Title: Comparing the Seizure-Induced Impairment of Short-Term Plasticity in Dorsal and Ventral Hippocampus in Kindled Mice

Running title: Seizure and Short-term Plasticity

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Abstract

There are many differences among dorsal and ventral hippocampal neural circuits that affect the synaptic plasticity. In this study we compared the occurrence of short-term plasticity in the field excitatory post synaptic potentials (fEPSP) in dorsal and ventral hippocampal CA1 area following kindled seizures. Animals (male C57 B6/J mice, 12 weeks of age) were kindled by intraperitoneal injections of pentylenetetrazole (PTZ) and fEPSPs were recorded from dorsal and ventral hippocampal slices. Short-term plasticity was evaluated by measuring fEPSP-slope and fEPSP-area following paired-pulse stimulation delivered at three inter-pulse intervals (20, 80 and 160 ms). Obtained results showed that in control slices fEPSP-slope was greater in ventral- compared to dorsal hippocampus, but there was no difference in fEPSP-area among two regions. In hippocampal slices of kindled animals, fEPSP-slope was similar in dorsal and ventral regions, but fEPSP-area was greater in ventral- compared to dorsal hippocampus. In addition, fEPSP-area was greater in kindled compared to control group only in ventral hippocampus. PTZ kindled slices showed impaired short-term facilitation and the paired-pulse index was reduced only at dorsal hippocampal slices. Kindling had no significant effect on paired-pulse ratio in ventral hippocampal slices. Our findings indicated that the seizure occurrence affected the neural activity of hippocampus in a regional dependent manner. Although kindling increased fEPSP-area in ventral hippocampus, kindling-induced changes in short-term synaptic plasticity was significant only in dorsal hippocampal slices compared to control group. The difference in the responses of hippocampal dorsal and ventral poles has to be considered in the future researches.

Keywords: Seizure, Hippocampus, Paired-pulse index, Synaptic plasticity, Kindling

Introduction

The hippocampus is one of the most important brain structures in learning and memory (Morris, 2007). Hippocampal dependent synaptic plasticity is involved in some physiological and pathological functions that can be affected/impaired by some conditions such as epilepsy (Krug et al., 1997) . Epilepsy is one of the most prevalent neurological diseases that influence the patients' individual and social quality of life and their cognitive functions (Dodrill, 1986; Kwan and Brodie, 2001). The effect of epileptic seizures on short-term and long-term synaptic plasticity can also be observed in chemical kindling (Palizvan et al., 2005) which develops by serial injections of a sub convulsive dose of pentylenetetrazol (PTZ), a $GABA_A$ receptor antagonist .

Short- and long-term synaptic plasticity, as the basic mechanisms involved in learning and memory (Martin and Morris, 2002; Morris, 2007), have been studied in the hippocampus. Paired-pulse facilitation or depression are relatively simple forms of short-term synaptic plasticity (Kamiya and Zucker, 1994) and can be observed when two stimuli are delivered to presynaptic afferent fibers at different intervals and the obtained response to the second pulse is higher or lower than response to the first pulse, respectively. Evaluating the changes in short-term plasticity gives us insights about the activity of neural circuits following seizures and helps in understanding the pathophysiology of epileptic brain.

It is important to note that the characteristics and magnitude of synaptic plasticity in dorsal and ventral hippocampus are different (Dougherty et al., 2012; Dubovyk and Manahan-Vaughan, 2018). Recent experimental data highlight the idea of functional separation along the longitudinal axis of the hippocampus (dorsoventral or septotemporal), with divers functions as cognition and emotionality in the dorsal hippocampus and ventral hippocampus respectively

(Poppenk et al., 2013; Bannerman et al., 2014). This diversification along the longitudinal axis may be due to: 1) different extrinsic connectivity of dorsal and ventral hippocampal segments with other brain structures, or 2) different local neural circuits in dorsal and ventral segments of the hippocampus. Based on early and recently electrophysiological and neurochemical studies, the dorsal and ventral hippocampus have different local network organization including principal cell properties, synaptic transmission, neurotransmitter receptors, and synaptic plasticity (for review please see (Papatheodoropoulos, 2018)).

Accordingly, for better understanding the effect of seizure on cognitive functions, it is necessary to determine the seizure-induced changes in short-term synaptic plasticity in dorsal and ventral parts of the hippocampus. Therefore, in the present study we examined the changes in paired-pulse facilitation of fEPSPs recorded from the CA1 region in DH and VH following PTZ kindling in mice. We were curios to find out whether PTZ kindling has different effects on the two poles of the hippocampus.

Materials and Methods

Animals

All experiments and manipulations conformed to the guidelines set by the Animal Care Commission of Faculty of Medical Sciences, Tarbiat Modares University, Iran. B6/J male mice (10-12 weeks of age) from Pasteur institute (Iran) were used in the experiments. Animals consisted of 9 kindled and 10 control mice. Prior to engaging in any experimental paradigms, the mice were provided with one week to acclimatize to the facility then, PTZ or saline injections were done every other day. Mice were maintained on a normal light cycle with access to Purina mouse chow and sterile water ad libitum throughout the study.

PTZ kindling

For kindling, a sub-threshold dose of 35 mg/kg PTZ was injected intraperitoneally (i.p.; 10 µl/g) every 48 h. Following injection, the convulsive behavior of each subject was observed for 20 min. PTZ was freshly prepared in a sterile isotonic saline prior to injections. Control mice were injected with the identical saline solution without PTZ. The resultant seizures were classified as following: stage 0: no response, stage 1: ear and facial twitching, stage 2: convulsive waves axially through the body, stage 3: myoclonic body jerk, stage 4: turn over into side position, tonic-clonic seizures and stage 5: turn over into back position, generalized tonic-clonic seizures (Dhir, 2012). All animals behaviorally showed three consecutive stages 4 or 5 to be considered as fully kindled.

Field potential recording in the hippocampal slices

24 hour after the last PTZ or saline injection the mice were anesthetized with carbon dioxide (CO_2) and decapitated. The brain was carefully transferred into a chamber contained chilled artificial cerebrospinal fluid (aCSF) bubbled by carbogen (95% O_2 and 5% CO_2). The aCSF contained (in mM): NaCl 124, $NaHCO_3$ 26, KH_2PO_4 1.25, KCl 5, $CaCl_2$ 2, $MgCl_2$ 2.06, and D-glucose 10 and its pH was 7.3-7.4. Then, the right hemisphere of brain was dissected. Transverse hippocampal slices were sectioned (400 µm thick) using a vibrotome (VT 1200, Leica, Germany). The slices were placed in a recovery chamber filled with aCSF for at least 60 min at room temperature. Then, they moved to an interface-type recording chamber and maintained at 32°C, at the interface between aCSF and warm, humidified oxygen gas. Slices were perfused at the rate of 1 ml/min with aCSF, which was aerated continuously with carbogen. The slices were allowed to incubate in this medium for 30 min prior to recording.

Field potentials were recorded from CA1 stratum radiatum in dorsal and ventral hippocampus. Both stimulating electrode (stainless steel, Teflon coated, A-M Systems, US) and recording electrodes (borosilicate glass, O.D.: 1.5 mm, I.D.: 0.86 mm, Sutter instrument, USA) were placed on the same layer. A reference electrode was also placed in recording chamber. After electrode implantation, square stimulating pulses (200 μs, 0.1 Hz) were applied through a bipolar stimulating electrode by an isolator and constant current unit apparatus (S403J, Nihon-Kohden, Japan). Since the stimulation strength required to evoke fEPSP of a given magnitude can vary from experiment to experiment, we made a normalized scale for stimulation intensity. To do this, the full scale of stimulation intensities was divided into ten steps according to the stimulation intensities required to elicit minimum and maximum fEPSP-slope. Extracellular potentials were recorded using a glass recording electrode (2-5 MΩ) filled with aCSF.

Signals were transferred to an amplifier (ME208300, Nihon-Kohden, Japan) through the recording electrode and visualized by custom-made software (Potentalize; ScienceBeam Co., Iran). Input/output curve was plotted to determine test pulse intensity. To record paired pulse responses, test pulse intensity was used throughout the experiments. Paired pulse stimulations at the inter-pulse intervals of 20, 80 and 160 ms were made.

Statistical analysis

fEPSP parameters were analyzed using repeated measure two way ANOVA followed by Sidak's multiple comparison test, paired pulse data were analyzed unpaired t student test. The values expressed as means ± SEM of the mean. The number of slices (n) used in control group were as follows: n=8 in dorsal hippocampal slices and n=7 in ventral hippocampal slices. In kindled group n=5 in dorsal hippocampal slices and n=6 in ventral hippocampal slices. In each experimental group, all slices were taken from 3 mice.

Paired pulse responses were quantified as the ratio of the second pulse evoked fEPSP to the first one. All statistical analyses were conducted using Graph pad Prism. To be considered significant, p values <0.05 were used.

Results

PTZ kindling procedure

Subjects were handled and acclimatized at least one week and intraperitoneal PTZ injections were done every other day (in control group saline was injected instead of PTZ). Approximately 80% of animals fulfilled the kindling criteria after 7-10 injections. The mean number of injections was 6.3±2.0.

Effect of kindling on single-pulse evoked fEPSPs

Field EPSPs evoked at test pulse stimulation intensity were recorded from the CA1 area of dorsal and ventral hippocampal slices (Fig. 1A). In the first step, we compared the minimum and maximum stimulus intensities needed for evoking fEPSP. Obtained data from whole slices (dorsal and ventral hippocampus) showed that the minimum and maximum stimulation intensities in control group were 20.6±1.1 µA and 124.6±4.2 µA. Similar data were achieved in kindled group so that the minimum intensity was 21.11±3.3 µA and maximum intensity was 118.35±23.4 µA (n=18). More specifically, the minimum and maximum stimulation values for dorsal hippocampal slices in control group were 20.7±0.7 µA and 127.1±3.8 µA (n=22), respectively, and in kindled group were 21.1±1.1 µA and 121.1±9.2 µA (n=9). The corresponding values for the ventral control slices were 20.6±0.4 µA and 122.1±5 µA (n=22) and for the ventral kindled slices were 21.1±1.1 µA and 115.6±6 µA (n=9). These data showed that there was no significant difference in minimum and maximum stimulus intensities between control and kindled slices in dorsal and ventral hippocampus.

Then, input/output curves were plotted using arbitrary units. From input/output curves we found that in relatively high intensities (numbered as 8-10) fEPSP-slope in ventral hippocampal slices was greater than fEPSP-slope in dorsal hippocampal slices in control group ($F_{(9,351)}$=9.713, p<0.0001). However, there was no significant difference in fEPSP-area between dorsal and ventral hippocampal slices at different stimulation intensities in control group ($F_{(9, 522)}$= 0.3849, p=0.9424) (Fig. 1B). In kindled group the differences in input/output curves between dorsal and ventral hippocampal slices were opposite to what observed in control slices, i.e. in PTZ kindled animals, there was no significant difference in fEPSP-slope between dorsal and ventral parts of the hippocampal slices ($F_{(9,280)}$=0.07886, p=0.9999), but a significant difference was observed in fEPSP-area between two regions. There was greater fEPSP-area in ventral compared to dorsal hippocampal slices in kindled group ($F_{(9,135)}$=2.008, p=0.0429) (Fig. 1C).

In the next step we compared the input/output curves of fEPSP-slope and fEPSP-area in dorsal and ventral hippocampal slices between control and kindled groups. PTZ kindling had no significant effect on fEPSP-slope in dorsal ($F_{(9,324)}$=2.415, p=0.0115) and ventral hippocampus ($F_{(9,279)}$= 2.080, p=0.0314) compared to the control group (Fig.2 A, C). While fEPSP-area significantly increased in the ventral hippocampus of kindled group compared to control group ($F_{(1,370)}$=13.49, p=0.0003, Fig.2 D). Kindling had no significant effect on fEPSP-area in dorsal hippocampal slices (Fig. 2 B).

Effect of kindling on short-term synaptic plasticity

We examined the short-term plasticity of fEPSPs by calculating paired-pulse ratio for fEPSP-slope or fEPSP-area in dorsal and ventral hippocampal slices of control and kindled groups. fEPSPs were evoked by stimulating the slices at test pulse intensity at inter-pulse intervals of 20, 80 and 160 ms. Test pulse intensities used to evoke fEPSPs in dorsal

hippocampal slices in control and kindled groups were 61.0±2.7 µA and 58.8±5.2 µA respectively. In ventral hippocampal slices, test pulse intensity was 59.02±2.6 µA in control group and 56.5±3.9 µA in kindled group. There was no significant difference in test pulse intensity between control and kindled groups.

In control group, there was significant difference in paired-pulse facilitation of fEPSP-slope between dorsal and ventral hippocampal slices only at inter pulse-interval 20 ms (p=0.0194) (Fig.3 B). When paired-pulse ratio was calculated for fEPSP-area, significant difference was observed in paired-pulse ratio (here as paired-pulse depression) between dorsal and ventral hippocampus of control slices at inter pulse-interval of 20 ms (p=0.0086) (Fig. 3C). However, at longer inter pulse-intervals (80 and 160 ms), paired-pulse facilitation was observed in both dorsal and ventral hippocampus of control slices and there was significant difference at inter-pulse intervals of 80 ms (p=0.0199) and 160 ms (p=0.0020) between dorsal and ventral hippocampal slices in control group (Fig. 3C).

To find out the effect of PTZ kindling on short-term plasticity, we calculated paired-pulse ratio for fEPSP-slope and fEPSP-area in dorsal and ventral hippocampal slices of PTZ kindled animals and compared them with control group. Obtained results showed higher facilitation at inter-pulse interval of 160 ms in dorsal compared to ventral hippocampus following PTZ kindling (p=0.05). At inter-pulse intervals of 20 and 80 ms no significant difference was seen between dorsal and ventral hippocampus in fEPSP-slope (Fig.3 D). Comparing the paired-pulse ratio for fEPSP-area at all inter-pulse intervals showed no difference between dorsal and ventral hippocampus in kindled slices (Fig. 3 E).

In comparing the slices of control and kindled groups, a decrease in paired-pulse facilitation of fEPSP-slope was seen at inter-pulse intervals of 20 ms (p=0.002) and 80 ms

(p=0.0062) in dorsal hippocampal slices of kindled group. In addition, paired-pulse ratio for fEPSP-area was significantly decreased in dorsal hippocampal slices of kindled group only at inter-pulse interval of 20 ms (p=0.0195) (Fig. 4 A, B). Kindling had no significant effect on paired-pulse ratio in ventral hippocampal slices (Fig. 4 C, D). Similar to control group, paired-pulse facilitation of fEPSP-area was observed at inter-pulse intervals of 80 and 160 ms in both dorsal and ventral slices of kindled mice.

Discussion

Obtained data showed that similar to previous reports (Fanselow and Dong, 2010; Dubovyk and Manahan-Vaughan, 2018; Papatheodoropoulos, 2018), the neural excitability was higher in ventral compared to dorsal hippocampus in both control and kindled animals. Kindling-induced seizure significantly increased the excitability in ventral, but not in dorsal hippocampal CA1 area. However, the significant effect of kindling on short-term plasticity was observed only in dorsal hippocampus.

Comparing fEPSP-slope and fEPSP-area between dorsal and ventral hippocampal slices following PTZ kindling

Our results indicated that changes in the slope and the area of fEPSPs are clearly different in dorsal and ventral hippocampal slices of control and kindled groups. Paired-pulse facilitation or depression is usually assessed by measuring the slope of the field excitatory postsynaptic potential (fEPSP). It is generally assumed that the facilitation or depression of the fast, early phase of fEPSP slope results from presynaptic mechanisms (Zucker and Regehr, 2002). Nevertheless, the facilitation or depression of the slow late component of fEPSP (decaying phase of the fEPSP) assessed by measuring the area of the recorded fEPSP, appears to require a more

complicated interaction between both presynaptic and postsynaptic mechanisms (Davies et al., 1990; Nathan and Lambert, 1991; Davies and Collingridge, 1996). The slope and the area are distinct features of the fEPSP that reflect partially different cellular events. The fEPSP-slope mainly depends on the number of activated synapses while the fEPSP-area depends not only on the activated synapses, but also to the slow component of the postsynaptic potential produced by the significant contribution of NMDA receptors (Andersen et al., 1980; Forsythe and Westbrook, 1988; Andreasen et al., 1989; Zucker and Regehr, 2002; Pandis et al., 2006). In the present study, the fEPSP-slope was higher in ventral- than dorsal hippocampus in control group. This may be due to neurotransmitter release probability that is lower in the dorsal hippocampus (Papatheodoropoulos, 2018). It should be noted that along longitudinal axis of the hippocampus a dorsoventral gradient of the GABAergic interneurons density was shown in control animals. Therefore, it could be suggested that high density of GABAergic interneurons in dorsal hippocampus may be involved in the observed differences of evoked responses between dorsal and ventral hippocampus (Czéh et al., 2013).

Interestingly, in the slices of kindled animals, the fEPSP-area was higher in ventral than dorsal hippocampus. It may be explained according to the effect of seizure on postsynaptic components, especially glutamate receptors. PTZ facilitates the NMDA receptors activity through blocking the $GABA_A$ receptors (Thomsen and Dalby, 1998; Ekonomou and Angelatou, 1999; Zhu et al., 2015). Therefore, the most effectiveness of PTZ on fEPSP-area in ventral hippocampus might be accounted for by the greater contribution of NMDA receptors in the postsynaptic response in ventral- compared to dorsal hippocampus (Pandis et al., 2006). (There is a higher expression of NMDA receptors in ventral hippocampus (Dubovyk and Manahan-Vaughan, 2018)). In addition, NMDA receptors of dorsal and ventral hippocampus differ in their

subunit composition. In the ventral pole of hippocampus higher amounts of the NR2B subunit are expresses. These subunits have an essential role in PTZ kindling, and result in prolonged decay time in NMDA receptor-mediated currents (Nabekura et al., 2002; Pandis et al., 2006; Zhu et al., 2015).

Facilitation of EPSP-slope and EPSP-area in DH and VH

We found that PTZ kindled slices displayed significantly lower magnitude of paired-pulse facilitation of fEPSP-slope compared to the control slices at short inter-pulse interval (20 ms). The reduction in paired-pulse facilitation was only significant in dorsal part of hippocampus. Taking into account that the magnitude of the facilitation is inversely related to the initial probability of release (Katz and Miledi, 1968; Zucker, 1989; Dobrunz and Stevens, 1997), it could be argued that the decrease in paired-pulse facilitation of fEPSP-slope in kindled group may result from higher release probability following PTZ kindling. The same pattern of reduction in paired-pulse facilitation of fEPSP-slope was observed in ventral hippocampus; however, it was not statistically significant. This non-significant difference of paired-pulse facilitation of fEPSP-slope may be because of masking effect of higher neural excitability of ventral hippocampus in both control and kindled group.

It is generally assumed that presynaptic mechanisms that involve a transient increase in the probability of transmitter release underlie the phenomenon of facilitation (Zucker and Regehr, 2002). Complex interaction between several biological and biophysical factors that influence the release of neurotransmitter and the postsynaptic responses may affect the facilitation of EPSP (Dutta Roy et al., 2014). The most generally accepted hypothesis for a mechanism to explain paired-pulse facilitation has been "residual Ca^{2+} hypothesis" (Zucker, 1989; Kamiya and Zucker, 1994; Zucker and Regehr, 2002). According to this hypothesis, a portion of Ca^{2+} that enters

during the first stimulus remains in the presynaptic terminal and adds to the calcium influx that occurs in response to the second stimulus, then resulting greater release of transmitter and greater postsynaptic response to the second stimulus. The effect of this transient increase in the intracellular concentration of calcium lasts a few hundred milliseconds. Predictably, the facilitation based on this presynaptic mechanism is maximal at short inter-pulse intervals and decays as the time interval increases between two stimuli.

In control animals, when we used fEPSP-area for calculation of paired-pulse indices, the pattern of changes in these indices was differed from what measured for fEPSP-slope. Paired-pulse index for fEPSP-area showed facilitation optimally at inter-pulse interval of 160 ms, while very low facilitation was observed in paired-pulse index for fEPSP-slope at this inter-pulse interval. Considering the fact that paired-pulse index at inter-pulse interval of 160 ms can be affected by activation of $GABA_B$ receptors, and at inter-pulse interval of 20 ms is modified by $GABA_A$ receptors activation (Papatheodoropoulos and Kostopoulos, 2000; Cutsuridis et al., 2010), the different patterns of paired-pulse indices at low (20 ms) and high (160 ms) inter-pulse intervals may be related to the action of these two receptors. In fact, fEPSP-slope is a fast phenomenon while fEPSP-area is a function of both fast and slow components of synaptic responses. Therefore, paired-pulse facilitation measured based on fEPSP-slope or fEPSP-area may be differently affected by GABA receptors at low and high inter-pulse intervals (for review see (Papatheodoropoulos, 2018)).

We should consider that $GABA_B$ receptors (pre- and post synaptically) may be activated at IPI 160 ms, and their activation results in depression of the postsynaptic inhibition leading to facilitation of the postsynaptic excitatory potential n(Nathan and Lambert, 1991; Davies and Collingridge, 1996; Chalifoux and Carter, 2011). On the other hand, the inter-pulse interval of

160 ms is similar to frequency of ≈ 6-7 Hz, i.e. the theta oscillation in the hippocampus (Buzsáki, 2002). These oscillations are associated with learning and memory as well as increased synaptic plasticity (Colgin, 2013), dominates during exploratory movement (Bland, 1986) and stimulation protocols based on the theta frequency are especially effective in inducing LTP in the hippocampal synapses (Larson and Munkácsy, 2015). More studies are needed to characterize the specific mechanisms of action of PTZ and its effects on short-term plasticity of CA1 region in kindled animals.

Conclusion

Taken together, the available evidences indicate dorsoventral/long axis intrinsic diversification/segregation in excitability and neural network in the two poles of hippocampus and the different sensibility to PTZ kindling especially in short-term synaptic plasticity. Kindling-induced changes in short-term synaptic plasticity was significant only in dorsal hippocampal slices compared to control group. The difference in the responses of dorsal and ventral hippocampus may be related to the difference in the activity of their GABAergic neurons and therefore the changes in their ability to undergo synaptic plasticity. It is highlighted that enhancement of our knowledge about the neuronal circuit and micro circuitry and the differences in control and disease conditions like epilepsy will be helpful to find out the involved mechanism in memory and learning impairments of epileptic patients.

Conflict of interest statement

There is no conflict of interest.

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Figure 1

Figure 2

EPSP-slope

EPSP-area

A — fEPSP slope (μV/mS) vs Stimulus intensity; Control DH, Kindled DH

B — Area of fEPSP ($\times 10^3$ μV.mS) vs Stimulus intensity; Control DH, Kindled DH

C — fEPSP slope (μV/mS) vs Stimulus intensity; Control VH, Kindled VH

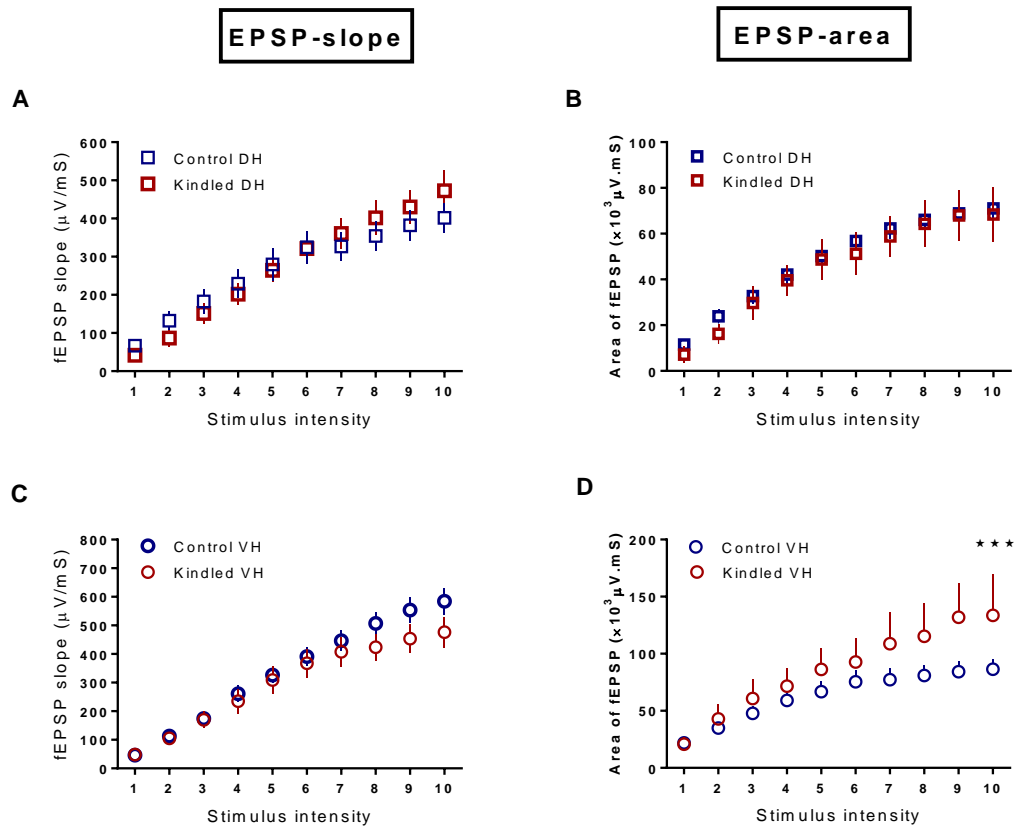D — Area of fEPSP ($\times 10^3$ μV.mS) vs Stimulus intensity; Control VH, Kindled VH
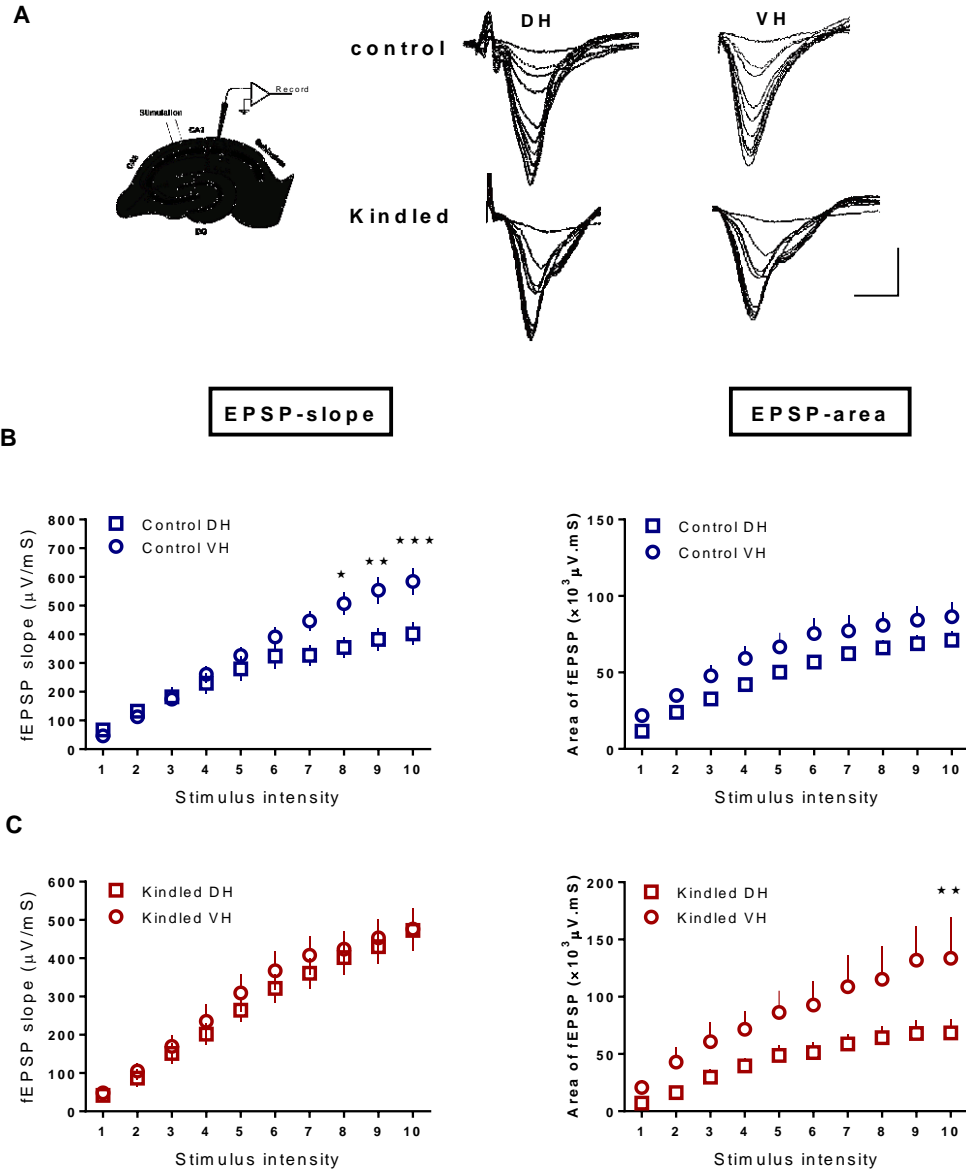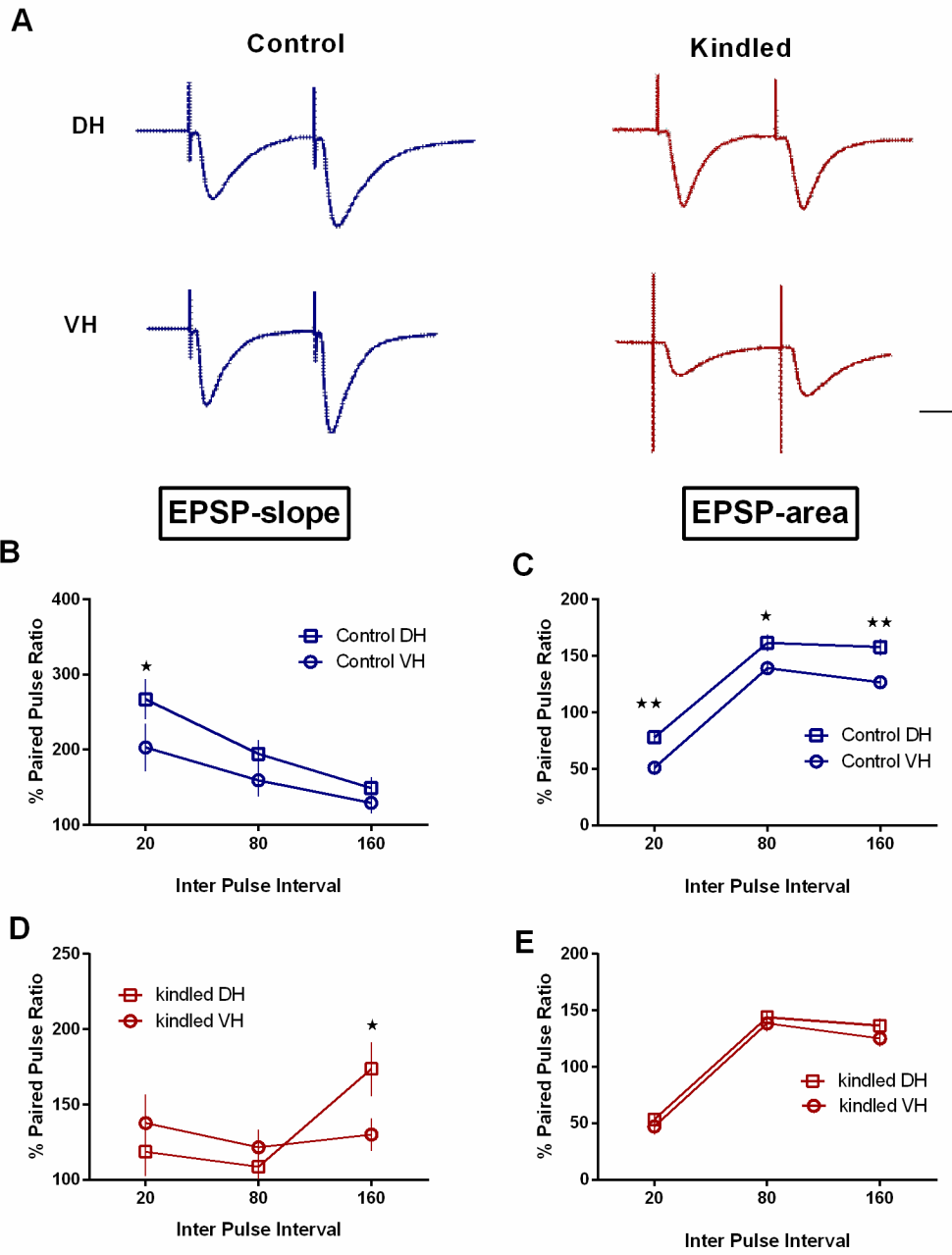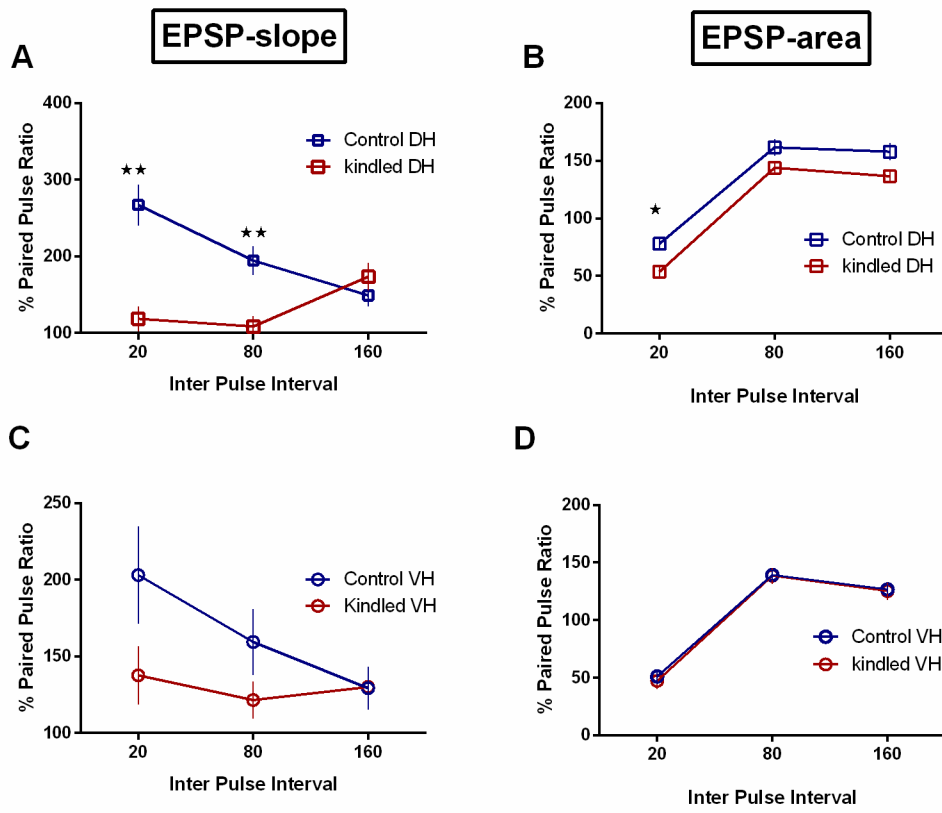
Figure 3

Figure 4

Figure legends:

Fig 1: Input-output curves in dorsal and ventral hippocampal slices of control and kindled mice. (A) Schematic location of stimulus electrode and recording electrodes in stratum radiatum layer of hippocampal CA1 region. Sample traces illustrating evoked fEPSPs in different steps of stimulus intensities applied to Schaffer collateral inputs to CA1 region of control and kindled group. (B) The input-output curve of fEPSP-slope (left graph) revealed a significance difference in dorsal hippocampus, compared to ventral hippocampus in high stimulus intensities. The input-output curve of fEPSP-area (right graph) showed no significant difference between dorsal and ventral hippocampus. (C) No difference in the input-output curve of fEPSP-slope (left graph) between dorsal and ventral hippocampus following PTZ kindling. The input-output curve of fEPSP-area (right graph) showed significant difference between dorsal and ventral hippocampus of PTZ kindled slices. Scale bar 0.2 mv, 5 ms. Data give the mean $\pm$ SEM. DH: dorsal hippocampus, VH: ventral hippocampus, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Fig 2: Comparing the input-output curves in dorsal and ventral hippocampal slices of control and kindled mice. (A,B) There was no significant difference in the input-output curve of fEPSP-slope (A) and -area (B) in dorsal hippocampus between control and kindled slices. (C) Comparing the input-output curves of control and kindled slices of ventral hippocampus showed no difference in fEPSP-slope, (D) but PTZ kindling changed the fEPSP-area of ventral hippocampus compared to control slices. Data give the mean $\pm$ SEM. DH: dorsal hippocampus, VH: ventral hippocampus, ***$p < 0.001$.

Fig 3: Comparing the paired pulse index in dorsal and ventral hippocampal slices of control and kindled mice. (A) Sample traces illustrating evoked paired pulse fEPSPs in inter-pulse interval of 20 ms applied to Schaffer collateral inputs to CA1 region of control (blue) and kindled (red) group. (B) Facilitation of fEPSP-slope at inter-pulse interval of 20 ms in dorsal hippocampus was significantly greater than ventral part of hippocampus in control mice. (C) Paired pulse ratio of fEPSP-area at all inter-pulse intervals was significantly greater in dorsal hippocampus in comparison with ventral hippocampus in control mice. (D) Facilitation of fEPSP-slope in dorsal hippocampus was greater than ventral hippocampus at inter-pulse interval of 160 ms in kindled slices. (E) PTZ kindled slices showed no significant difference in paired pulse ratio of fEPSP-area at different inter-pulse intervals between dorsal and ventral hippocampus. Scale bar 0.2 mv, 5 ms. Data give the mean ± SEM. DH: dorsal hippocampus, VH: ventral hippocampus, *p < 0.05, **p < 0.01.

Fig 4: Comparing the paired-pulse ratio of EPSP-slope and EPSP-area in dorsal and ventral hippocampal slices of control and kindled mice. (A) Comparison of paired pulse facilitation of fEPSP-slope in dorsal hippocampus of kindled slices with control group showed significant reduction at inter-pulse intervals of 20 and 80 ms. (B) Decrement of paired pulse ratio of fEPSP-area in dorsal hippocampus of kindled slices at inter-pulse intervals of 20 ms. (C) The changes of paired pulse ratio of fEPSP-slope in ventral hippocampus of kindled slices at inter-pulse intervals of 20 and 80 ms was not significant. (D) No significant difference was observed in paired pulse ratio of fEPSP-area in ventral hippocampus after PTZ kindling. Data give the mean ± SEM. DH: dorsal hippocampus, VH: ventral hippocampus, **p < 0.01.