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# Effects of Environmental Enrichment on Hippocampal Electrophysiological Changes in the Pentylenetetrazole Model of Epilepsy

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## Pentilentetrazol İle Oluşturulmuş Epilepside Zenginleştirilmiş Çevrenin Hipokampal Elektrofizyolojik Değişikliklere Etkisi

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## Summary

**Objectives:** Epilepsy is a neurological disorder characterized by functional/morphological changes in the hippocampus. These functional changes arise as increase or decrease in synaptic plasticity in experimental animals. The present study was an investigation of the effect of enriched environment on hippocampal functional changes in epileptic rats.

**Methods:** The pentylenetetrazole (PTZ) kindling model was used on young male Wistar rats. Rats in the epileptic and control groups were reared for 1 month in standard cage or enriched cage (EC). Subsequently, all animals were given Morris water maze (MWM) test and in vivo recording of long-term potentiation (LTP) in medial perforant pathway-dentate gyrus synapses in hippocampus was made.

**Results:** Statistically significant earlier kindling epileptogenesis in rats housed in EC was observed. Epileptic rats had poor performance in MWM, but enriched environment improved their performance. However, according to electrophysiological recordings, environmental enrichment did not provide positive effect on LTP in epileptic rats.

**Conclusion:** Enriched environment with ongoing PTZ-induced kindling procedure may lead to exaggeration of seizures due to stress as result of corruption of safe, familiar environment.

Keywords: Environmental enrichment; epilepsy; hippocampal plasticity, long-term potentiation (LTP).

## Özet

**Amaç:** Epilepsi, hipokampusta işlevsel/morfolojik değişikliklerle karakterize nörolojik bir hastalıktır. Deney hayvanlarında bu işlevsel değişiklikler sinaptik plastisitede artma ya da azalma şeklinde ortaya çıkmaktadır. Sunulan çalışmada amacımız, zenginleştirilmiş çevrenin hipokampal işlevsel değişiklikler üzerine olan etkisini epileptik sıçanlarda araştırmaktı.

**Gereç ve Yöntem:** Pentilentetrazol (PTZ) ile oluşturulan kindling modeli sıçanlara uygulandı. Sıçanlar epileptik ve kontrol grubu olarak standart kafes ya da zenginleştirilmiş kafeste bir ay kaldılar. Ardından bütün hayvanlara Morris yüzme testi yapıldı ve hipokampusa ait medial perforan yol dentat girus sinapslarından in vivo olarak uzun süreli güçlenme (USG) kaydı alındı.

**Bulgular:** Çalışmamızda zenginleştirimiş kafeste bulunan epileptik sıçanların daha erken tutuştuğu görüldü. Epileptik sıçanlar morris yüzme testinde zayıf performans gösterdiler ve zenginleştirilmiş çevre bu durumu iyileştirdi. Bununla birlikte elektrofizyolojik kayıt bulgularımızda, zenginleştirilmiş çevre epileptik sıçanlarda USG üzerinde pozitif etki göstermedi.

**Sonuç:** Sonuç olarak, PTZ-nedenli kindling modeli ile birlikte zenginleştirilmiş çevre uygulaması, sıçanlarda alışkın olunan güvenli çevrenin bozulması nedeniyle ortaya çıkan strese bağlı olarak nöbetleri şiddetlendirebilir.

Anahtar sözcükler: Zenginleştirilmiş çevre; epilepsi; hipokampal plastisite; uzun süreli güçlenme (USG).

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## Introduction

Kindling, originally described by Goddard and considered to be an elementary model of learning, is also generally accepted as a model of epilepsy development.[1] This model can be elicited either by electrical stimulation or by chemical convulsants such as pentylenetetrazole (PTZ). Repeated application of subconvulsive stimuli induces progressive seizure activity, which culminates in tonic-clonic convulsions.[2] Clinical investigations and experimental findings show that repeated epileptic attacks can induce learning and memory impairment. Previous studies have shown that establishment of kindling by repeated administration of PTZ led to impaired learning behavior and deterioration of long-term potentiation (LTP) in the hippocampus.[3–6]

Central nervous system synapses have an intrinsic plastic capacity to adapt to new conditions with rapid changes to their structure. Such activity-dependent refinement occurs during development and learning, and shares features with some diseases such as epilepsy.[7] Environmental enrichment is a well-established paradigm for studying the naturally occurring changes in synaptic efficacy in the hippocampus that underlie experience-induced modulation of learning and memory in rodents.[8] A vast number of studies have focused on the positive effects of environmental enrichment in brain regions involved in learning and memory such as the hippocampus and neocortex.[9–11] LTP induced by high frequency stimulation (HFS) of the afferents has been recognized as one of the components of the cellular basis of learning and memory.[12] Previous experiments have shown that synaptic contacts on the granule cells are similar to those described for LTP. Such changes could be associated with enhancement of synaptic efficiency and may be important in epileptogenesis.[7] Animals from enhanced environment display enhanced hippocampal LTP (Region CA1).[13,14] Another study on environmental enrichment showed enhancement in both LTP and long-term depression.[15]

The aim of the present study was to investigate the further effects of environmental enrichment during the kindling epileptogenesis of a rat model. For this purpose, the PTZ kindling model of epilepsy was applied, followed by behavioral test and LTP response recordings of rats housed in standard or environmental enrichment cages between postnatal day (PND) 30 and PND65.

## Materials and Methods

### Animals and housing conditions

The experiments were carried out on 37 male Wistar rats aged 30 days and weighing between 100–150 gr. All rats were fed with tap water and Purina rodent chow. The experimental protocol was approved by the Erciyes University committee on ethics in animal experimentation. Beginning at weaning on PND30, rats were separated into 4 groups: control group in standard cages (CN; n=9), control group in enriched cages (CE; n=9), epileptic group in standard cages (EN; n=9), and epileptic group in enriched cages (EE; n=9).

The environmentally enriched conditions consisted of housing 8 to 10 animals per 50x40x80 cm cage equipped with horizontal and vertical boards, chains, swings, wooden blocks, balls, rings, and other objects of different sizes and materials for 7 weeks. The distance between boards and objects was changed twice per week.[16] After the injection procedure, all rats were exposed to Morris water maze (MWM) test to record electrophysiological data.

### Chemical kindling

In epileptic groups, rats were given 1 mL of PTZ while control group rats were given 1 mL of saline intraperitoneally (i.p.) on alternate days for total of 15 to 19 injections within 5 to 7 weeks starting at PND30 and continuing to PND65. PTZ was dissolved in 0.9% sodium chloride (NaCl ) solution and injected i.p. once every 48 hours at an initially subconvulsant dose of 35 mg/kg.

After each injection, rats were placed singly in Plexiglas cages (30x30x50 cm) and observed for 20 min. Their behavior (seizure intensity) was classified according to the Racine scale: stage 0, immobility; stage 1, ear and facial twitching; stage 2, convulsive waves through the body (spasms); stage 3, myoclonic jerks (with or without rearing) in the upper extremities; stage 4, clonic convulsions in all extremities, turn over onto side and stage 5, clonic-tonic convulsions in all extremities, turn over onto back.[17,18] Animals showing more than 3 consecutive stage 4 or 5 seizures (tonic-clonic seizures) were considered to be fully kindled.[19] Epileptic rats in standard and enriched cages were compared according to number of injections required to reach kindling status. Total number of seizures and latency of seizures in epileptic rats were also evaluated.

**Morris water maze test**

All of the rats were evaluated using MWM test 72 hours after last injection of PTZ.[20] Prior to MWM test, rats were transferred to the testing room to acclimate.

Performance on MWM was used for measurement of spatial memory. Evaluation was done according to Morris method with several modifications.[20] After the acquisition phase of MWM test, conducted over 4 days, animals were evaluated with probe trial on fifth day. Latency to find the platform (escape latency), the time spent in the half that contained the platform, and the number of quadrants traversed were measured for each individual animal. The escape latency of rats that could not reach the platform within 60 seconds was accepted as 60 seconds.[21] The experimenter was always in the same position. All the trials were completed between 10:00 am and 12:00 pm.

**Electrophysiology: stimulation, recording, experimental procedures, and data analysis**

Rats were anesthetized with urethane (1.5 g/kg i.p.) and placed in stereotaxic frame (David Kopf Instruments, Tujunga, Calif., USA). A bipolar tungsten electrode (stainless steel, Teflon-coated, 127 µm in diameter, insulated except at tips) was used to stimulate medial perforant pathway (anterior-posterior [AP]: -8.0 from the bregma; mediolateral [ML]: 4.4; dorsoventral [DV]: 2.0–2.5 below the dura) of left hemisphere.[22] A glass micropipette was inserted into the granular cell layer of ipsilateral dentat gyrus (DG) (AP: 3.5; ML: 2.15; DV: 2.5-3.0 below the dura). The barrel was filled with 3 M NaCl to record field excitatory postsynaptic potentials (fEPSP). A silver/silver chloride reference disc electrode was positioned under the neck skin. The entire system was shielded using a Faraday cage. The depth of recording was adjusted to obtain large positive fEPSPs, and superimposed negative-going population spikes (PS) were recorded with 0.1 mm step. After typical response was obtained, final depth of stimulating electrode was adjusted to maximize PS amplitude in response to perforant pathway stimulation. Scope program (ADInstruments, Dunedin, NZ) was used to control both stimulation and recording. Waveforms were digitized online at a rate of 4x10 sec displayed on a computer monitor, and stored using Scope for offline analysis.

Each experiment began with recording an input-output (I/O) curve consisting of resultant effects of 15 stimuli ranging from 0 to 525 µA, applied every 10 seconds. Stimulus intensity producing 50% of maximum response (i.e., test pulse amplitude) was used in subsequent recordings. After stimulation intensity for test pulse was determined, experiment was initiated; test stimuli were applied every 30 seconds. To evaluate effect of LTP induction, initial 10-minute interval was designated as baseline period. At the 15th, 20$^{th}$, 25$^{th}$, and 30$^{th}$ minute, HFS (100 sec–1, 1 sec) protocol was applied. Following delivery of tetanic stimuli, test stimuli application was continued every 30 seconds up to 210$^{th}$ minute.

LTP data analysis was described in our previous report.[22] Briefly, mean values of EPSP or PS during the first 20-minute period were taken as 100%; mean value of responses at 40 time points was defined as the baseline. Subsequent data were expressed as percentage of changes from the baseline. Five time windows were specified: 1) baseline, 0–10 minutes; 2) first post-tetanic induction phase of LTP, 15 minutes; 3) fourth post-tetanic induction phase of LTP, 30 minutes; 4) maintenance phase of early LTP (E-LTP ), 90 minutes, and 5), late phase (L-LTP), 210 minutes relative to the beginning of experiment. Time periods for E-LTP and L-LTP were determined accordingly as well.[23]

**Statistical analysis**

The number of injections required to reach kindling state, the number of seizures, seizure latency, and seizure duration were compared between epileptic groups with Mann-Whitney U test. MWM test parameters were analyzed with one-way analysis of variance followed by post-hoc Scheffe test for all groups.

Both slope and amplitude values were averaged over 10-minute periods. Slope and amplitude data for each period were compared among groups using Kruskal-Wallis H test followed by the Mann-Whitney U test, since data did not fit a normal distribution. All values were taken as means±SEM. Probabilities of zero hypothesis below 0.05 were considered to be significant.

## Results

**Evaluation of epileptic activity**

In this study, kindling status was reached earlier in the EE group than the EN group ($p<0.05$). There was no significant difference between EE and EN groups in total number of stage 4 and 5 seizures. When we compared latency of seizure, a statistically significant difference was found in intra-group results ($p<0.05$), but no differences were seen between groups.

**Results of Morris water maze test**

The MWM test indicated escape latency decreased in all experimental groups during acquisition trials, but there were no significant differences between groups. The time spent in the target quadrant in acquisition trials of EN group was less than that of EE group at first, third, fourth ($p<0.001$), and second ($p=0.001$) days. The time spent in the target quadrant in acquisition trials by EN group was less than CN group on first, third, and fourth day ($p<0.001$) (Figure 1a). During acquisition trials, the number of traversed quadrants in EN group was considerably lower than in EE group on first day ($p<0.01$), second day ($p=0.05$), third, and fourth days ($p<0.05$) (Figure 1b).

In the probe trial, when we compared time spent in target quadrant, there was no significant difference between CN and CE groups. In comparison of epilepsy groups, EN group results were significantly lower than EE group ($p<0.01$). According to number of quadrants traversed, CN group showed poorer performance than CE group ($p<0.01$) (Figure 1c). Number of traversed quadrants was not significantly different in EN and EE groups (Figure 1d). Results revealed more exploratory activity in control group enriched cage rats and spatial memory deterioration in epilepsy groups. Spatial memory deterioration was improved by environmental enrichment.

**Results of electrophysiological recording**

**I/O functions**

Changes in the EPSP slope and PS amplitude were recorded from DG for 8 different stimuli ranging from 0.1 mA to 1.5 mA before induction of LTP. EPSP slopes were significantly

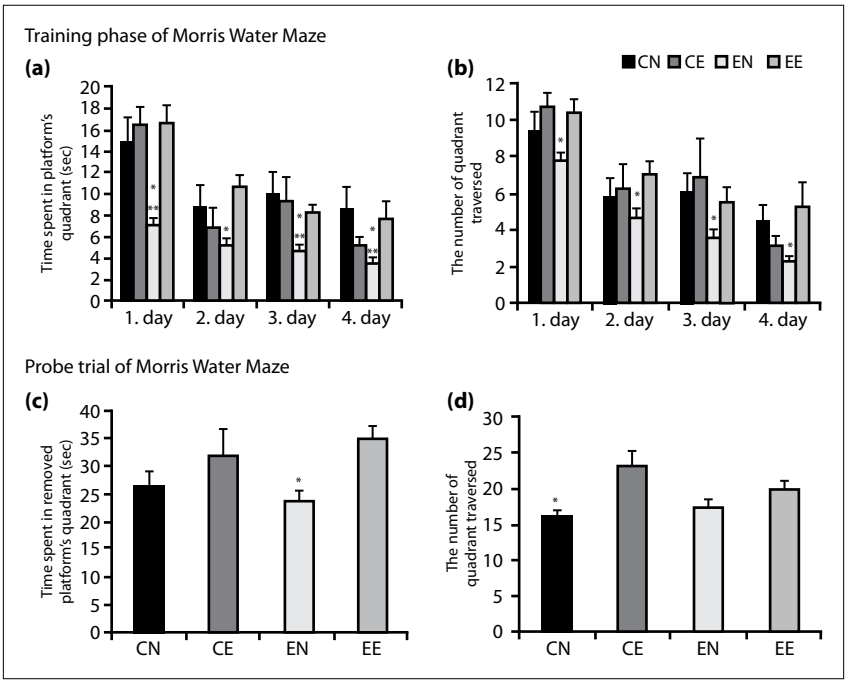


**Fig. 1.** Morris water maze parameters measured during trial and probe phases (columns represent mean±SEM). Acquisition trials: **(a)** Time spent in target quadrant *EN group time was less than EE group on first day ($F=14.93$; $p<0.001$), second day ($F=6.52$; $p=0.001$), third day ($F=8.66$; $p<0.001$), and fourth day ($F=4.73$; $p<0.001$). **EN group statistically significant lower than CN group for first, third, and fourth days ($p<0.001$); **(b)** *EN group traversed number of quadrants statistically significant lower than EE group for first ($F=4.48$; $p< 0.01$), second ($F=2.79$; $p=0.05$), third ($F=3.49$; $p<0.05$), and fourth day ($F=2.98$; $p<0.05$). Probe phase: **(c)** Time spent in half without platform. *EN group result was statistically significantly lower compared to EE group ($F=6.12$; $p<0.01$); **(d)** Number of quadrants traversed *CN group lower compared with CE ($F=5.83$; $p<0.01$). CE: Control group in enriched cage; CN: Control group in standard cage; EE: Epileptic group in enriched cage; EN: Epileptic group in standard cage.

higher in EN group than CN group in response to 8 different stimulus intensities: 0.3 mA ($p<0.05$), and 0.5 mA, 0.7 mA, 0.9 mA, 1.1 mA, 1.3 mA, 1.5 mA ($p<0.001$). Furthermore, response to 0.9 mA stimulus intensity was significantly higher in EN group than EE group ($p<0.001$) (Figure 2a). PS amplitudes were not different between groups for any of the 8 stimulus intensities (Figure 2b).

**Findings of HFS and LTP**

Measurements taken at 5 specified points in time were used for statistical evaluation: baseline recording, after first HFS, fourth HFS, E-LTP and L-LTP. Average of percentages of EPSP slope and PS amplitude changes were used. Results were more powerful in the EN group, but results were not statistically different for the 5 time windows (Figure 3, Table 1).

## Discussion

The purpose of this study was to evaluate the effect of environmental enrichment during the acquisition of kindling and to determine whether it improves cognitive function in early life and whether it causes functional changes at perforant pathway of hippocampus in epileptic rats. Healing effects of environmental enrichment were investigated in order to investigate alternative treatment for epilepsy using environmental enrichment.

Data revealed that kindling occurs earlier in epileptic rats housed in EC than rats in standard cages. It has been demonstrated that exposure to prenatal stress causes exacerbation of kainic acid-induced seizures.[24] Early kindling in the epileptic group in enriched cages may be result of exposure to repeated experimental stress.

Indeed, exposure to repeated experimental stress accelerates development of limbic epileptogenesis, and seizure duration was significantly longer in stressed rats.[25] Young et al. showed that kindled-enriched rats acquired kindled state more quickly than kindled-isolated rats.[26] Auvergne et al. reported that kindling epileptogenesis occurred later in animals kept in enriched conditions both before and during kindling procedure than animals housed in EC only during kindling procedure and isolated conditions.[27] These results indicate that exposure to environmental enrichment before and during kindling procedure will be useful to protect them from seizure. Another study demonstrated that environmental enrichment from PND25 to PND40 has no effect on seizure threshold in status epilepticus.[28] On the other hand, environmental conditions protect against kainate-induced seizures and excitotoxic injury.[29] According to Korbey et al., their study using an enrichment housing model from PND21 to PND49 re-

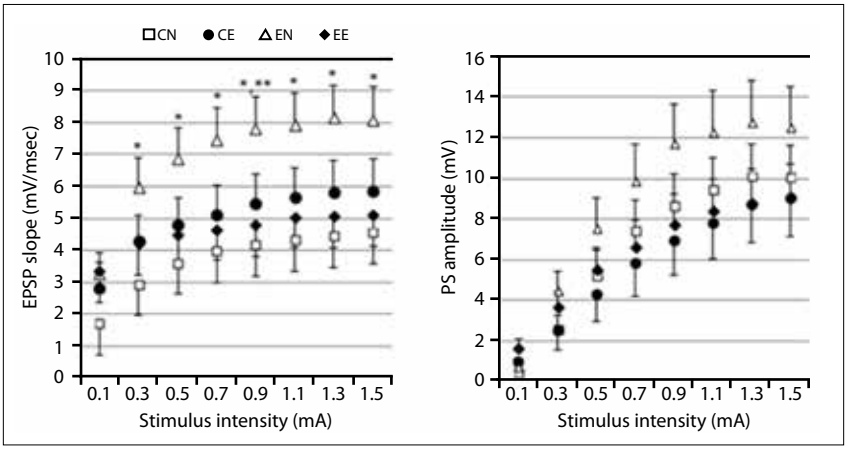


**Fig. 2.** **(a)** Input-output curves of EPSP slope and **(b)** PS amplitude for 8 stimulus intensities ranging from 0.1 mA to 1.5 mA recorded from dentate gyrus before induction of LTP. *EN statistically higher than CN (0.3 mA: $F=3.29$, $p<0.05$; 0.5 mA: $F=3.73$, $p=0.01$; 0.7 mA: $F=4.18$, $p=0.01$; 0.9 mA: $F=4.63$, $p<0.001$; 1.1 mA: $F=4.31$, $p=0.01$; 1.3mA: $F=4.36$, $p=0.01$; 1.5 mA: $F=3.94$, $p=0.01$). **EN statistically higher than EE (0.9 mA: $F=4.63$, $p<0.001$). PS amplitudes were not different between groups for any of the 8 stimulus intensities. Values are given as mean ± SEM. CE: Control group in enriched cage; CN: Control group in standard cage; EE: Epileptic group in enriched cage; EN: Epileptic group in standard cage; EPSP: Excitatory postsynaptic potentials; LTP: Long-term potentiation; PS: Population spikes.

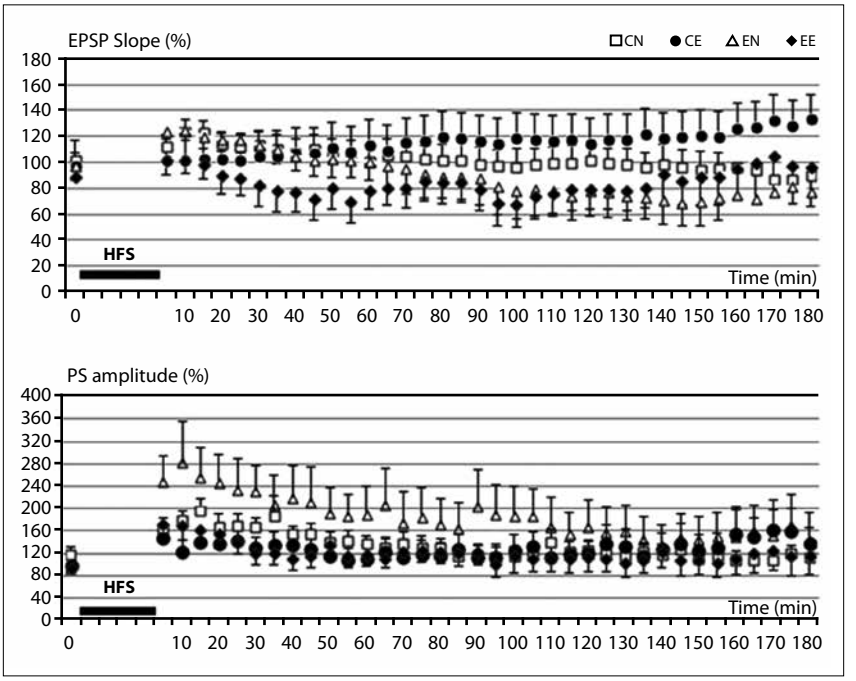


**Fig. 3.** The average of the change in EPSP slope and PS amplitude at dentate gyrus after high frequency stimulation (HFS) of medial perforant pathway. Values are percentage of the baseline. HFS bar shows HFS period. Data points are shown as SEM of groups.

vealed 100% decrease in seizure susceptibility in EI mice with multifactoral temporal lobe epilepsy as well as 100% decrement in stress-related responses in seizure-associated regions of the epileptic brain.[30] This study was conducted at PND80 and PND90 to test susceptibility to seizures after exposure to environmental enrichment and animals were not exposed to other applications such as the injection during period of environmental enrichment. As a genetic model, EI mice may demonstrate different response to environmental enrichment. Results indicated that environmental enrichment has no beneficial effect when administered during the kindling procedure. These results may be due to the fact that susceptibility to seizures was tested with different methods and because tests were performed some time after exposure to environmental enrichment.

**Table 1.** Mean values of slope of field excitatory postsynaptic potentials and population spike amplitude of all experimental groups recorded in five time windows. Values are given as mean±SEM

| | Baseline recording | After 1st HFS | After 4th HFS | Early LTP | Late LTP |
|---|---|---|---|---|---|
| EPSP slope | | | | | |
| CN | 96.0±2.9 | 117.9±8.4 | 120.5±7.1 | 112.2±7.4 | 97.8±13.6 |
| CE | 100.1±1.5 | 114.9±10.4 | 104.6±10.2 | 105.2±6.8 | 97.1±9.8 |
| EN | 99.6±0.4 | 134.2±3.6 | 137.8±2.8 | 112.6±6.6 | 80.3±18.5 |
| EE | 92.8±3.1 | 118.8±12.4 | 122.3±10.7 | 88.0±15.5 | 85.8±20.2 |
| PS amplitude | | | | | |
| CN | 101.6±4.2 | 178.3±21.8 | 178.2±22.5 | 162.8±17.2 | 123.7±15.45 |
| CE | 100.9±1.0 | 143.8±16.3 | 142.7±23.3 | 130.0±21.3 | 128.0±26.85 |
| EN | 103.7±2.5 | 257.6±56.3 | 277.7±48.9 | 227.2±51.5 | 167.0±48.37 |
| EE | 96.4±3.3 | 170.2±23.4 | 178.8±29.3 | 139.5±27.4 | 116.6±30.05 |

CE: Control group in enriched cage; CN: Control group in standard cage; EE: Epileptic group in enriched cage; EN: Epileptic group in standard cage; EPSP: Excitatory postsynaptic potentials; HFS: High-frequency stimulation; LTP: Long-term potentiation; PS: Population spikes.

Present study results indicated that PTZ-induced kindling caused a significant impairment of spatial learning and memory, compatible with previous studies.[31–33] Prenatal exposure to maternal seizure induced by PTZ leads to significant impairment of learning and memory.[34] According to our results, environmental enrichment had a positive effect on spatial memory in epilepsy groups. Behavioral results have revealed that enriched groups, regardless of their age, achieved better performance in the spatial task. [35] Xie et al., found that environmental enrichment reversed spatial learning deficits induced by prenatal maternal PTZ seizure.[36] Another study reported that status epilepticus resulted in cognitive impairment within days of the seizure, but housing in an environmental enrichment cage after status epilepticus had a beneficial effect on cognitive performance in rats.[37] These results were compatible with previous data in MWM tests, but revealed poor performance compared to control group in enriched cages.

According to the results of the present study, enriched environment had no effect in terms of LTP records. Previous studies showed that exposure to environmental enrichment for 3 months had no effect on LTP in aged animals. [38,39] It was found that environmental enrichment must be initiated before the age corresponding to median lifespan and/or environmental enrichment must be continued for a long period (>3 months) to have an effect on cognitive aging.[34] In addition, Eckert et al., did not find any detectable period of environmental enrichment inducing change in synaptic efficacy in DG in vivo, but there was an increase in cellular excitability.[40] Mazzocchi-Jones et al. found that LTP was facilitated by environmental enrichment in embryonic striatal grafts, and thus concluded that environmental enrichment provides a potential physiological substrate for enrichment-induced improvement in motor and cognitive performance.[41]

Previous study results have demonstrated that LTP was suppressed in kindled rats.[6,42] Morelli et al. analyzed effects of environmental enrichment in a seizure-prone mouse. Their model showed 1-month environmental enrichment starting at P21 reduced seizure severity, preserved LTP, and restored paired-pulse synaptic responses in the hippocampal CA1 neuronal population.[43] Our results showed nonsignificant differences in strength of EPSP in the kindling group and neither LTP suppression nor increment in kindled rats was demonstrated.

Environmental enrichment had no effect on LTP in the present study, though learning process improved on MWM. Studies related to patients with hippocampal lesions have led to a new understanding of the existence of multiple memory systems in the human brain. Many types of memories, including motor learning and many types of associative conditioning, were found to be hippocampus-independent. A specific type of associative learning was described in great detail at the circuit, synaptic, and molecular levels in the cerebellum. The amygdala has also been implicated specifically in human fear responsivity and in learned fear, and the amygdala has been implicated in contributing to human emotional behavior in general.[44] We recorded LTP responses from DG of hippocampus, but MWM results are not just related to hippocampus; they are also related to amygdala, cerebellum, and even brainstem. In this context, MWM results may not always be in line with LTP results.

In conclusion, present study results revealed PTZ-induced kindling caused significant impairment of spatial learning in MWM and that this impairment was reversed by environmental enrichment. Previous studies have suggested that aberrant seizure-induced neurogenesis might contribute to increment of learning impairment in chronic epilepsy.[45] In the current study, we did not find any effect of enrichment environment on LTP in epileptic rats. It may be result of difference in duration of exposure to enrichment environment and kindling model. Furthermore, results of spatial learning tested with MWM may not necessarily be parallel to LTP results. Additionally, enriched environment with ongoing PTZ-induced kindling procedure may lead to exaggeration of seizures due to stress as result of corruption of safe environment that was familiar to the rats.

**Conflict of Interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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