamin E may reduce the oxidative trigger for astrogliosis, while VPA may directly temper the pro-inflammatory state of reactive glia.

The unexpected finding that VPA alone did not protect PV+ interneurons and even appeared to worsen their loss warrants further investigation. It is possible that at the dose and duration used, VPA's HDAC-inhibiting effects could have unintended consequences on gene expression in already stressed neurons. However, the clear benefit of the VPA+Vitamin E combination underscores the importance of a multi-target approach, where the antioxidant shield provided by Vitamin E may create a more favorable environment for VPA's neuroprotective mechanisms to operate.

In conclusion, this study demonstrates that cypermethrin exposure significantly exacerbates the neuropathology associated with PTZ-induced seizures in the septal nucleus. The damage is characterized by pronounced astrogliosis, loss of critical inhibitory interneurons, and disrupted tissue architecture. The combined administration of Vitamin E and Valproic Acid emerged as a promising therapeutic strategy, effectively modulating the astroglial response and offering superior neuroprotection compared to either agent alone. These findings underscore the potential of combining antioxidant and anticonvulsant therapies to address the complex pathophysiology of epilepsy, particularly in contexts of environmental neurotoxicant exposure.

CONCLUSION

The resulting damage within the septal nucleus, characterized by reactive astrogliosis and a marked loss of GABAergic interneurons, highlights a mechanism by which environmental toxins can exacerbate seizure disorders, however, monotherapy with Valproic Acid or Vitamin E offered limited protection, their combination synergistically mitigated astrogliosis and promoted histological recovery.

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