Original Article

Anticonvulsant Effects and Histopathological Changes in the Hippocampus of Pentylenetetrazole (PTZ)-induced Epileptic Mice Model following Mentat Treatment

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Abstract

Background: Epilepsy is a neurological illness that disturbs the central nervous system and is characterized by regular convulsions. Over 70 million people worldwide are thought to have epilepsy, with the prevalence rate estimated to be around 1%. **Aims:** The objective of this study was to assess antiepileptic activities and histological changes after Mentat administration in the hippocampus of pentylenetetrazole (PTZ)-induced seizure mice. **Materials and Methods:** Twenty Swiss albino mice (18–28 g) were divided into four groups (n = 5) and were given the following intraperitoneally, 2 ml/kg distilled water and 50 mg/kg PTZ to Groups 1 and 2 animals, respectively. Groups 3 and 4 animals were given 200 mg/kg and 400 mg/kg of Mentat, respectively, 1 h before the administration of PTZ and were observed for 300 s. After the experiment, all surviving animals in the various groups were humanely sacrificed and the brains were harvested and preserved in 10% buffered formalin. The brain tissues were processed using routine histological procedures and stained with hematoxylin and eosin. **Results:** Results of this revealed that Mentat was able to delay the onset time of seizure and offered quantal protection to the animals. Mentat also showed a dose-dependent ameliorative effect against histological changes following PTZ administration in mice. **Conclusion:** Mentat attenuates PTZ-induced seizure in mice.

Keywords: *Herbal supplement, histopathology, Mentat, neurological disorder, seizure*

Introduction

Epilepsy is a neurological condition characterized by persistent seizures. The aberrant electrical activity in the brain that causes seizures can cause a variety of symptoms, including loss of consciousness, convulsions, and sensory problems. Estimates of the prevalence of epilepsy range from 5 to 10 cases per 1000 people worldwide.[1] It is estimated that 50 million people worldwide suffer from epilepsy, making it one of the most prevalent neurological conditions worldwide.[2] Studies on the prevalence of epilepsy in Nigeria have produced numbers between 3.1 and 37/1000, resulting in one of the greatest differences in the prevalence of epilepsy globally.[3]

The temporal lobe is one of the areas of the brain that is frequently impacted by epilepsy. This is due to the temporal lobe's role in memory and sensory input processing, as well as the fact that it frequently serves as the origin of seizures in persons with epilepsy.[4] A key structure of the temporal lobe, the hippocampus, is frequently linked to the pathophysiology of temporal lobe epilepsy (TLE).[5] The hippocampus is essential for the creation and consolidation of memories as well as spatial navigation.[6] The hippocampus frequently experiences pathological alterations in TLE, such as cell loss and gliosis, which can lead to hippocampal sclerosis (HS).[7] Up to 80% of TLE patients have HS, making it a frequent neuropathological finding in those with the condition.[8] The hippocampus has been identified in human research as a crucial focus for the beginning and progression of seizures in TLE.[7]

Pentylenetetrazole (PTZ)-induced convulsions in rodents are a widely used

How to cite this article: Ekpo UU, Igiri AO. Anticonvulsant effects and histopathological changes in the hippocampus of pentylenetetrazole (PTZ)-induced epileptic mice model following Mentat treatment. J Neurobehav Sci 2024;11:19-24.

Ethics committee approval: The Faculty of Basic Medical Sciences Committee on Animal Use and Care, University of Calabar, approved the use of experimental animals for this research project by the institution's established policies and procedures.

Received : 07-01-2024
Accepted : 01-03-2024
Published : 25-03-2024

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Access this article online

Website: https://journals.lww.com/jons

DOI: 10.4103/jnbs.jnbs_2_24

Quick Response Code:

experimental paradigm for researching epilepsy.[9] Because PTZ-induced seizures can resemble some features of human epileptic seizures, including the activation of neural networks and the production of epileptiform activity, they are frequently utilized in epilepsy research.[10] PTZ is commonly administered intraperitoneally or subcutaneously in animal models, with the dosage and route of administration depending on the species and strain of the animal used.[11] PTZ-induced seizures are used by researchers to investigate the onset, progression, and termination of seizures as well as the impact of possible antiepileptic medicines.[11]

Mentat is an herbal remedy made from a variety of plant extracts that are frequently used in conventional Ayurvedic medicine to treat neurological conditions, including epilepsy. According to reports, the medication contains antiepileptic and neuroprotective properties that have been attributed to its phytochemical ingredients.[12,13] Mentat has been shown in numerous studies to enhance cognitive performance and lessen the intensity and frequency of seizures brought on by PTZ.[14,15] Thus, this study aims at assessing the antiepileptic activities and histological changes in PTZ-induced epileptic mice.

Materials and Methods

Ethical committee approval

The Faculty of Basic Medical Sciences Committee on Animal Use and Care, University of Calabar, approved the use of experimental animals for this research project by the institution's established policies and procedures.

Breeding of animals

In the Animal House of the Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Nigeria, 20 adult Swiss albino mice of either sex, weighing between 18 and 28 g, were raised. The mice were housed in well-ventilated plastic cages with iron nettings. They were fed with typical animal feed and given access to free water while being housed in a sanitary environment and at regular room temperature.

Drugs and chemicals

Mentat and PTZ were purchased from the Pharmacology Department of the University of Calabar in Calabar and were of analytical quality. For the experiment, ketamine (50 mg/mL ketamine hydrochloride injection USP) was utilized as the anesthetic. It was procured from Swiss Parenterals Pvt. Ltd., Gujarat, India.

Drug preparation

Nine hundred and fifty-one milligrams of Mentat was dissolved in 10 mL of injection water. This served as the stock solution from which working solutions were taken. Twenty grams of PTZ was also dissolved in 10 mL of injection water and was given to the animals at a dose of 50 mg/kg body weight by taking quantities from the stock that were equal to the dose for each mouse.

Experimental design and treatment of animals

Twenty animals were randomly assigned into four groups (n = 5): Groups 1, 2, 3, and 4. The mice in group 1 served as the general control group (n = 5) and were given 2 mL/kg of distilled water. The mice in group 2 served as the epileptic control group (n = 5). Animals in this group, each received a dose of 50 mg/kg body weight of PTZ dissolved in injection water. The mice in the experimental groups (3 and 4) were given Mentat at varying doses. Group 3 received 200 mg/kg body weight of Mentat, and Group 4 animals, each received 400 mg/kg body weight of Mentat. Both Mentat and PTZ were given to the animals intraperitoneally. Mentat was given to the animals 1 h before the administration of PTZ and the animals were observed for 300 s (5 min).

Animal sacrifice and histology

At the end of the experiment, the mice that survived were anesthetized with chloroform and humanely sacrificed. The brains of the animals were removed and quickly fixed in fixative (10% buffered formalin) for 48 h to prevent putrefaction and autolysis and stained with hematoxylin and eosin.

Data analysis

All results were calculated using a one-way analysis of variance to test statistical differences between the test groups and the epileptic control group. Data were expressed as mean ± standard error of the mean. The final results arrived at were considered significant at $P \leq 0.05$.

Results

Antiepileptic activity

The results of the antiepileptic effects of Mentat and PTZ are presented in Table 1.

Histological observations

Histological studies were conducted on the section of the hippocampus CA1 in Group 1, which was administered with 2 mL/kg of distilled water. The results of the study showed that the nerve fibers appeared normal, and there were scattered small neurons observed in the molecular cell layer. In the pyramidal cell layer, large pyramidal-shaped neurons with a coarse chromatin pattern and prominent nuclei were present. Additionally, in the polymorphic cell layer, there were scattered neuronal cell bodies observed, some of which had fusiform shapes, while others had triangular or ovoid cell bodies, but their numbers were relatively low [Figure 1].

Section of the hippocampus CA1 of the group that received 50 mg/kg body weight of PTZ revealed intact molecular, pyramidal, and polymorphic cell layers of the hippocampus with sparsely populated pyramidal shape neurons in the

Table 1: Antiepileptic activities of Mentat on pentylenetetrazole-induced mice

Groups (*n*=5)	Treatments	Dose (mg/kg)	Mean onset of convulsion (s)	Quantal protection	Protection (%)	Mortality (%)
1	Distilled water	2	0.00±0.00	5/5	100	0
2	PTZ	50	120±24.49*	0/5	0	100
3	Mentat I + PTZ	200+50	180±37.95*	4/5	80	20
4	Mentat II + PTZ	400+50	120.00±26.83*	3/5	60	40

*P<0.05 when the PTZ-induced group was compared to the control group. n=5; mean±SEM, one-way ANOVA, Tukey *post hoc* test.
SEM: Standard error of the mean, PTZ: Pentylenetetrazole, ANOVA: Analysis of variance

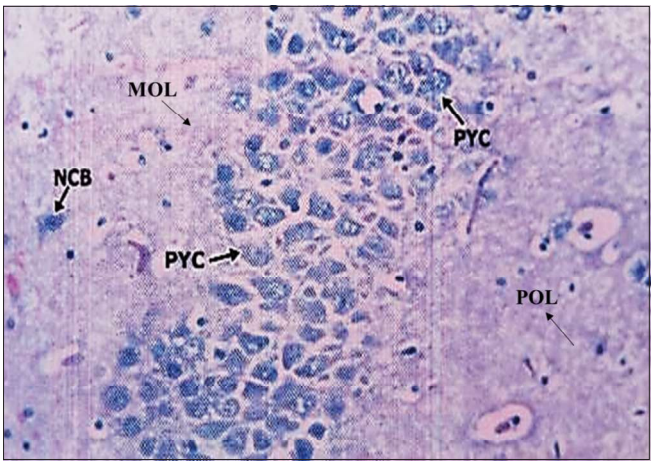

Figure 1: Photomicrograph of the hippocampus (CA1) of group 1 (normal control) showing the normal histological architecture of the CA1 and neuronal cells. Molecular layer (MOL); Pyramidal layer (PYL); Pyramidal cell (PYC); Polymorphic layer (POL); Neuronal cell body (NCB). H & E (Mag. X 400)

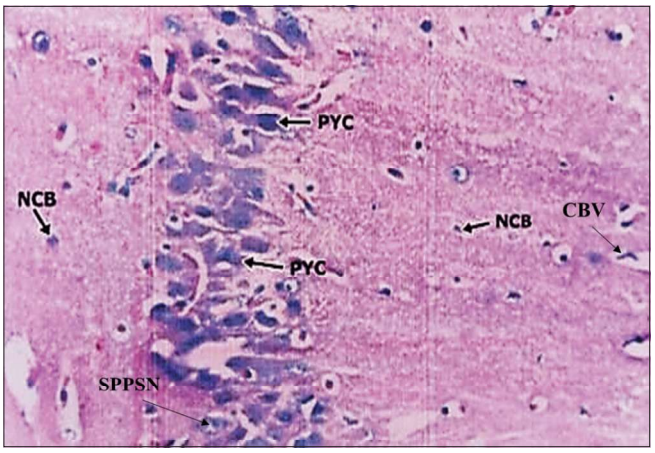

Figure 2: Photomicrograph of the hippocampus (CA1) of group 2 (epileptic control) administered with 50 mg/kg PTZ showing intact molecular, pyramidal, and polymorphic cell layers of the hippocampus with sparsely populated pyramidal shape neurons (SPPSN) in the pyramidal cell layer and congested blood vessels (CBV) in the polymorphic cell layer. Pyramidal cell (PYC); Neuronal cell body (NCB). H & E (Mag. X 400)

pyramidal cell layer and congested blood vessels in the polymorphic cell layer [Figure 2].

The hippocampal CA1 section of Group 3 treated with 200 mg/kg body weight of Mentat and 50 mg/kg body weight of PTZ revealed the three cortical layers of the hippocampus with densely packed pyramidal cells with poor nuclei outline and some cells displaying chromatolysis in the pyramidal cell layer and congested blood vessels in the polymorphic cell layer [Figure 3].

Section of the hippocampus CA1 of group 4 treated with 400 mg/kg body weight of Mentat and 50 mg/kg body weight of PTZ revealed the three cortical layers of the hippocampus with densely packed medium to large pyramidal-shaped neurons with deeply stained nuclei having a clumped chromatin pattern and inconspicuous nucleoli in the pyramidal cell layer [Figure 4].

Discussion

Epilepsy continues to be a serious public health concern, impacting people of all ages, genders, and races, despite advancements in medical research and treatment choices. It can have a significant effect on a person's life, including social stigma, diminished cognitive and physical functioning, and an elevated risk of harm or death.[16]

It is generally known that the hippocampus is susceptible to seizures. The hippocampus is a crucial brain area for memory formation, spatial navigation, and learning.[17] In addition, it is one of the most typical places for seizure onset in patients with TLE, the most prevalent type of epilepsy in adults.[17]

PTZ has been used experimentally to research seizure events and find drugs that could reduce seizure susceptibility.[18] One of these medications is called Mentat, which is an herbal combination of many Ayurvedic herbs.[19] It is well-known that Mentat improves memory and learning. In addition, it is utilized to treat neurological conditions such as epilepsy and seizures.

In this study, Mentat offered a dose-dependent protection against the convulsion effect. The low dose of Mentat showed more antiepileptic effects than the high dose group. The seizure was delayed more in the low-dose treated group than in the high-dose treatment group. The low-dose treatment group also showed less mortality rate compared to the high-dose group. The fact that seizures took longer to start after Mentat treatment in this research is proof of the drug's effectiveness. This indicates that the medication is successful in lessening the frequency and intensity of seizures, which may result in a longer period of seizure-free time.[20] It is complicated and not entirely known how antiepileptic medications delay the onset of seizures. However, it is thought that these medications work by controlling the activation of ion channels and neurotransmitters in the brain.[20]

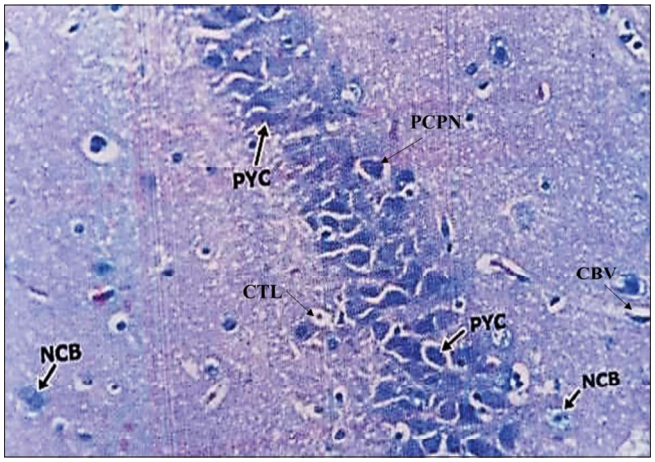

Figure 3: Group 3 (200 mg/kg Mentat + 50 mg/kg PTZ) showing densely packed pyramidal cells with poor nuclei outline (PCPN) and some cells displaying chromatolysis (CTL) in the pyramidal cell layer and congested blood vessels (CBV) in the polymorphic cell layer. Pyramidal cell (PYC); Neuronal cell body (NCB). H & E (Mag. X 400)

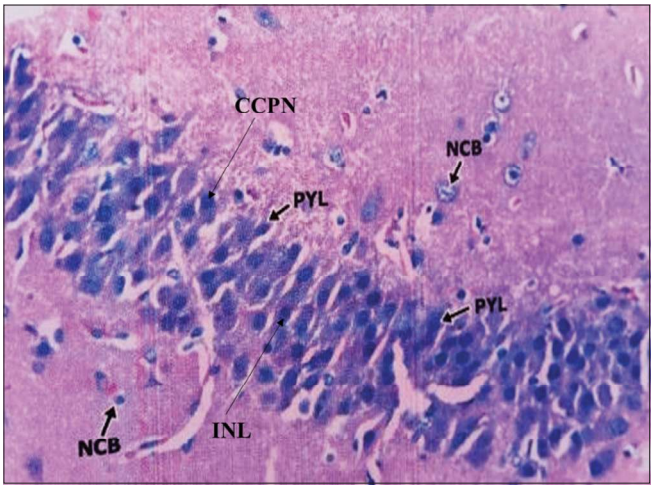

Figure 4: Group 4 (400 mg/kg Mentat + 50 mg/kg PTZ) of the hippocampus CA1 showing neurons with deeply stained nuclei having a clumped chromatin pattern (CCPN) and inconspicuous nucleoli (INL)in the pyramidal cell layer. Pyramidal layer (PYL); Neuronal cell body (NCB). H & E (Mag. X 400)

There is limited scientific research on the mechanism by which Mentat exerts its antiepileptic effects. However, some research points to its active ingredients as having the potential to control the brain's neurotransmitter levels, thereby decreasing the likelihood of seizure initiation. According to a study that appeared in the *Journal of Ethnopharmacology*, the main component of Mentat, *Bacopa monnieri*, can raise the brain's levels of gamma-aminobutyric acid (GABA). It has been suggested that the inhibitory neurotransmitter GABA has a role in the pathophysiology of epilepsy and helps regulate neuronal activity. *B. monnieri* may lessen neuronal excitability and delay the onset of seizures by raising GABA levels.[21] Another study examined the impact of *Convolvulus pluricaulis*, another component of Mentat, on seizure activity in animal models of epilepsy. According to the research, *Convolvulus pluricaulis* extract has anticonvulsant properties and could delay the beginning of seizures indicating that the extract may work by modifying the amounts of neurotransmitters in the brain, such as GABA and glutamate.[13] Overall, Mentat's antiepileptic actions are probably a result of the combination of its active components, which may work in concert to modify neurotransmitter levels and lessen neuronal excitability.

Analogous to this study is the study by Kulkarni and George,[22] on the effect of Ashwagandha or BR - 16 (Mentat) on reserpine (RES)-induced catalepsy. They noticed a higher catalepsy score (40.9 3.0) in the low dose of Mentat (50 mg/kg body weight) compared to the high dose (28.48 3.9 mg/kg body weight) of the same medication. Furthermore, Choudhary *et al*.[23] found that the antiepileptic potential of Mentat in Wistar rats was greater at lower doses than at higher levels. Subsequent investigations have revealed that higher doses of Mentat exhibit significantly greater antiepileptic activity compared to lower doses.[24-26]

Histological study revealed normal histology and neuronal cells in the hippocampus of the control group with distinct layers of molecular, pyramidal, and polymorphic layers, while group 2 administered with only PTZ showed histopathological conditions such as congested blood vessels and sparsely populated neurons. Groups 3 and 4 were treated with Mentat and showed a dose-dependent improvement in the cytoarchitecture of the hippocampus. PTZ can, according to studies, lead to neuronal apoptosis and necrosis in the hippocampus, especially in the dentate gyrus (DG) area.[27,28] There are several causes for this cell death, such as oxidative stress, excitotoxicity, and inflammation.[29,30] Altering synaptic structure and function is another histological effect of PTZ on the hippocampus. PTZ has been demonstrated to have an impact on dendritic spine density and architecture in the hippocampus, particularly in the CA1 and CA3 areas.[31,32] These alterations could play a role in the emergence and maintenance of epileptic activity in the hippocampal region. In addition, PTZ can affect the hippocampus' neurogenesis. PTZ can lessen the amount of newly formed neurons in the DG region, according to studies, which may be a factor in the cognitive impairments connected to epilepsy.[33,34]

Mentat may help treat a variety of neurological conditions, including epilepsy, as it has been demonstrated to have a neuroprotective impact on the brain. Numerous researchers have looked into how Mentat affects the hippocampus, a part of the brain that is important for memory and learning and frequently impaired in epilepsy. In a study conducted by Mohan *et al*.,[35] examining the effect of Mentat on seizure-induced hippocampal mutilation in rats found that treatment with Mentat remarkably reduced the amount of hippocampal damage caused by seizures. Another study conducted by Al-Otaibi *et al*.[36] investigating the effect of Mentat on oxidative stress and inflammation in the hippocampus of rats with seizures revealed that treatment

with Mentat remarkably reduced oxidative stress and inflammation in the hippocampus, indicating that Mentat may have a protective effect on this brain region. Goyal *et al*.,[37] in their study on the effect of Mentat on cognitive function and hippocampal neurogenesis in rats with seizures, revealed that treatment with Mentat significantly boosted hippocampus neurogenesis and improved cognitive performance in the rats, indicating that Mentat may benefit brain plasticity.

Conclusion

The results of this study imply that Mentat has a protective effect against seizure-induced mice and may be employed in the control and treatment of seizures and other neurological diseases.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The Faculty of Basic Medical Sciences Committee on Animal Use and Care, University of Calabar, approved the use of experimental animals for this research project by the institution's established policies and procedures.

Financial support and sponsorship

No funding was received.

Conflict of interest

There is no conflict of interest to declare.

Author Contributions subject and rate

- Ekpo Ubong Udeme (60%): Design the research, data collection, and analyses
- Igiri Anozeng Oyono (40%): Supervision and research organization.

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