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Research paper

Comparing the synaptic potentiation in schaffer collateral-CA1 synapses in dorsal and intermediate regions of the hippocampus in normal and kindled rats

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ABSTRACT

There is growing evidence that the hippocampus comprises diverse neural circuits that exhibit longitudinal variation in their properties, however, the intermediate region of the hippocampus has received comparatively little attention. Therefore, this study was designed to compared short- and long-term synaptic plasticity between the dorsal and intermediate regions of the hippocampus in normal and PTZ-kindled rats. Short-term plasticity was assessed by measuring the ratio of field excitatory postsynaptic potentials' (fEPSPs) slope in response to paired-pulse stimulation at three different inter-pulse intervals (20, 80, and 160 ms), while long-term plasticity was assessed using primed burst stimulation (PBS). The results showed that the basal synaptic strength differed between the dorsal and intermediate regions of the hippocampus in both control and kindled rats. In the control group, paired-pulse stimulation of Schaffer collaterals resulted in a significantly lower fEPSP slope in the intermediate part of the hippocampus compared to the dorsal region. Additionally, the magnitude of long-term potentiation (LTP) was significantly lower in the intermediate part of the hippocampus compared to the dorsal region. In PTZ-kindled rats, both short-term facilitation and long-term potentiation were impaired in both regions of the hippocampus. Interestingly, there was no significant difference in synaptic plasticity between the dorsal and intermediate regions in PTZ-kindled rats, despite impairments in both regions. This suggests that seizures eliminate the regional difference between the dorsal and intermediate parts of the hippocampus, resulting in similar electrophysiological activity in both regions in kindled animals. Future studies should consider this when investigating the responses of the dorsal and intermediate regions of the hippocampus following PTZ kindling.

1. Introduction

According to the World Health Organization, epilepsy affects over 50 million individuals with an incidence of 2.4 million annually and is one of the most common neurological disorders (Levesque and Avoli, 2013). Epilepsy is characterized by repetitive seizures caused by abnormal, hyper-excitable and hyper-synchronized neural networks (Göbel-Guéniot et al., 2020). Patients with epilepsy usually face challenges in terms of cognitive function, and impairments in learning and memory: These have detrimental effects on patients' quality of life at the individual and social level (Dodrill, 1986, Holmes, 1991, Kwan and Brodie, 2001).

Kindling is an animal model used to induce seizures experimentally. This model involves repeated exposure to electrical stimuli or the administration of convulsive chemicals, which gradually results in escalating seizure activity and ultimately leads to an epileptic-like state (McNamara et al., 1985). Among epilepsy types, temporal lobe epilepsy is one of the most common epileptic disorders (McNamara, 1999), and

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chemical kindling is a popular animal model used to study temporal lobe seizures (Gilbert et al., 2006). Pentylenetetrazol (PTZ) is a commonly utilized epileptogenic agent that functions as a GABAA receptor chloride channel antagonist, interacting with the picrotoxin site (Huang et al., 2001). Sub-convulsive doses of PTZ can induce chemical kindling, making it one of the most widely employed agents for this purpose (Giorgi et al., 1991). PTZ enhances the excitability of the central nervous system by reducing the threshold for seizure occurrence (Corda et al., 1990). The hippocampus is one of the most susceptible brain regions to epileptic activity under normal conditions (Andy and Akert, 1955, Green and Shimamoto, 1953), and exposure to PTZ leads to enduring alterations in neuronal and synaptic activity within this region (Krug et al., 1997).

In rodents, the hippocampus has an elongated structure with a longitudinal axis extending in a septal (dorsal)-to-temporal (ventral) curved fashion that corresponds to the posterior-to-anterior axis in the primate brain (Milior et al., 2016, Trompoukis and Papatheodoropoulos, 2020). Although the hippocampus retains a similar circuitry along its entire longitudinal axis, its dorsal, intermediate, and ventral regions exhibit distinct connectivity patterns with cortical and subcortical regions (Bast et al., 2009, Strange et al., 2014), and their functions, based on the input and information processing within the neuronal circuits, are differentiated from each other (Dubovyk and Manahan-Vaughan, 2018).

Previous studies have indicated regional variations in the electrophysiological properties between the dorsal and ventral regions. For example, long-term potentiation (LTP) induced in the dorsal region is significantly stronger than in the ventral (Kouvaros and Papatheodoropoulos, 2016, Maggio and Segal, 2007, Maruki et al., 2001, Papatheodoropoulos and Kostopoulos, 2000) and intermediate regions (Dubovyk and Manahan-Vaughan, 2018, Kenney and Manahan-Vaughan, 2013). This gradient also applies to short-term synaptic plasticity, such as paired-pulse facilitation (Maruki et al., 2001, Papatheodoropoulos and Kostopoulos, 2000, Roohi et al., 2020). Short- and long-term synaptic plasticity are crucial for neural information processing, including learning and memory (Martin and Morris, 2002). The dorsal, intermediate, and ventral regions of the hippocampus contribute to diverse aspects of memory processing (Bast et al., 2009, Hong and Kaang, 2022). These functional differences in distinct regions of the hippocampus may be supported by differences in electrophysiological properties.

Due to the limited of data regarding the intermediate potion of the hippocampus, we decided to investigate the synaptic plasticity between dorsal and intermediate regions of the hippocampus. Prior research also has shown that PTZ kindling leads to a disruption in short- and long-term synaptic plasticity (Palizvan et al., 2005, Roohi et al., 2020). Since there are known functional distinctions along the longitudinal axis of the hippocampus, it is crucial to investigate potential differences in the changes in synaptic plasticity induced by PTZ kindling in the distinct regions of the hippocampus. In this study, we sought to characterize the changes in short- and long-term synaptic plasticity in the dorsal and intermediate regions of the hippocampus in normal condition and following PTZ kindling, in order to gain a better understanding of the effects of kindling on these distinct regions.

2. Materials and methods

2.1. Experimental subjects and ethical standards

All experiments and treatments were carried out based on the ethics guidelines established by the Ethics Committee of the Faculty of Medical Sciences of Hamedan University, that are completely in accord with the "NIH Guide for the Care and Use of Laboratory Animals" and were conducted under animal permit IR.UMSHA.REC.1398.924. Proper measures were implemented to reduce the subjects' pain and discomfort. 45 adult male Wistar rats were used (8–10 weeks at the beginning of experiments) obtained from the Laboratory Animal Center of Hamadan University of Medical Sciences, Hamadan, Iran. Subjects consisted of 17 saline-injected control rats and 28 PTZ-injected animals, of which 22 achieved full kindling state. Animals were handled for one week to acclimatize them to the environment before beginning the injections (PTZ or saline). Rats were accommodated in individual cages and with an ambient temperature of 22–25 °C and a 12:12 light: dark schedule (lights on from 7:00 a.m. - 7 p.m.) with access to rodent pellets and sterile water ad libitum throughout the study. Each animal included in the study was used only once to ensure data integrity and comply with ethical considerations. After the conclusion of the experiments, the animals were euthanized. All experiments were performed at the same time of day to rule out the bias of circadian rhythms.

2.2. PTZ kindling

For kindling, a sub-threshold dose of *pentylenetetrazol* (PTZ; Sigma -Aldrich, India) was injected into experimental subjects intraperitoneally (37.5 mg/kg; 0.1 ml/100 g body weight) every other day. PTZ was freshly prepared in a sterile isotonic saline (0.9% NaCl) prior to injections. Control subjects were given the same saline solution without PTZ and were treated in the same manner as kindled subjects. Body weight was measured prior to each injection. After each PTZ injection, the animals were placed in a Plexiglas chamber (40 × 40 × 40 cm), and the seizure intensity was observed for a duration of 20 min

The seizure stages were classified as follows: Stage 0: no response; Stage 1: ear and facial twitching; Stage 2: convulsive waves through the body; Stage 3: myoclonic jerks, rearing; Stage 4: tonic-clonic convulsions, turnover into side position; Stage 5: generalized tonic-clonic seizures, loss of postural control (Becker et al., 1992). Seizure parameters, such as seizure stage (SS), and the number of injections required to induce stage five seizures, were tracked to assess the development of kindling in the experimental subjects. Experimental subjects were considered fully kindled after the manifestation of three consecutive occurrences of stages of 5 seizures. PTZ kindling, accompanied by substantial hippocampal cell loss (Zhu et al., 2015), has been shown to elicit modifications in synaptic plasticity and gene expression within 24 h following full kindling. These changes persist for up to 8 days (Davoudi et al., 2013), indicating a lasting impact on the molecular and functional properties of the hippocampus.

2.3. Stereotaxic surgery

Twenty-four hours after the last PTZ or saline injection, subjects were anesthetized with urethane (1.5 g/kg; Sigma -Aldrich, China), and their head was fixed in a stereotaxic apparatus (RWD life science, China) for surgery, electrode implantation, and field potential recording. A heating pad (Narco bio-systems rat temp control unit, USA) was used to maintain animals' body temperature at 37 °C. Subjects' blood glucose levels were also controlled during the experiment. The recording and stimulating electrodes were inserted either in the dorsal or intermediate parts of the hippocampus.

The stereotaxic coordination of the recording electrode in the dorsal hippocampus was 2.8 mm posterior to the bregma, 1.8 mm to the right and 1.8–2.8 mm below dura. The stimulating electrodes were 3.1 mm posterior to the bregma, 3.1 mm to the right and 2–3.2 mm below dura. For subjects with stimulation and recording in the intermediate region of the hippocampus, the recording electrode was placed 5.3 mm posterior to the bregma, 5.4 mm to the right and 3.8 − 4.2 mm below dura. The coordination of stimulating electrodes in the intermediate part of the hippocampus was 4.7 mm posterior to the bregma, 4.3 mm to the right and 3.8–4.4 mm below dura (Paxinos and Watson, 2006).

Before electrode implantation, two stainless steel screws were positioned on the skull as reference and ground electrodes. The recording and stimulating electrodes were lowered very slowly to minimize trauma to the brain tissue. Electrodes (127 μm in diameter; stainless steel, Teflon coated, A.M. Systems Inc., USA) were insulated, except 0.5

mm at the tips. *In vivo* field excitatory post-synaptic potentials (fEPSPs) recording was done in anesthetized animals.

2.4. Input-output curves

The appropriate stimulation intensity for recording the evoked field potentials was determined by utilizing test-pulse stimulation of the Schaffer collaterals and obtaining an input-output curve. To accomplish this, single 0.1 ms monophasic square wave pulses were applied to the Schaffer collaterals at varying intensities ranging from 40 μA to 900 μA, with evoked field potentials monitored in the stratum radiatum every 10 s. Input-output curves were plotted by calculating the fEPSP slope's rise after averaging six evoked responses at different stimulus intensities. The test pulse, which produced 50 % of the maximum response, was identified and used in subsequent experiments.

2.5. Evoked field potential recording

To record the evoked field potentials, Schaffer collaterals were stimulated with monophasic square wave pulses of 0.1 ms stimulus duration at an intensity equivalent to their test pulse and a frequency of 0.1 Hz, which were sustained for 20 min. For each time point, twelve evoked responses were averaged, and the fEPSP slope was calculated in the linear portion (10–90 % of amplitude). Stability of the baseline recording was achieved when the variation in the slope of fEPSP was less than ± 10 % for 20 min. LTP was induced through primed burst stimulation (PBS), which consisted of a single priming pulse, followed 170 ms later by a burst of 10 pulses delivered at 200 Hz. Following PBS, evoked potentials were recorded for 60 min. All responses were amplified 500 times, filtered (1–400 Hz band pass filters), and digitized at a sampling rate of 10 kHz, using a data acquisition system (Model: C9804U; ScienceBeam Co., Tehran, Iran). The digital data was then transferred to a computer and stored for easy offline analysis.

2.6. Paired pulse ratio

During the recording of field potentials, paired-pulse stimulations were conducted using the intensity of the test pulses. Six sweeps were averaged for each of three inter-pulse intervals (20, 80, 160 ms), which were randomly selected, with pulse pairs separated by 10 s to achieve a frequency of 0.1 Hz. The paired pulse responses were quantified by calculating the ratio of the second pulse evoked fEPSP slope to the first pulse, with a ratio greater than 1 indicating paired-pulse facilitation and a ratio less than 1 indicating paired-pulse depression. This index was used to evaluate the short-term plasticity in the synapses of the pyramidal neurons of the Schaffer collaterals in the CA1 region.

2.7. Statistical analysis

GraphPad Prism version 9.0.0 for Windows (GraphPad Software, USA) was used for statistical analysis. The normal distribution of the data was assessed using the Kolmogorov-Smirnov test. The data were presented as mean ± SEM. Statistical tests such as Student's unpaired *t-test* or one-way ANOVA followed by Sidak's multiple comparisons test were used to analyze the evoked fEPSP parameters and paired-pulse data. In field potential recording, the average and SEM were calculated from the data on 12 evoked responses, and the mean value was defined as the baseline (100 %). The subsequent data were expressed as the percent change from the baseline. The paired-pulse indices were measured as the ratio of the second pulse-evoked fEPSP to the first one.

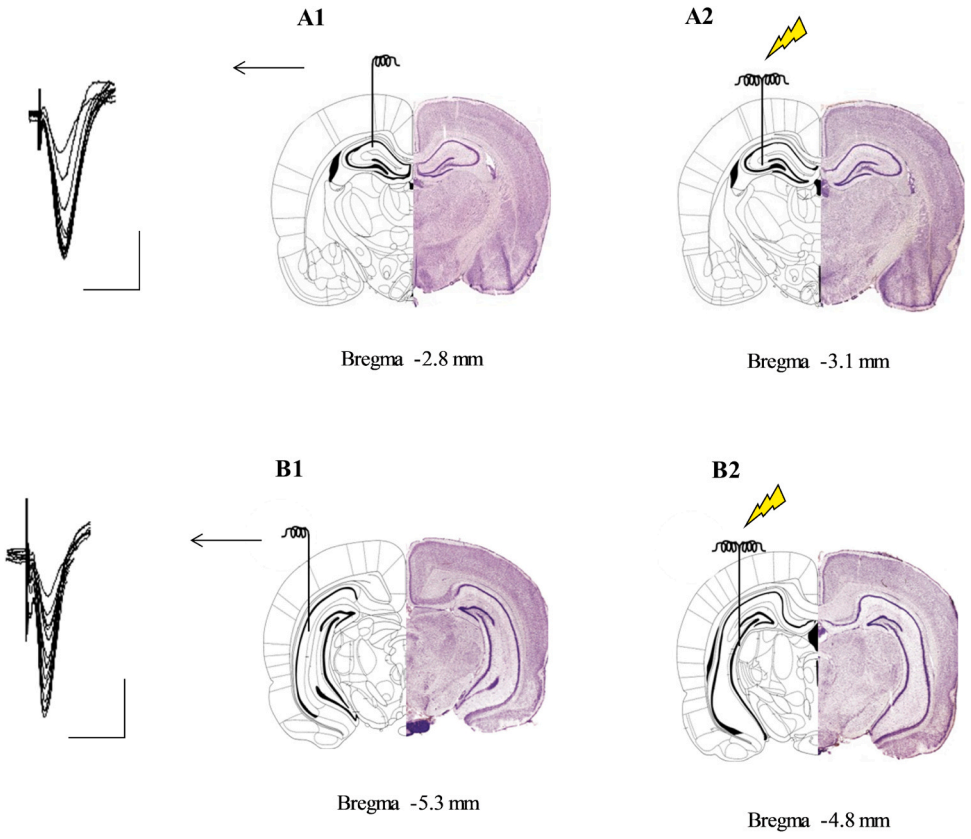


Fig. 1. The schematic loci of the recording and stimulating electrodes on the CA1 and CA3 of the dorsal and intermediate regions of the hippocampus. Schematic location of recording electrodes (A1, B1) and stimulating electrodes (A2, B2) in the stratum radiatum layer of the dorsal and intermediate regions of the hippocampus, respectively based on the Paxinos and Watson atlas (Paxinos and Watson, 2006). Sample traces illustrated evoked fEPSPs in various steps of stimulus intensities applied to Schaffer collateral inputs to the CA1 region. Scale bar 0.2 mv, 5 ms.

The differences were considered significant at $p < 0.05$ Fig. 1.

3. Results

There was no significant variance in seizure parameters between the kindled groups. As expected, giving PTZ repeatedly led to increasingly strong clonic-tonic seizures. In these groups, approximately 80 % of the animals achieved a fully kindled state after receiving between 11 and 16 PTZ injections, with a mean number of injections of 13.81 ± 1.99 (Fig. 2 A, B).

3.1. Basal synaptic transmission in the dorsal and intermediate regions of the hippocampus in control and kindled groups

First, we recorded evoked fEPSPs in the dorsal and intermediate regions of the hippocampus. Fig. 1 shows the loci of the recording and stimulating electrodes in the dorsal (A1, A2) and intermediate (B1, B2) regions of the hippocampus based on the Paxinos and Watson atlas (Paxinos and Watson, 2006). In Fig. 3(A, B) the input/output curves are plotted for the control and kindled groups separately, while (C, D) provide a comparative analysis of the input/output curves between the control and kindled groups. Based on the input/output curves, we found that over a wide range of stimulus intensities (from 60 to 200 μA), the fEPSP slope in the dorsal region of the hippocampus was greater than in the intermediate region of the hippocampus in the control groups ($F_{(21, 165)} = 12.62$, $p < 0.0001$). In PTZ kindled animals, the fEPSP-slope in the dorsal region was also significantly greater compared with the intermediate region, but in these groups, differences in fEPSP-slope were observed over a narrower range of stimulus intensities (from 80 up to 160 μA) ($F_{(17, 180)} = 9.032$, $p < 0.0001$). There was no significant difference in fEPSP-slope observed between the control and kindled groups, either in the dorsal or intermediate region of the hippocampus (Fig. 3C, D).

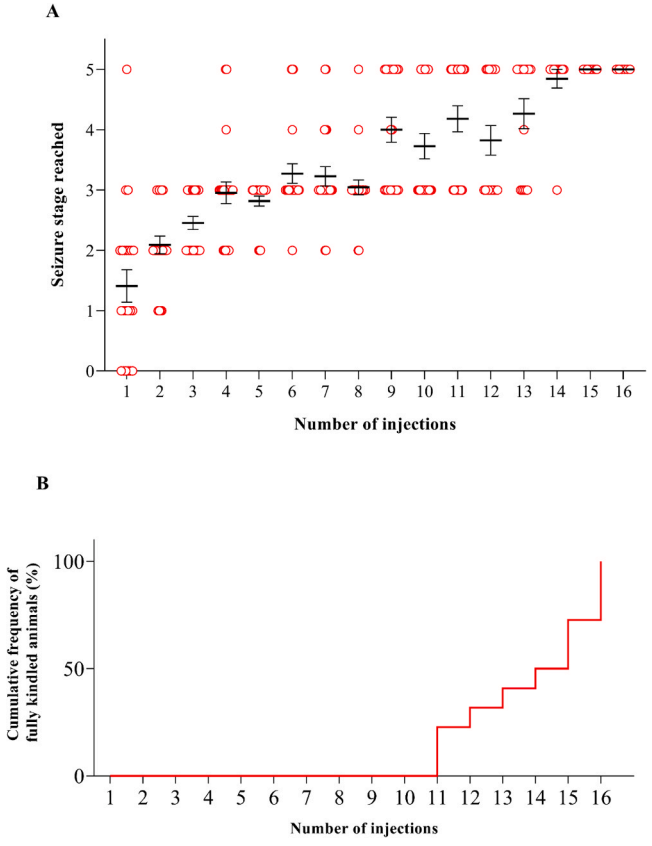


Fig. 2. (A) Seizure stage reached by the rats on each injection day. (B) Cumulative frequency of fully kindled animals.

In the control groups, the intensity of the test pulse in the dorsal region of the hippocampus (82.77 ± 20.63 μA) was significantly lower than in the intermediate part (154.37 ± 52.06 μA) ($p < 0.01$) (Fig. 4A1). Similarly, in the kindled groups, the intensity of the test pulse in the dorsal region of the hippocampus (73.84 ± 21.90 μA) was lower than in the intermediate region (142.22 ± 60.31 μA) ($p < 0.01$) (Fig. 4B1). There was no significant difference in test pulse intensity between the control and kindled groups either in the dorsal or intermediate regions of the hippocampus.

In the control groups, the threshold intensity (the minimum stimulus intensity required to induce fEPSP) and the maximum intensity (the stimulus intensity required to achieve the maximum response) in the dorsal hippocampal region (62.22 ± 21.08 μA and 191.11 ± 48.07 μA, respectively) were significantly lower than in the intermediate part (138.75 ± 58.66 μA and 348.75 ± 200.88 μA, respectively) ($p < 0.01$ for the threshold intensity; Fig. 4. A2 and $p < 0.05$ for maximum intensity; Fig. 4A3).

In the kindled groups, the threshold intensity in the dorsal region of the hippocampus (47.69 ± 10.12 μA) was significantly lower than in the intermediate region (111.11 ± 51.09 μA) ($p < 0.001$; Fig. 4. B2). In addition, the maximum intensity was lower in the dorsal region of the hippocampus (149.23 ± 37.07 μA) compared to the intermediate region (245.55 ± 99.88 μA) ($p < 0.01$; Fig. 4. B3).

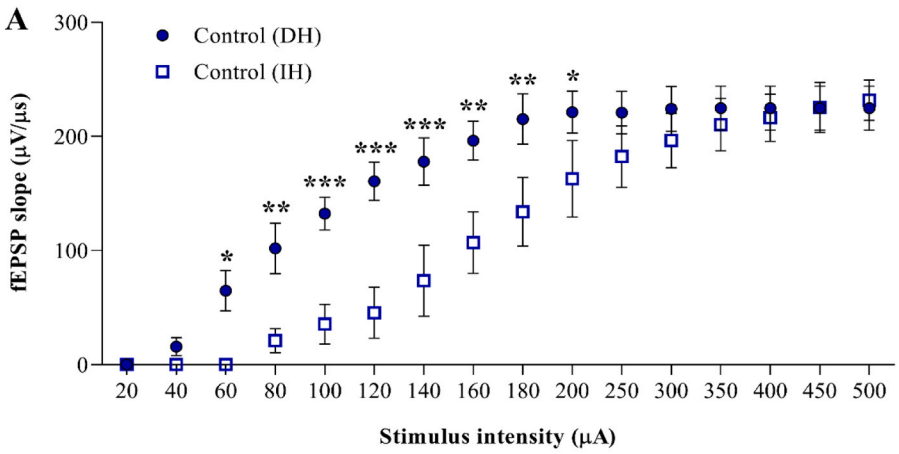
The kindled groups exhibited no significant difference in the minimum and maximum values of fEPSP slope between the dorsal and intermediate regions of the hippocampus, similar to the control groups. In the control groups, the minimum values of fEPSP slope were 76.97 ± 37.07 μA/μs and 61.31 ± 13.59 μA/μs for the dorsal and intermediate regions, respectively. Furthermore, the maximum values of fEPSP slope for the dorsal and intermediate regions were 224.61 ± 58.24 μA/μs and 210.76 ± 38.27 μA/μs, respectively.

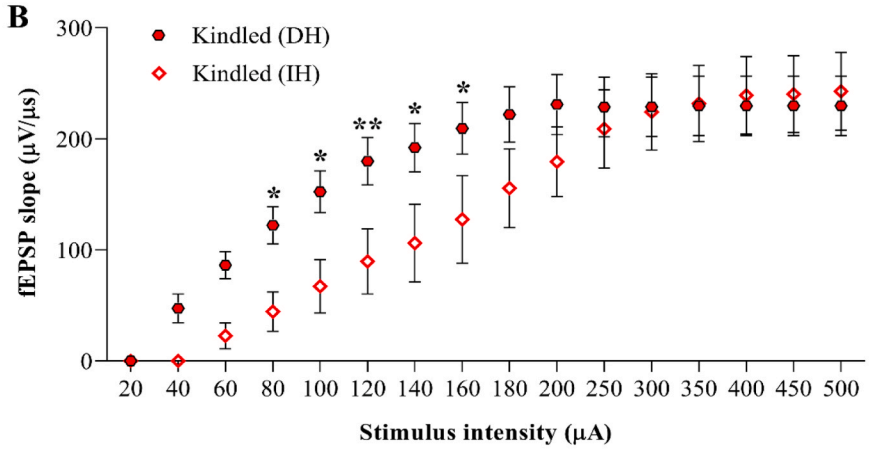
3.2. Effect of kindling on long and short-term synaptic plasticity in the dorsal and intermediate regions of the hippocampus

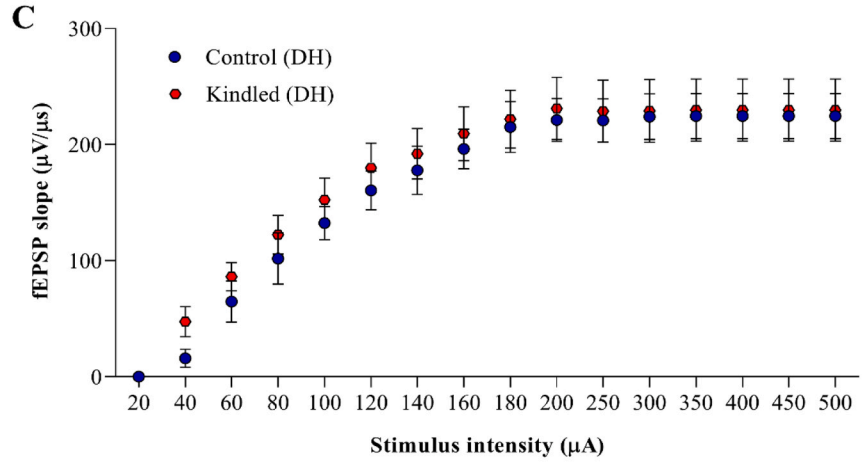
In the next step, we compared the generation of LTP in Schaffer collateral-CA1 pyramidal neuron synapses of the dorsal and intermediate regions of the hippocampus in the control and kindled groups (Fig. 5A, B). Our analysis revealed that the magnitude of LTP in the dorsal region was significantly higher than in the intermediate CA1 region in control groups ($p < 0.01$). However, in kindled groups, there was no significant difference in magnitude of LTP between these two regions ($p = 0.8049$). In addition, PTZ kindling decreased the magnitude of LTP in both dorsal and intermediate regions compared to the control groups ($p < 0.001$) (Fig. 5C).

Then, we evaluated paired-pulse ratio (PPR) as a form of short-term plasticity in the dorsal and intermediate regions of the hippocampus of control and kindled groups. As shown in Fig. 6. A, B, there was a significant difference in PPR at inter-pulse intervals of 20 ms and 80 ms ($p < 0.01$) between dorsal and intermediate regions of the hippocampus in the control groups. However, at the longer inter-pulse interval (160 ms), there was no significant difference in PPR values between these two regions ($p = 0.7805$) (Fig. 6C).

Compared to the control condition, kindling had a significant effect on PPR in both dorsal and intermediate regions of the hippocampus. In kindled subjects, there was a significant decrease in PPR only at inter-pulse intervals of 20 ms (control dorsal vs. kindled dorsal, $t = 9.52$, $p < 0.0001$; control intermediate vs. kindled intermediate, $t = 6.65$, $p < 0.0001$) and 80 ms (control dorsal vs. kindled dorsal, $t = 6.67$, $p < 0.0001$; control intermediate vs. kindled intermediate, $t = 3.59$, $p = 0.0065$). No significant difference in paired-pulse facilitation was observed at inter-pulse interval of 160 ms in dorsal and intermediate regions of the hippocampus between control and kindled groups (control dorsal vs. kindled dorsal, $p = 0.0840$; control intermediate vs. kindled intermediate, $p = 0.7688$). In contrast to control groups, there







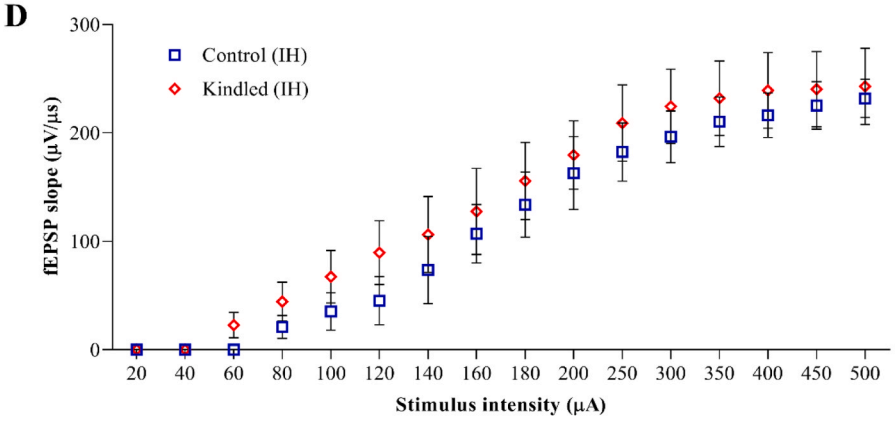


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Fig. 3. Input-output curves in the dorsal and intermediate regions of the hippocampus of control and kindled rats. The input-output curve of the fEPSP-slope revealed a significant difference in the dorsal compared to the intermediate region of the hippocampus in stimulus intensities between 60 and 200 μA in control groups (A) and 80–160 μA in kindled groups (B). However, no significant difference was observed between the control and kindled groups in the dorsal (C) and intermediate (D) regions of the hippocampus. Data give the mean ± SEM. DH: dorsal hippocampus, IH: intermediate hippocampus, n = 8–9 in control groups, n = 9–13 in kindled groups. * $p < 0.05$, * * $p < 0.01$, * ** $p < 0.001$.

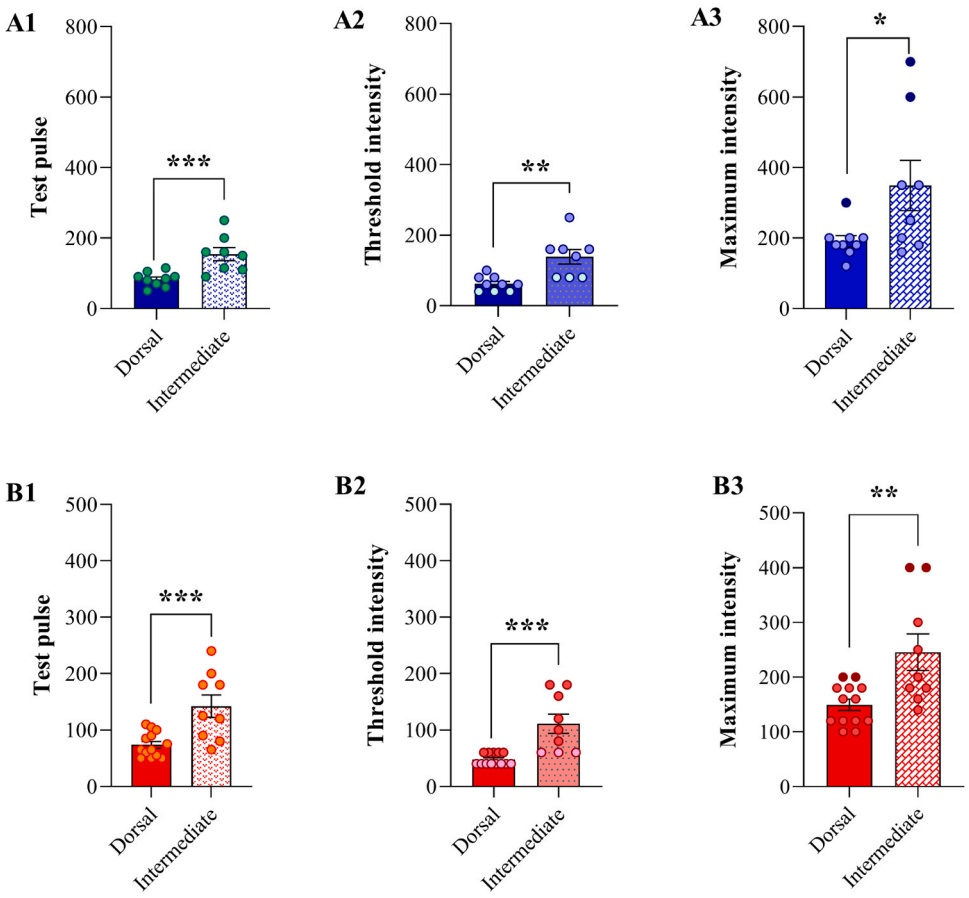

Fig. 4. The differences in minimum, maximum, and test pulse intensities between the dorsal and intermediate regions of the hippocampus. There was a significant difference in the test pulses (half-maximum level of stimulus intensities) between the dorsal and intermediate parts of the hippocampus in the control groups (A1) and in the kindled groups (B1). Minimum levels of stimulus intensities illustrated a significant difference between the dorsal and intermediate parts of the hippocampus of the control groups (A2) and in the PTZ-kindled groups (B2), lower intensities are shown with light colors. Maximum levels of stimulus intensities manifested a significant difference between the dorsal and intermediate regions of the hippocampus of the control groups (A3) and in kindled groups (B3), higher intensities are shown with dark colors. Data give the mean ± SEM. n = 8–9 in control groups, n = 9–13 in kindled groups. * $p < 0.05$, * * $p < 0.01$, * ** $p < 0.001$.

was no significant difference in PPR in dorsal and intermediate regions of the hippocampus in kindled groups.

4. Discussion

The findings of the present study indicated that the basal synaptic transmission in the dorsal hippocampus was higher than in the intermediate region, and this distinction holds true for both control and kindled animals. In the control groups, the magnitude of long-term potentiation and the level of paired-pulse facilitation were higher in the dorsal region compared to the intermediate CA1. However, kindling led to a decrease in the magnitude of long-term potentiation and the paired-pulse ratio in both regions, and there was no significant difference in these factors between the two regions in kindled animals.

Comparing basal synaptic transmission between dorsal and intermediate parts of the hippocampus in normal and PTZ- kindled rats.

The basal synaptic transmission differed between the dorsal and intermediate parts of the hippocampus in both control and kindled condition. Indeed, when employing equivalent levels of stimulation intensities, the fEPSP slope in the intermediate region exhibited a smaller magnitude compared to the dorsal CA1. Consequently, the minimum, maximum, and test pulse intensities in the intermediate region were higher than those observed in the dorsal CA1.

While there are limited reports regarding in vivo field potential recordings from the intermediate hippocampus area, a study in freely moving rats demonstrated that the population spikes in the intermediate dentate gyrus were weaker than those observed in the dorsal region (Kenney and Manahan-Vaughan, 2013). In contrast, two in vitro studies showed no significant differences in evoked potentials between slices prepared from the dorsal and intermediate regions of mice (Milior et al., 2016) and rat hippocampi (Dubovyk and Manahan-Vaughan, 2018). However, comparing in vitro and in vivo results may not be reasonable due to the disruption of intact circuits and reduced inhibitory neurotransmission in vitro. The presence of inhibitory connections on granule cells in the dentate gyrus may impact CA3 and subsequently CA1, providing a plausible explanation for the observed differences between in vivo and in vitro findings (Andersen et al., 2007, Buckmaster and Schwartzkroin, 1995).

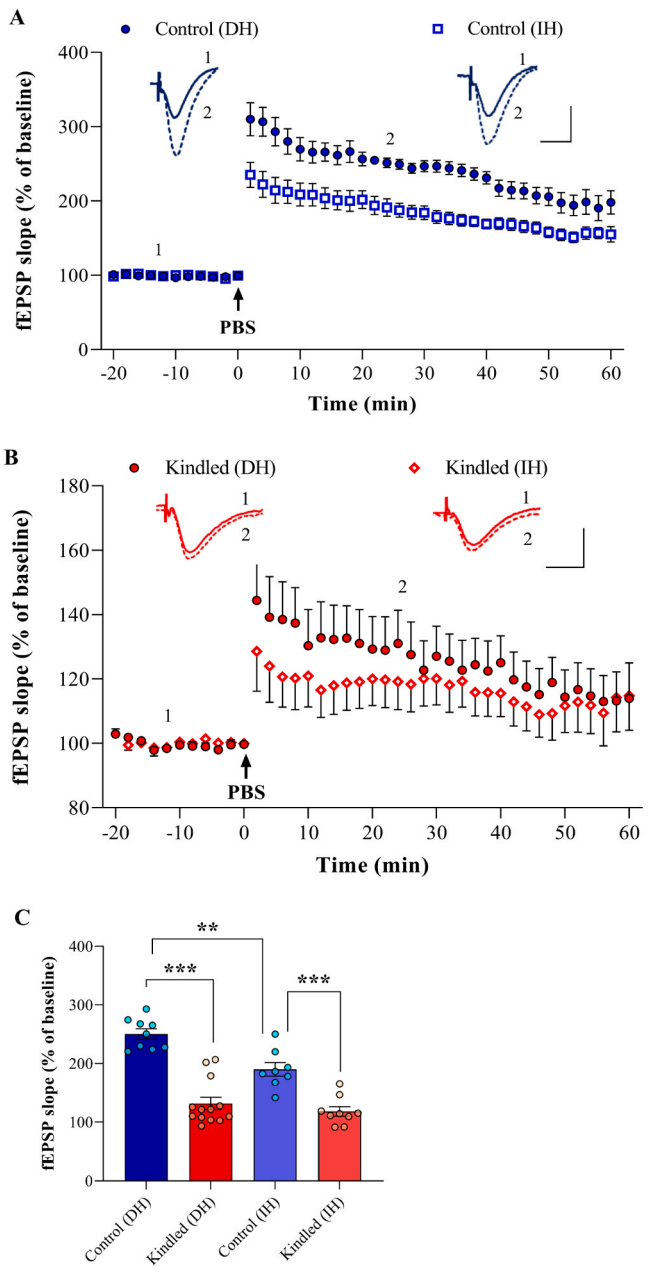

Fig. 5. Comparing the fEPSP slope changes (%) in the dorsal and intermediate regions of the hippocampus in control and kindled rats. (A) Comparing the fEPSP slope changes (%) in the dorsal and intermediate parts of the hippocampus showed the magnitude of long-term potentiation (LTP) elicited in the intermediate region is significantly smaller than that induced in the dorsal area. (B) There was no significant difference between the magnitude of LTP between dorsal and intermediate parts of the hippocampus in PTZ-kindled groups. (C) The summary bar chart shows mean values of fEPSP slope changes (%) measured during 60 min after PBS in the dorsal and intermediate regions of the hippocampus between control and kindled groups. Scale bar 0.2 mv, 5 ms. Data give the mean ± SEM. DH: dorsal hippocampus, IH: intermediate hippocampus, PBS: primed burst stimulation, 1: before PBS, 2: after PBS. n = 8–9 in control groups, n = 9–13 in kindled groups. * * $p < 0.01$, * ** $p < 0.001$.

The difference in basal synaptic characteristics between the dorsal and intermediate regions of the hippocampus may be partially related to structural factors. Previous studies have demonstrated that the total dendritic length, surface area, and generally total dendritic volume are significantly greater in dorsal neurons compared to ventral neurons (Dougherty et al., 2012, Malik et al., 2016). The transition for most of the structural properties from the ventral to the dorsal pole is gradual, therefore the total dendritic length and surface area in pyramidal cells of the dorsal region is greater than the intermediate part of the hippocampus.

Another possible explanation for the higher test pulse intensities observed in the intermediate region compared to the dorsal region of the hippocampus could be the differential interaction between pyramidal cells and interneurons in these regions. Existing evidence suggests that the distribution of GABAergic interneurons varies along the longitudinal axis of the hippocampus, with higher densities found in the ventral region (Caballero et al., 2013, Jinno et al., 1998). However, the density of interneurons in the intermediate region of the hippocampus and their potential impact on pyramidal cells in this specific region have not been thoroughly investigated and required further research.

It should be noted that in evoked field potential recordings, responses are recorded from the CA1 region following stimulation of the CA3 pyramidal cells. Therefore, it seems necessary to pay attention to the electrophysiological properties of CA3 pyramidal cells. Sun et al. (2020) reported that ventral CA3 pyramidal neurons exhibit lower intrinsic excitability (Sun et al., 2020). Hence, stimulation of ventral CA3 neurons may require higher intensity than dorsal CA3 neurons. As yet there are no data on the excitability of pyramidal neurons in CA3 region of the intermediate hippocampus, further research is needed to investigate this issue.

PTZ kindling does not appear to be associated with a direct increase in basal synaptic transmission. This finding aligns with previous studies by Piredda et al. (1986), Krug et al. (1997), and Ruethrich et al. (1996), which also reported no differences in input/output (I/O) curves and stimulus thresholds between kindled animals and control groups.

Comparing LTP magnitude and paired-pulse facilitation between dorsal and intermediate regions of the hippocampus in normal condition and following PTZ kindling.

The present results also indicated a lower magnitude of LTP in the intermediate compared to the dorsal region of the hippocampus in the control groups. The difference in LTP generation may link to the structural properties, including greater total dendritic surface in pyramidal cells of the dorsal region than in the intermediate CA1, as mentioned earlier (Dougherty et al., 2012, Malik et al., 2016). Meanwhile, the expression gradient of plasticity-related receptors in the longitudinal axis of the hippocampus may also play a role in the difference in LTP generation in dorsal and intermediate regions of the hippocampus. Specifically, there is a higher expression level of the GluN2B subunit in the intermediate region compared to the dorsal CA1 region. So, the NMDARs demonstrate distinct 2 A/2B ratios along the axis of the hippocampus (Dubovyk and Manahan-Vaughan, 2018). According to this fact that GluN2B subtype plays vital roles in synaptic plasticity (Plattner et al., 2014; Tang et al., 1999) suggests that differential expression of the GluN2B subunit and the varying 2 A/2B ratios of NMDARs along the hippocampus axis may contribute to the distinctions observed in LTP generation between the dorsal and intermediate regions of the hippocampus.

Previous studies have also demonstrated that the distribution of ion channels, such as Kv7/M, GIRK, HCN, and SK-type K+ channels in the dorso-ventral axis, is not identical, contributing to the increased intrinsic excitability of CA1 ventral neurons compared to the dorsal neurons (Dougherty et al., 2013, Dubovyk and Manahan-Vaughan, 2018, Honigsperger et al., 2015, Kim and Johnston, 2015, Marcelin et al., 2012). Considering the fact that higher neuronal excitability can reduce the ability of synaptic potentiation, this may explain the lower magnitude of LTP in the intermediate region compared to the dorsal region of the hippocampus.

A noteworthy finding of this study was that kindling eliminated the difference in LTP generation between the dorsal and intermediate regions of the hippocampus. Considering the heterogeneous distribution of NMDA receptors and ion channels along the dorsoventral axis of the hippocampus, further research is needed to investigate whether PTZ

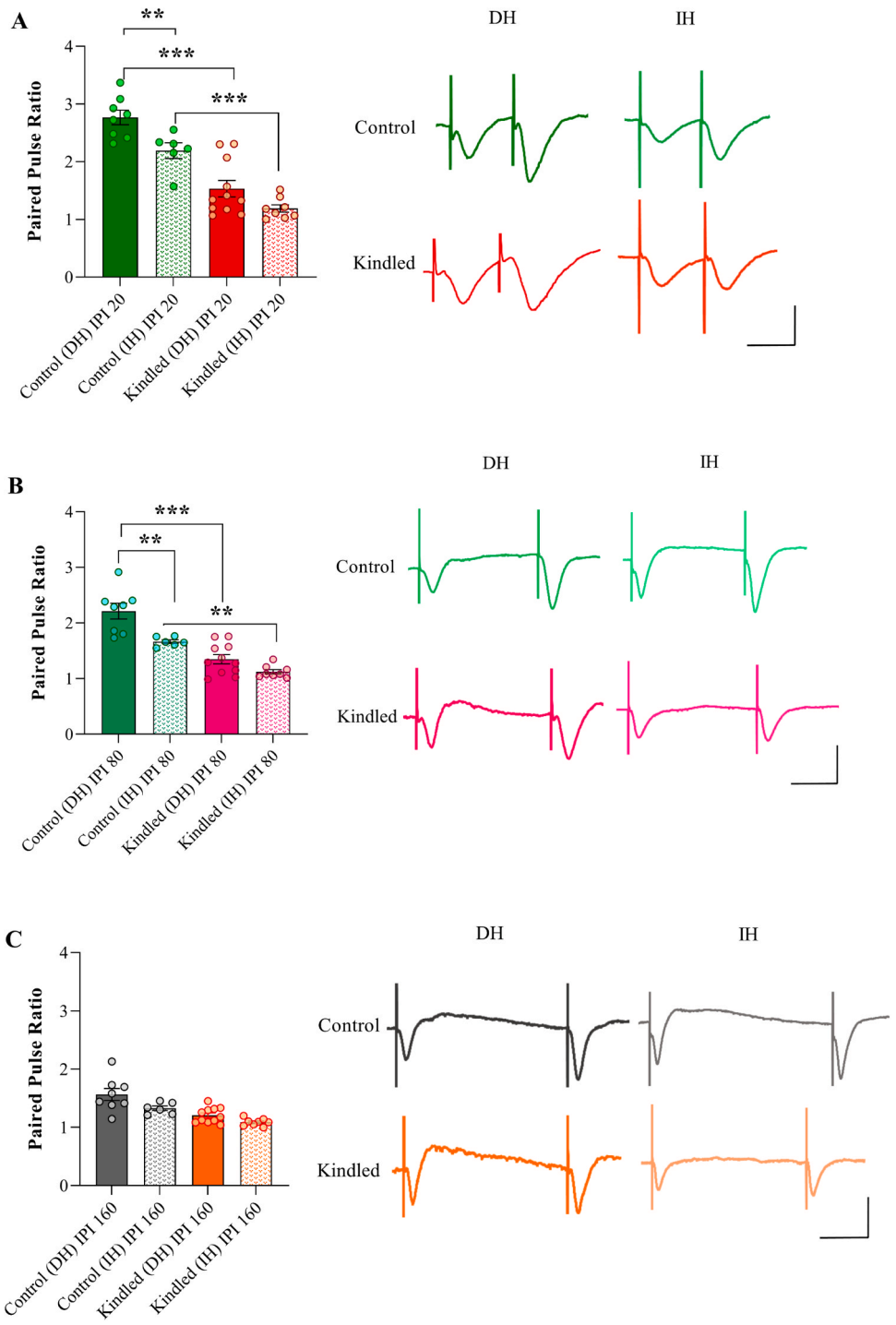

Fig. 6. Comparing the paired-pulse ratio in the dorsal and intermediate regions of the hippocampus in control and kindled rats. (A) Facilitation of the fEPSP-slope was weaker in the intermediate compared to the dorsal part of the hippocampus following stimulation at the inter-pulse interval of 20 ms in control groups. However, PTZ-kindled groups showed no significant difference in the paired-pulse ratio of the fEPSP-slope at this inter-pulse interval in these regions. Comparison of the paired-pulse ratio of fEPSP-slope in the dorsal and intermediate regions of the hippocampus of kindled groups with control groups showed significant reduction at the inter-pulse interval of 20 ms. (B) The facilitation of the fEPSP-slope at the inter-pulse interval of 80 ms in the dorsal region of the hippocampus was significantly greater than the intermediate part in the control groups. No significant difference was observed in the paired-pulse ratio of the fEPSP-slope between the dorsal and intermediate parts of the hippocampus in kindled groups in this inter-pulse interval. PTZ kindling also decreased the paired-pulse facilitation in both regions of the hippocampus at the inter-pulse interval of 80 ms. (C) There was no significant difference in the paired-pulse ratio of the fEPSP-slope at the inter-pulse interval of 160 ms in control groups, kindled groups, and also between control and kindled groups. Sample traces from CA1 stratum radiatum in response to paired-pulse stimulation at the inter-pulse intervals of 20, 80, and 160 ms of dorsal and intermediate regions of the hippocampus in control and kindled groups. Scale bar 0.2 mv, 5 ms. Data give the mean ± SEM. DH: dorsal hippocampus, IH: intermediate hippocampus. n = 6–8 in control groups, n = 8–11 in kindled groups. * * $p < 0.01$, * ** $p < 0.001$.

kindling can affect these kinds of receptors or channels. For example, Arnold et al. (2019) showed that in a status epilepticus model, the excitability of dorsal CA1 neurons was increased by reducing HCN ion channels. This made dorsal CA1 neurons more similar to ventral CA1 neurons and therefore more prone to epileptiform and seizure activity (Arnold et al., 2019).

A significant impairment in the induction of LTP was observed in the PTZ-kindled groups compared to the control groups. Seizures disrupt the balance between excitatory and inhibitory neurotransmission (Corda et al., 1992, Samokhina and Samokhin, 2018) and affect synaptic plasticity (Han et al., 2016). Interestingly, seizures enhance excitatory synaptic transmission through mechanisms similar to LTP, involving the activation of NMDAR, which inhibits further LTP formation in the hippocampus (Abegg et al., 2004). Additionally, severe seizures can lead to cell loss particularly in the hippocampus (Zhu et al., 2015) which may contribute to the disruption of synaptic plasticity in PTZ-kindled animals.

The study found a significant difference in short-term plasticity between the dorsal and intermediate regions of the hippocampus in the control groups, but not in the kindled groups. In the control groups, the paired-pulse facilitation of the fEPSP slope was weaker in the intermediate region compared to the dorsal region of the hippocampus at inter-pulse intervals of 20 and 80 ms. This difference in facilitation is inversely related to the presynaptic release probability, meaning that synapses with higher release probability have lower facilitation probability (Dobrunz and Stevens, 1997, Zucker and Regehr, 2002). The ventral hippocampus is known to have stronger terminals of neuromodulators and neuropeptides compared to the dorsal regions (Strange et al., 2014). Additionally, GABA and glutamate release probability is higher in the ventral CA1 than in the dorsal CA1 (Milior et al., 2016). These factors suggest that there may be a difference in short-term plasticity between the dorsal and intermediate areas of the hippocampus.

Furthermore, we found that PTZ kindling caused a significant reduction in paired-pulse facilitation in the experimental group compared to the control group at inter-pulse intervals of 20 ms and 80 ms in both the dorsal and intermediate parts of the hippocampus. Considering that PTZ kindling increases the releasing probability (Dobrunz and Stevens, 1997, Zucker and Regehr, 2002), paired-pulse facilitation may decrease in both region hippocampus.

Regional differences in synaptic plasticity and the effects of PTZ kindling on it.

The dorsal hippocampus is primarily associated with visuo-spatial memory and receives projections from the entorhinal cortex, while the intermediate region of the hippocampus is involved in rapid place learning and behavioral performance. The intermediate region of the hippocampus receives projections not only from the entorhinal cortex but also from subcortical regions, resulting in a convergence of connections dedicated to visuospatial processing and behavioral control (Bast et al., 2009). The differences in short and long-term plasticity within these regions, as well as their interactions, may play a crucial role in explaining the diverse functions of memory.

The important fact that must be considered is the effect of kindled seizures on the strength of synaptic plasticity in the dorsal and intermediate regions of the hippocampus. This effect was so strong that the differences in short- and long-term plasticity between the dorsal and intermediate regions were removed by the kindling. As the hippocampal regional differences in neuronal action and plasticity under healthy and normal circumstances are crucial, seizure occurrence may impact hippocampal-related functions through region-specific changes in neural activities.

5. Conclusion

Overall, the findings of the present investigation showed that the electrophysiological properties of CA1 neurons differ between the dorsal and intermediate regions of the hippocampus. However, the sensitivity of both areas to PTZ kindling seems to be similar. Kindling-induced changes in short and long-term plasticity in both regions were significant compared to the control groups. Comparison of neuronal plasticity in control and disease conditions, like epilepsy, in different parts of the hippocampus can be helpful in understanding the effect of seizure on hippocampal neural activity.

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CRediT authorship contribution statement

Maryam Sharifi conducted the experiment, analyzed the data, and wrote the first draft of the manuscript; Alireza Komaki contributed to the experimental design and laboratory work; Victoria Barkley contributed in final revision of the manuscript; Shahrbanoo Oryan, Abdolrahman Sarihi, and Javad Mirnajafi-Zadeh collaborated on designing the experiments, analyzing the data, writing the manuscript, and securing funding. All authors have reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Access to the data supporting the findings of this study is available upon request from the corresponding authors.

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