Cellular and Molecular Neurobiology (2019) 39:287–300
https://doi.org/10.1007/s10571-018-00647-3

ORIGINAL RESEARCH

Transient Switching of NMDA-Dependent Long-Term Synaptic Potentiation in CA3-CA1 Hippocampal Synapses to mGluR$_1$-Dependent Potentiation After Pentylenetetrazole-Induced Acute Seizures in Young Rats

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Received: 20 August 2018 / Accepted: 29 December 2018 / Published online: 3 January 2019

Abstract

The mechanisms of impairment in long-term potentiation after status epilepticus (SE) remain unclear. We investigated the properties of LTP induced by theta-burst stimulation in hippocampal slices of rats 3 h and 1, 3, and 7 days after SE. Seizures were induced in 3-week old rats by a single injection of pentylenetetrazole (PTZ). Only animals with generalized seizures lasting more than 30 min were included in the experiments. The results revealed that LTP was strongly attenuated in the CA1 hippocampal area after PTZ-induced SE as compared with that in control animals. Saturation of synaptic responses following epileptic activity does not explain weakening of LTP because neither the quantal size of the excitatory responses nor the slopes of the input–output curves for field excitatory postsynaptic potentials changed in the post-SE rats. After PTZ-induced SE, NMDA-dependent LTP was suppressed, and LTP transiently switched to the mGluR$_1$-dependent form. This finding does not appear to have been reported previously in the literature. An antagonist of NMDA receptors, D-2-amino-5-phosphonovalerate, did not block LTP induction in 3-h and 1-day post-SE slices. An antagonist of mGluR$_1$, FTIDS, completely prevented LTP in 1-day post-SE slices; whereas it did not affect LTP induction in control and post-SE slices at the other studied times. mGluR$_1$-dependent LTP was postsynaptically expressed and did not require NMDA receptor activation. Recovery of NMDA-dependent LTP occurred 7 day after SE. Transient switching between NMDA-dependent LTP and mGluR1-dependent LTP could play a role in the pathogenesis of acquired epilepsy.

Keywords Long-term potentiation · Group I mGlu receptor · mGluR-dependent plasticity · NMDA receptor · Epilepsy · Animal model

Introduction

Prolonged continuous epileptic seizures (i.e., status epilepticus [SE]) in humans often result in disturbances in cognitive functions, especially memory (Halgren et al. 1991; Lynch et al. 2000; Mameniskiene et al. 2006; Thompson 1991). In animal models, even single episodes of convulsive status seizures can lead to memory deficiency (Aniol et al. 2013; Kalemenev et al. 2015). The mechanisms responsible for memory deficits after seizures are not entirely clear. One mechanism may be neuronal loss in the hippocampus, a structure that plays an important role in memory consolidation processes (Dudai et al. 2015). Neuronal loss has frequently been observed in human epilepsy (Malmgren and Thom 2012; Mathern et al. 2002) and animal models (Holmes 2002; Wolf et al. 2016). However, memory deficiencies following SE can persist for a long time, even in the absence of neuronal loss (Zhou et al. 2007). This finding suggests that, in addition to neuronal loss, some synaptic and molecular mechanisms of memory formation may be altered in human epilepsy. The ability of synapses

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to undertake long-term increases or decreases in strength in response to activity patterns is thought to be crucial for the processes of learning and memory formation. Currently, long-term potentiation (LTP) and long-term depression (LTD) are widely accepted experimental models to explore synaptic mechanisms of memory; with Schaffer collateral inputs to CA1 synapses the most common object of such studies (Bliss and Collingridge 1993; Ju et al. 2004). Both forms of plasticity typically require the activation of NMDARs to initiate the insertion or removal of AMPARs from the synapse (Huganir and Nicoll 2013). However, LTP and LTD are not unitary phenomena, and their mechanisms vary depending on the synapses and conditions in which they operate (Malenka and Bear 2004). For example, the coexistence of two distinct activity-dependent systems of synaptic plasticity: one that is based on the activation of NMDARs and the other one based on the involvement of mGluRs was recently described in the same synapses (Wang et al. 2016).

Studies in animal models of epilepsy have shown substantial impairment of hippocampal LTD and LTP after epileptic seizures (Carpenter-Hyland et al. 2017; Cunha et al. 2015; Ivanov and Zaitsev 2017; Kryukov et al. 2016; Muller et al. 2013; Plata et al. 2018; Postnikova et al. 2017; Zhou et al. 2007). Despite numerous studies, the exact mechanisms of impairment of LTP and LTD after SE remain unidentified. It was reported that alterations in the expression level and subunit composition of NMDARs determine changes in synaptic plasticity after seizures (Amakhin et al. 2017; Di Maio et al. 2013; Muller et al. 2013; Peng et al. 2016; Postnikova et al. 2017). We propose the following hypothesis: if several mechanisms of plasticity coexist in the same synapse, after SE, alterations in NMDAR- and mGluR-dependent mechanisms of LTP may vary, and their relative roles in plasticity may change.

To test this hypothesis, we used the pentylenetetrazole (PTZ) model of epileptic seizures. SE induced by a single injection of PTZ, an antagonist of gamma-aminobutyric acid type A receptors, typically does not result in substantial loss of neurons or the development of spontaneous recurrent seizures (Aniol et al. 2011; Gallyas et al. 2008; Vasil'ev et al. 2014, 2018). However, it leads to cognitive impairment (Aniol et al. 2013). In this study, we investigated the effect of PTZ-induced SE on the magnitude of LTP in CA3-CA1 hippocampal synapses in rats and examined the impact of NMDAR- and mGluR-dependent mechanisms on LTP induction. Furthermore, we investigated whether spatial learning of post-SE rats was altered after PTZ-induced SE.

Materials and Methods

Animals

Wistar rats aged 20–22 days (35–40 g) were used in this study. All the rats were kept under standard conditions at room temperature, with free access to water and food. All the experiments were carried out in accordance with the Guidelines on the Treatment of Laboratory Animals effective at the Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences, and these guidelines comply with Russian and international standards. The animal experiments in this study were approved by the Sechenov Institute of Evolutionary Physiology and Biochemistry Ethics Committee. All efforts were made to minimize the number and suffering of animals used.

PTZ Model of Acute Seizures

Seizures were evoked by intraperitoneal administration of PTZ (70 mg/kg; Sigma, USA) dissolved in saline. Only animals with generalized tonic-clonic seizures lasting at least 30 min (i.e., exhibited SE) were included in further experiments. The control rats were given a normal saline solution at the same age.

Hippocampal Brain Slice Preparation

Acute brain slices were prepared as described previously (Plata et al. 2018) from PTZ-induced SE (post-SE) rats and control rats following decapitation and removal of brains. Horizontal 400-μm-thick brain slices containing the dorsal hippocampus were cut using a vibratome (HM 650V; Microm International, Germany) in ice-cold artificial cerebrospinal fluid (ACSF). ACSF composed of 126 mM NaCl, 24 mM $NaHCO_3$, 2.5 mM KCl, 2 mM $CaCl_2$, 1.25 mM NaH_2PO_4, 1 mM $MgSO_4$, and 10 mM glucose was bubbled with carbogen (95% O_2 and 5% CO_2). The slices were then transferred to oxygenated ACSF and incubated for 1 h at 35 °C before electrophysiological recordings.

Field Potential Recordings

For the electrophysiological study, the hippocampal slices were transferred to a recording chamber, where they were perfused with a constant flow of ACSF at a rate of 5 mL/min at 25 °C for 15–20 min before the recordings. Extracellular field excitatory postsynaptic potentials (fEPSPs) were registered from the CA1 stratum radiatum using glass microelectrodes (0.2–0.8 MΩ). Synaptic responses were evoked by local extracellular stimulation of the Schaffer collaterals using a twisted nichrome electrode placed in the stratum radiatum at the CA1–CA2 border, approximately 500–1000 µm away from the stimulating electrode. At the beginning of each experiment, input/output (I/O) relationships were measured by increasing the current intensity from 25 to 300 µA (current step = 25 µA) via an A365 stimulus isolator (WPI, USA). fEPSPs were registered using a Model 1800 amplifier (A-M Systems, USA) and were digitized and recorded to a personal computer using ADC/DAC NI USB-6211 (National Instruments, USA) and WinWCP v5.x.x software (University of Strathclyde, UK). The electrophysiological records were investigated using the Clampfit 10.2 program (Axon Instruments, USA). The amplitude and slope of the 20–80% rising phase were measured for each fEPSP. The paired-pulse ratio (PPR, the interstimulus interval of 50 ms) was measured as the ratio of the second fEPSP amplitude with respect to the first fEPSP amplitude.

LTP of Excitatory Synaptic Transmission

LTP was examined 3 h and 1, 3, and 7 days after the seizures. The value of the stimulation current was adjusted to elicit a response with a magnitude of 40–50% of maximal and was then fixed at this level. The slices received one paired stimulation pulse (interstimulus interval, 50 ms; duration of the pulse, 0.1 ms) every 20 s. Once unchanging fEPSPs were obtained for 20–25 min (baseline), theta-burst stimulation (TBS) protocol (5 trains applied five times every 10 s consisting of 5 bursts of 5 100-Hz pulses; interburst interval—200 ms, Fig. 1a) was applied to induce LTP. fEPSPs were recorded 40 min after LTP induction. The LTP magnitude was defined as the average slope of the fEPSP 30–40 min after the TBS normalized to the mean value of the slope for the 10-min period immediately before the TBS.

Two groups of control rats were tested 1 day (*n* = 39 slices) and 7 days (*n* = 8) after saline injection (22- and 28-days-old, respectively). No difference was found between these two groups. Therefore, we compared LTP properties in the post-SE rats with that in the 22-days-old control group.

Drugs

4-[1-(2-fluoropyridin-3-yl)-5-methyltriazol-4-yl]-N-methyl-N-propan-2-yl-3,6 dihydro-2H-pyridine-1-carboxamide (FTIDC) (5 µM), a potent and selective antagonist of mGlu_1 receptors, was purchased from Alomone Labs. D-2-amino-5-phosphonovalerate (AP-5) (50 µM), a competitive NMDAR antagonist, was obtained from Sigma (St. Louis, MO). These drugs used for the electrophysiology experiments were diluted in distilled water and bath-applied.

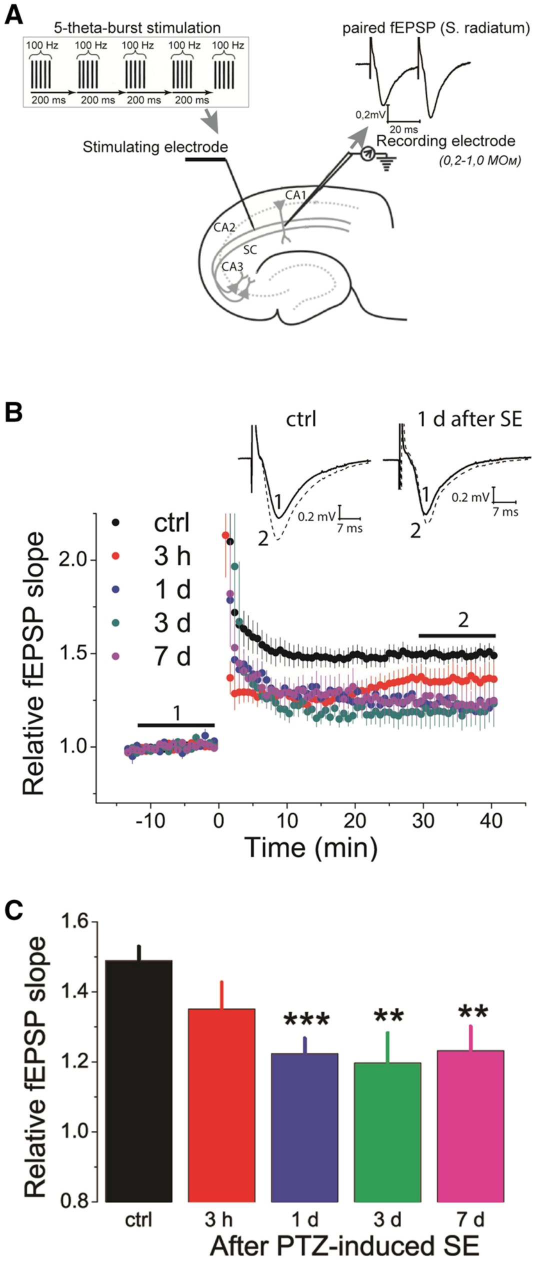

Fig. 1 LTP is attenuated in the CA1 hippocampal area after PTZ-induced SE. **a** Schema showing the positions of electrodes in the hippocampus, parameters of TBS protocol for LTP induction, and representative example of fEPSP. **b** Diagram showing the normalized slope of fEPSP in control (ctrl) and post-SE groups (3 h; 1 day; 3 days; 7 days) before and after TBS. The inset (above) shows the examples of fEPSP before induction (1) and 40 min after TBS (2). **c** Diagram illustrating differences in LTP value between groups. All data in this and the following figures are presented as a mean ± standard error of the mean. One-way ANOVA $F_{4,79}$ = 5.82, $p < 0.001$; LSD post hoc test, the significant difference with control group: $^{**}p < 0.01$, $^{***}p < 0.001$

Whole-Cell Patch Clamp Recording of mEPSCs

Visualization of CA1 pyramidal neurons was done using a BX51WI microscope (Olympus, Japan) equipped with differential interference contrast optics and a Watec video camera (model WAT-127LH, USA). Patch electrodes (2–4 MΩ) were filled with an internal solution containing 114 mM K-gluconate, 10 mM HEPES, 6 mM KCl, 4 mM ATP-Mg, 4 mM ATP-Mg, and 0.2 mM EGTA. pH was adjusted to 7.25 with KOH. Pyramidal neurons were voltage-clamped at − 80 mV. Access resistance was 15–20 MΩ and remained stable during the experiments (≤ 30% increase) for the cells included in the analysis. Recordings of mEPSCs were done at 30 °C. Tetrodotoxin (0.5 µM, Sigma) was added to prevent the spontaneous firing of neurons and evoked release of glutamate., Bicuculline (10 µM; Sigma), an antagonist of gamma-aminobutyric acid type A receptors, and AP-5 (50 µM; Sigma) were added to the recording solution to isolate AMPAR-mediated responses pharmacologically. Clampfit 10 software (Molecular Devices Corporation, USA) was used for detection and analysis of mEPSCs.

Open Field Test

Behavioral tests were started 7 days after PTZ or saline injections. They were performed during the period of high activity in rats (from 6:00 PM to 10:00 PM). Video registration of spontaneous locomotor–exploratory behavior in a circular open field arena (1 m diameter) was conducted. The illuminance was set at 40 lx on the surface of the arena. Each rat was tested twice on consecutive days, with each session lasting 5 min. The experimental arena was carefully wiped after each animal had explored the arena.

Analysis of the distances covered was performed using custom software Pole 7 (Institute of Experimental Medicine, St. Petersburg, Russia). The index of habituation was defined as the ratio of the distance traveled on the second day versus that on the first day (in %).

Morris Water Maze (MWM)

Ten days after PTZ-induced SE, hippocampal-dependent spatial learning and memory were tested using the MWM as previously described (Kalemenev et al. 2015). A 1.5-m diameter circular pool was filled with water made opaque by the addition of milk. A square platform 10 × 10 cm (clear plexiglass) was placed approximately 1 cm below the surface of the water. It was positioned in a fixed location. There were clues on the walls of the pool (four geometric figures). The water temperature was maintained at 23 °C. The ability of the rats to locate the hidden platform in the MWM was tested over a 4-days period. Daily training comprised of four trials with 90-s intervals. The animals were placed in the pool in a pseudorandom order at one of four start points (N, S, W, or E), with their snouts pointing to the wall. The start position was varied in each trial. Learning was estimated according to the reduction in the time spent seeking the platform and to the decrease in trajectory length. The movement of the rats was monitored by a video camera, with subsequent analysis performed using custom "Tracking" software (Institute of Experimental Medicine, St. Petersburg, Russia).

Statistical Analysis

All numerical values were expressed as the mean ± the standard error of the mean (SEM), and all error bars on graphs represent the SEM. Statistical significance was determined using an unpaired Student's *t*-test for independent samples (two groups) or one-way analysis of variance (ANOVA) (≥ 3 groups), with Fisher's least significant difference (LSD) post hoc test.

The results were considered significant when $p < 0.05$. All data are presented as the mean, with the SEM.

Results

LTP was Attenuated in the CA1 Hippocampal Area After PTZ-Induced SE

We examined TBS-induced LTP at CA3-CA1 synapses in acute hippocampal brain slices from control and post-SE rats. LTP was measured at different time points after PTZ-induced SE: 3 h ($n = 12$ slices), 1 day ($n = 13$), 3 days ($n = 9$), and 7 days ($n = 11$). Control rats ($n = 39$) were tested 1 day after saline injection. TBS resulted in robust LTP in hippocampal CA1 neurons of control rats (1.49 ± 0.04 of baseline). The post-SE rats showed significantly reduced LTP as compared with that in the control rats (Fig. 1b, c, $F_{4,79} = 5.82$, $p < 0.001$,). The post hoc test revealed that 3 h after SE, there was no difference in the level of LTP as compared with the control value (1.35 ± 0.08, $p > 0.05$). However, LTP was significantly decreased 1, 3, and 7 days after SE (1 day: 1.22 ± 0.04, $p < 0.001$; 3 days: 1.20 ± 0.09, $p < 0.01$; 7 days: 1.23 ± 0.07, $p < 0.01$). These results demonstrated that LTP is diminished in the CA1 hippocampal area after PTZ-induced SE.

AMPAR-Mediated Excitatory Synaptic Responses were Not Enhanced in Post-SE Rats

The decrease in the magnitude of LTP in post-SE rats might be explained by the saturation of synaptic responses caused by previous epileptic activity (Cunha et al. 2015; Schubert et al. 2005). An earlier study suggested that epileptiform activity led to NMDAR-dependent enhancement of AMPAR-mediated transmission of CA3-CA1 synapses, thereby preventing additional synaptic potentiation (Abegg et al. 2004). Such a saturation effect in response to both experimental and pathological conditions has been observed in many studies (Moser and Moser 1999; Remigio et al. 2017; Schubert et al. 2005; Weng et al. 2011). To test whether the saturation effect took place in our experimental model, we performed two sets of experiments. First, we recorded mEPSCs in CA1 pyramidal neurons in control and 1 day post-SE groups (Fig. 2). An increase in the mEPSC amplitude would confirm the saturation of synapses. The amplitude (control: 23.5 ± 0.9 pA, $n = 7$ vs. post-SE: 27.3 ± 1.7 pA, $n = 8$, $p > 0.05$) did not change significantly. The kinetic properties of mEPSCs have not changed either (20–80% rise time in control: 0.72 ± 0.08 ms vs. post-SE: 0.73 ± 0.09 ms; tau in control: 5.2 ± 0.4 vs. post-SE: 4.6 ± 0.4). These data suggested that PTZ-induced seizures did not alter the quantal size of synaptic responses and, consequently, the synapses were not saturated. The frequency of events (control: 0.26 ± 0.03 Hz, $n = 7$ vs. post-SE: 0.22 ± 0.03 Hz, $n = 8$, $p > 0.05$) also remained unchanged. Second, as the postsynaptic target and presynaptic origin of spontaneous and evoked release may differ (Peled et al. 2014; Ramirez and Kavalali 2011), we performed experiments to investigate the I/O relationships for the amplitude of fEPSPs recorded in CA1 (Fig. 3). A steeper slope in the I/O curve would indicate an increase in synaptic strength. To exclude the possible contribution of NMDARs to the fEPSP magnitude, the recordings were done in the presence of AP-5 (50 µM). The results revealed that the shapes of the I/O curves for the fEPSP amplitudes did not change significantly in post-SE slices as compared with those in

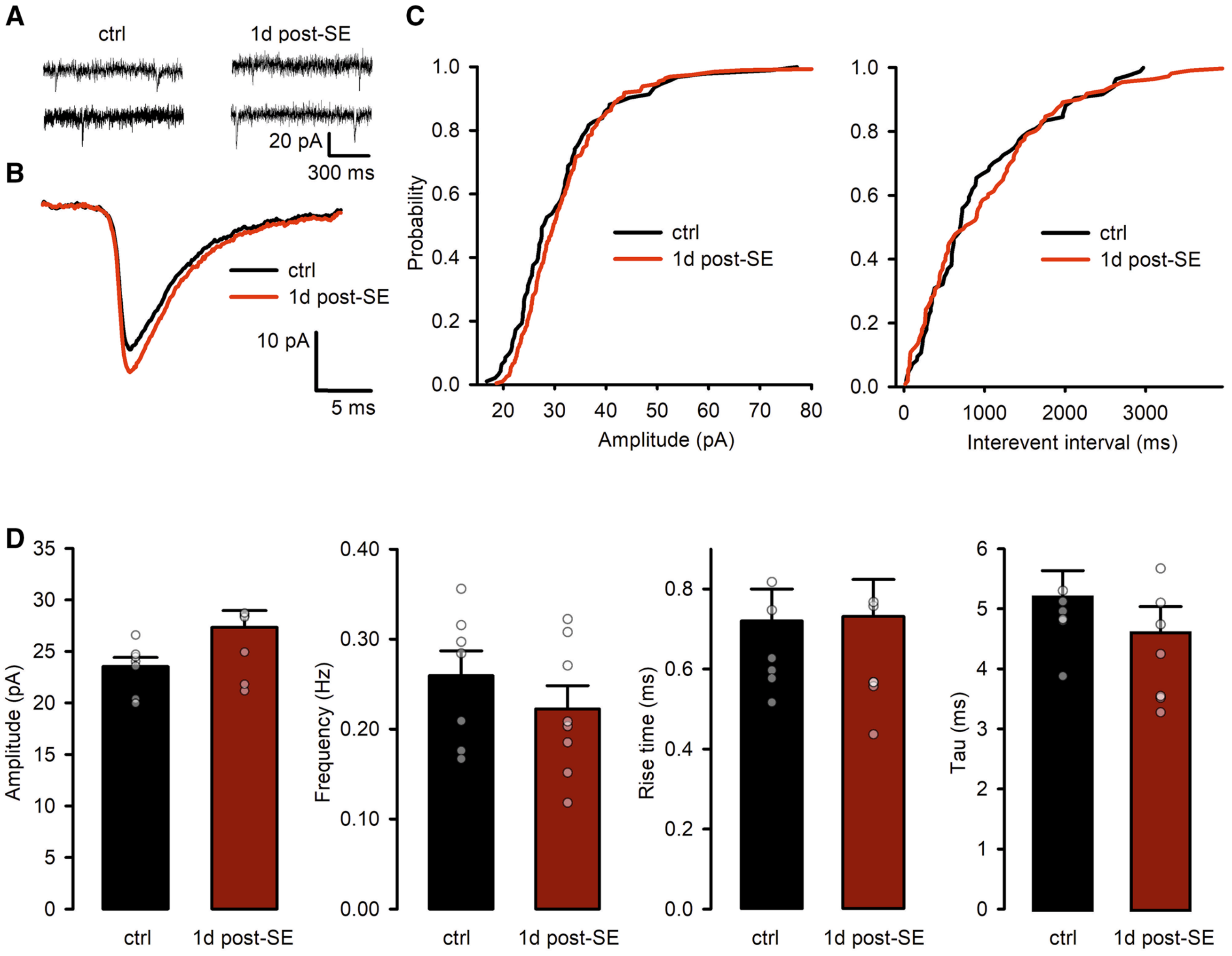

Fig. 2 Properties of mEPSCs do not change after PTZ-induced SE. **a** Representative examples of recording traces for CA1 pyramidal neurons in control and post-SE slices. **b** The representative examples of averaged mEPSC in control (shown in black) and post-SE (red) are superimposed. **c** Representative examples of cumulative amplitude and frequency histograms. **d** Diagrams showing the average amplitude, frequency, 20–80% rise time, and tau decay of mEPSCs in two groups. Note that all parameters do not differ. Circles represent individual data points

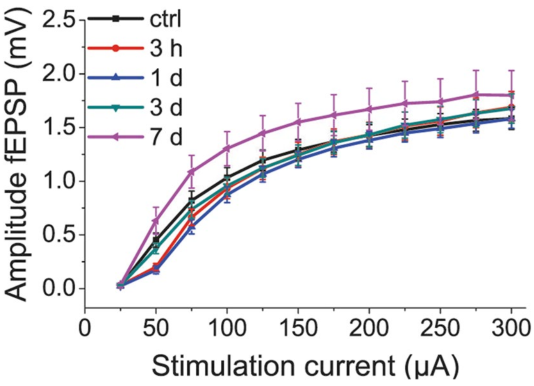

Fig. 3 Input/output relationships for fEPSP amplitudes recorded from the hippocampal CA1 area. Recordings were done in the presence of AP-5. Each point represents the mean and standard error of the mean

control (Fig. 3, repeated-measures ANOVA, $F_{44,1111} = 1.35$, $p = 0.07$). Therefore, the data suggested that excitatory synaptic responses were not enhanced in post-SE rats and that the decline in the magnitude of LTP could not be explained by the saturation of synapses.

LTP Induction was Transiently NMDA Independent After PTZ-Induced Seizures

The weakening of LTP induction may be determined by impairment of molecular mechanisms of induction caused by SE. Previously, we found that PTZ-induced convulsions resulted in multiple disturbances in the hippocampus, including morphological alterations (Vasilev et al. 2018; Zaitsev et al. 2015) and changes in the subunit composition of NMDARs (Postnikova et al. 2017). A number of previous studies showed the induction of LTP was due to the activation of NMDARs in the CA1 region of the hippocampus (Bliss and Collingridge 1993; Citri and Malenka 2008; Grover et al. 2009; Malenka and Nicoll 1993; Mayford et al. 2012; Neves et al. 2008).

To determine whether the NMDAR-dependent mechanism of LTP induction remained unaltered after SE, LTP was induced in the presence of the NMDAR antagonist AP-5 (50 μM) (Fig. 4). In control slices, inhibition of NMDARs by AP-5 resulted in a significant reduction in LTP magnitude (ACSF + AP-5: 1.12 ± 0.04, $n = 12$; ACSF: 1.49 ± 0.04, $n = 39$, t-tests = 6.54; $p < 0.001$, Fig. 4a). These data are in line with those of previous reports (Bliss and Collingridge 1993; Citri and Malenka 2008; Grover et al. 2009; Malenka and Nicoll 1993; Mayford et al. 2012; Neves et al. 2008), which found that the activation of NMDARs was involved in LTP induction in hippocampal CA1 neurons. In post-SE rats, the effect of AP-5 on LTP induction differed from that in the control animals. Despite AP-5-induced inhibition of NMDARs, TBS induced moderate potentiation of synaptic responses in slices from two post-SE groups (3 h: 1.18 ± 0.07, $n = 11$; 1 day: 1.27 ± 0.07, $n = 15$, Fig. 4b, c), and these LTP values did not differ from those observed without inhibition of NMDARs. Therefore, NMDAR activation was not required to induce LTP in hippocampal synapses 3 h and 1 day after PTZ-induced SE. Later, 3 days and 7 days after SE, inhibition of NMDARs completely prevented LTP induction in slices (1.06 ± 0.06, $n = 12$ and 1.05 ± 0.05, $n = 10$, accordingly; Fig. 4d, e). These results pointed to transient activation of a mechanism that did not involve NMDARs in LTP induction at CA3-CA1 excitatory synapses in post-SE rats.

An mGluR$_1$-Dependent Form of LTP was Temporarily Observed After SE

The enhancement of fEPSPs induced by TBS in the presence of AP-5 developed relatively slowly and reached a maximum in 25–40 min. A similar time course of EPSP enhancement was shown in a study in which LTP was chemically induced by an mGluR agonist, 1S,3R-ACPD, in the CA1 hippocampal area (Bortolotto and Collingridge 1993). A previous study reported a slowly developed group I mGluR-dependent LTP of CA3-CA1 synapses after high-frequency tetanus stimulation in the absence of NMDAR activation (Wang et al. 2016). To test whether the observed LTP was group I mGluR-dependent in a subsequent LTP experiment, we bath-applied FTIDC (5 μM), which is a specific mGluR$_1$ antagonist (Suzuki et al. 2007). The results revealed that mGluR$_1$ inhibition by FTIDC did not affect the magnitude of LTP in the control group (Fig. 4a, FTIDS: 1.41 ± 0.06, $n = 15$, t-test = 1.17, $p = 0.25$). The FTIDS application also did not affect LTP induction in any of the post-SE groups (Fig. 4b, d, e) other than in the 1-day post-SE group (Fig. 4c; 1.04 ± 0.06, $n = 13$, t-test = 2.50, $p < 0.05$). These findings suggested that SE transiently activated the group I mGluR-dependent form of LTP that is usually hard to induce in CA3-CA1 synapses.

The Locus of LTP Expression Did Not Change in Post-SE Rats

Next, we attempted to identify the LTP expression locus. Previous research suggested that the PPR change may indicate a presynaptic locus of expression and may be associated with changes in neurotransmitter release probability (Buonomano 1999; Zaitsev and Anwyl 2012). We assumed that constant PPR indicated a postsynaptic locus of expression. We compared the PPR before (baseline) and after the induction of LTP (Fig. 5). In the control group, the PPR did not change after TBS (baseline: 1.38 ± 0.02; after potentiation, 1.35 ± 0.03; $n = 38$; paired t-test = 1.50,

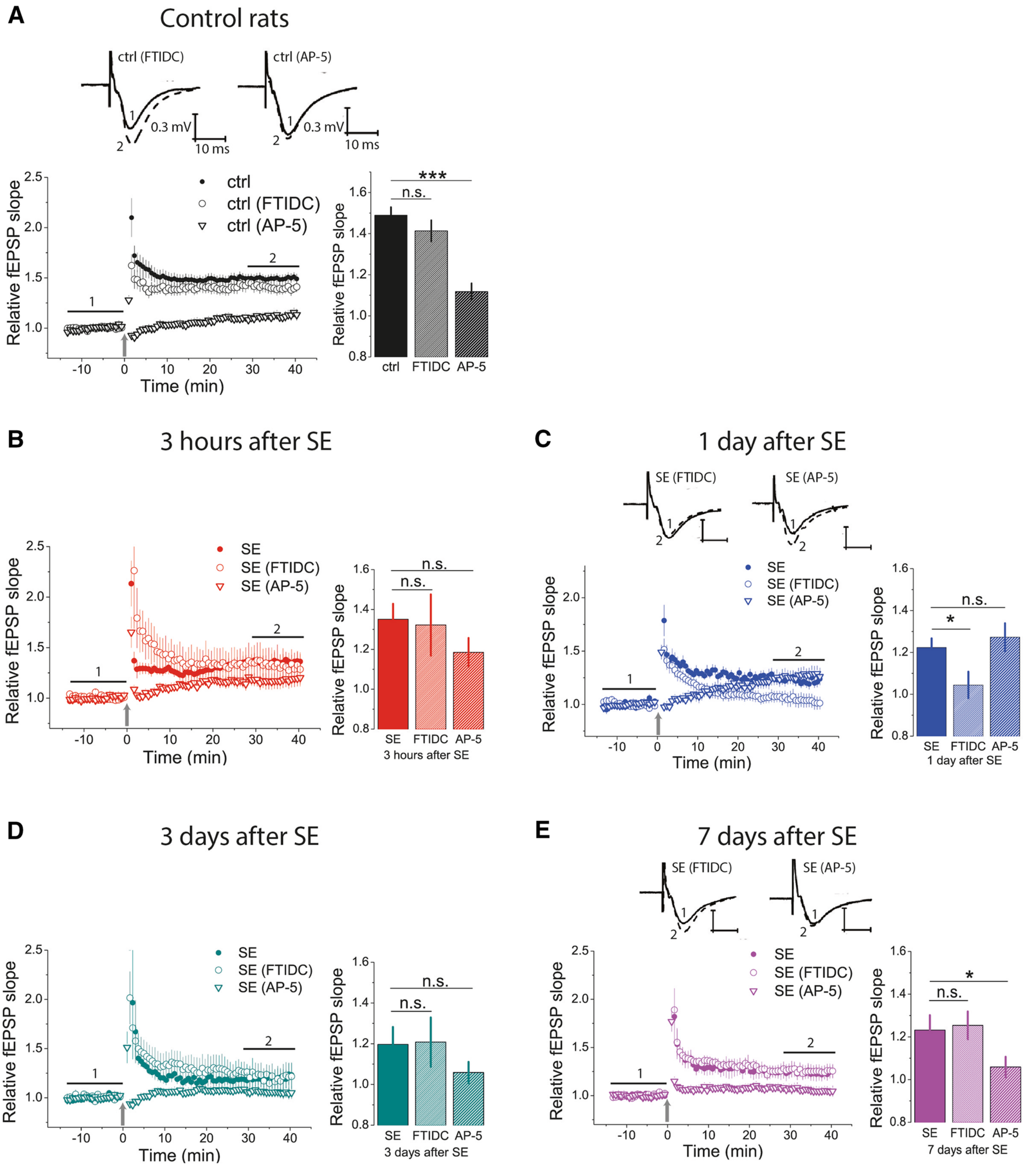

Fig. 4 NMDAR-dependent mechanism of LTP induction is disturbed following PTZ-induced SE. Diagrams showing the normalized slope of fEPSP in control (**a**) and post-SE groups (**b**–**e**: 3 h; 1 day; 3 days; 7 days after PTZ-induced SE). Black circles: LTP experiments in control slices without NMDAR or mGluR blockade, regular ACSF (ctrl) was used; filled color circles: LTP experiments in control slices in post-SE slices without NMDAR or mGluR blockade (SE); open circles: experiments conducted while mGluRs were selectively blocked by FTIDS (5 µM); open triangles: experiments conducted while NMDARs were blocked by D-AP5 (50 µM). On the right of each panel: bar graphs (means ± SEM) showing the effect of mGluR inhibition by FTIDS and NMDAR inhibition by AP-5 on LTP magnitude in different groups (t-test, *n.s.* no significant differences, $*p<0.05$, $***p<0.001$)

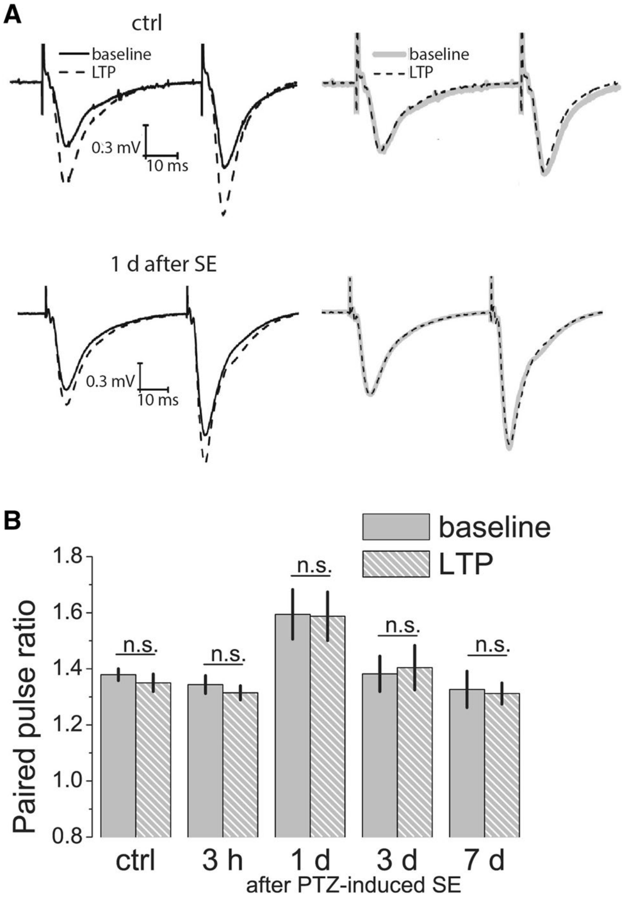

Fig. 5 The ratio of fEPSP amplitudes before and after the TBS. **a** Representative examples of fEPSP responses before induction (baseline) and 40 min after induction of plasticity (LTP) in hippocampal field CA1 from the control group (control) and the post-SE group. On the right hand side, the same recordings with LTP traces normalized to the 1st responses in baseline recordings. **b** Diagram showing that the PPR before and after the TBS in different groups. Note that PPR does not change after the induction protocol in any group

$p = 0.14$); the PPR did not change in any of the post-SE groups (Fig. 5). These data suggest a postsynaptic site of LTP expression.

Of note, the paired-pulse facilitation of responses in the rats 1 day after SE was initially higher (1.59 ± 0.09, $n = 12$) than that in the control group (1.38 ± 0.02, t-test = 2.36, $p < 0.05$). This finding may indicate a decrease in the probability of release of the excitatory mediator glutamate in the synapses of the hippocampus after seizures.

Post-SE Rats Exhibited Hippocampal-Dependent Spatial Memory Deficits

To investigate whether the behavior of the post-SE rats was altered, we performed two behavioral tests 7–13 days after PTZ administration.

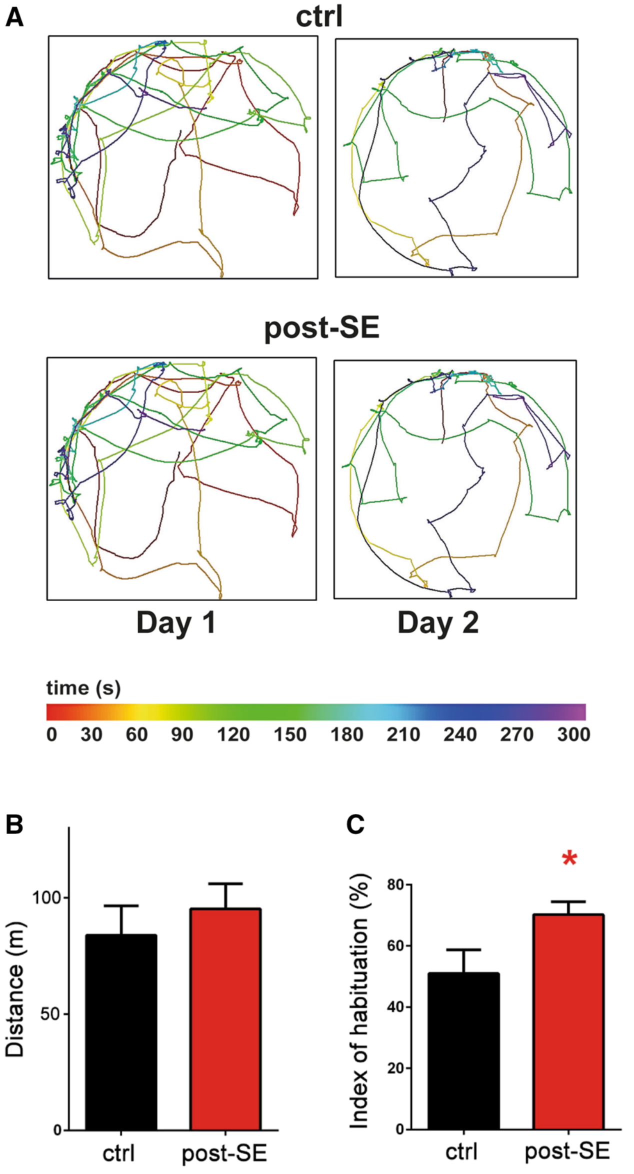

Fig. 6 Post-SE rats exhibited hippocampal-dependent spatial memory deficits in the open field test. **a** The representative tracks of control and post-SE rats in open field arena in two consecutive days. **b** The diagram showing no differences in the distance traveled of the control ($n = 7$) and post-SE ($n = 7$) rats (t-test = 0.69; $p = 0.51$). **c** Diagram showing that habituation of investigative behavior is more expressed in the control rats ($t = 2.18$; $p = 0.05$)

Open Field Test

The animals were tested on two consecutive days. On the first day, their reactions to the new space were evaluated by the distance traveled (Fig. 6a). There were no differences in the reactions of the control ($n = 7$) and post-SE ($n = 7$) rats (t-test = 0.69; $p = 0.51$; Fig. 6b). Habituation of activity in the open field was measured as the ratio of the distance traveled on the second day vs. that on the first day (in %). Habituation of investigative behavior was more expressed in the control rats ($t = 2.18$; $p = 0.05$; Fig. 6c). Attenuation of habituation may indicate space memory impairment in the experimental rats.

MWM

In the MWM, spatial learning ability was assessed by changes in the traveling distance before the hidden platform was found (Fig. 7a). The post-SE and control rats did not differ in this parameter (Fig. 7b, two-way ANOVA $F_{15,180} = 0.62$; $p = 0.86$). Taken together, these results demonstrated that the post-SE rats possessed only mild impairments in spatial memory.

Discussion

The NMDAR-Dependent LTP Induction Mechanism was Altered After SE

In this study, we revealed that generation of LTP in the hippocampus was diminishing for at least 1 week after SE induced by intraperitoneal administration of PTZ. Previous studies proposed that the diminishing of LTP might be explained by the saturation of synaptic responses caused by epileptic activity (Abegg et al. 2004; Cunha et al. 2015; Debanne et al. 2006). Epileptic activity enhances the AMPAR-mediated transmission of CA3-CA1 synapses through the NMDA-dependent mechanism, thereby preventing additional synaptic potentiation (Abegg et al. 2004). We suggested that saturation did not occur in the present study, as evidenced by the lack of changes in both the shape of the

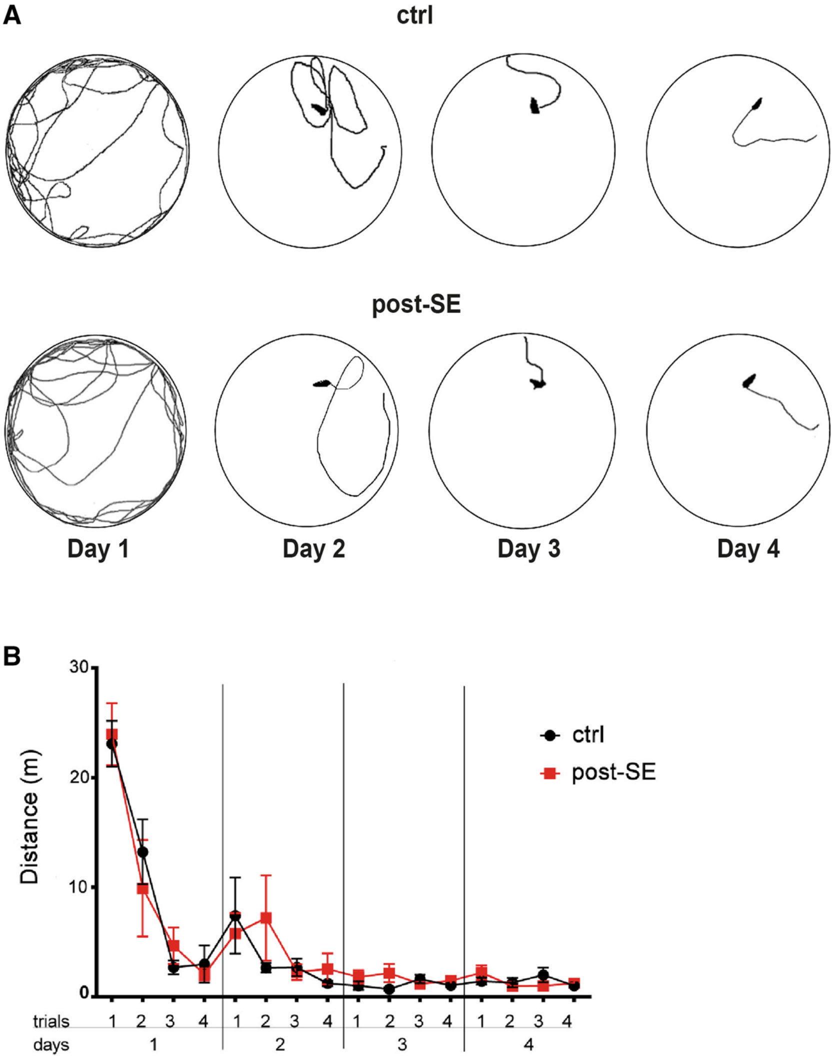

Fig. 7 The dynamic of learning in MWM of the control and post-SE rats. **a** The ability of the rats to locate the hidden platform in the MWM was tested over a 4-days period. Daily training comprised four trials with 90-s intervals. The diagrams show the representative tracks of control and post-SE rats in the pool for the first trials in each day. **b** The post-SE ($n = 7$, red line) and control ($n = 7$, black line) rats did not differ in the trajectory length (two-way ANOVA $F_{15,180} = 0.62$; $p = 0.86$)

I/O curves for fEPSPs and the amplitude of mEPSCs in the post-SE group.

Epileptic seizures may alter the functional properties of NMDARs, which in turn may weaken LTP. For example, in a lithium-pilocarpine model of epilepsy, SE led to the fast relocation of obligate GluN1 subunits from the interior to the cell surface and an increasing number of NMDARs per synapse (Naylor et al. 2013). The incorporation of already existing NMDARs into the synapses may be accompanied by alterations in gene expression of different NMDAR subunits. Stronger inhibition of NMDAR-mediated responses by ifenprodil in post-SE animals suggested that the proportion of GluN2B-containing NMDARs increased in an SE model (Amakhin et al. 2017; Naylor et al. 2013). Recently, we showed that 3 h after PTZ-evoked convulsions, the mRNA expression of the GluN1 subunit augmented considerably in the hippocampus indicating a growth in the number of NMDARs (Postnikova et al. 2017). In the same study, 24 h after PTZ-evoked convulsions, we found an increased mRNA level of GluN2B subunit suggesting growth in the proportion of GluN2B-containing NMDARs.

The properties of NMDARs depend on their subunit composition (Cull-Candy et al. 2001; Paoletti et al. 2013). The prevalence of NMDARs with particular subunit compositions may vary the sign of synaptic plasticity. Genetic and pharmacological evidence has implicated GluN2A subunits in generating LTP and GluN2B subunits in triggering LTD (Liu et al. 2004; Paoletti et al. 2013; Sakimura et al. 1995). GluN2A-knockout mice exhibited reduced LTP at CA3–CA1 synapses (Sakimura et al. 1995), whereas the loss of GluN2B abolished LTD (Brigman et al. 2010). Ifenprodil or Ro 25-6981 (GluN2B-selective antagonists) specifically blocked LTD, whereas NVP-AAM077, a GluN2A-preferring antagonist, inhibited LTP but not LTD (Liu et al. 2004). However, other studies showed that both GluN2A and GluN2B subunits play roles in LTP and LTD (Bartlett et al. 2007; Fox et al. 2006). It was suggested that the GluN2A and GluN2B subunit production ratio is more significant than either subunit alone in determining the sign of synaptic plasticity (LTP vs. LTD) (Xu et al. 2009).

Another possible mechanism that can affect NMDAR-dependent plasticity is the redistribution of receptors of different subunit composition between extrasynaptic and synaptic sites after seizures. The increased localization of the GluN2B subunit in extrasynaptic and presynaptic sites together with a concomitant decrease at postsynaptic compartments was reported in epileptic tissue (Frasca et al. 2011). NMDARs positioned at postsynaptic sites contribute to LTP generation, whereas NMDARs located at extrasynaptic sites contribute mainly to LTD (Papouin et al. 2012; Parsons and Raymond 2014). Thus, the decrease in NMDA-dependent LTP in the present study may be explained by enhanced proportions of GluN2B-containing NMDARs.

The observed diminished level of LTP may be involved in the origin of cognitive deficits following SE. The present study demonstrated that post-SE rats exhibited mild impairments in spatial memory in the open field test. These findings are in line with those of previous studies, which concluded that a single dose of PTZ might produce a prolonged cognitive deficit in rodents (Aniol et al. 2013; Assaf et al. 2011).

Transient mGluR-Dependent LTP After SE

In the present study, for the first time, we revealed a transient form of mGluR$_1$-dependent LTP induced by TBS in CA3-CA1 synapses of post-SE rats. The application of FTIDS, a specific antagonist of mGluR$_1$, completely prevented LTP in 1-day post-SE slices; whereas the FTIDS treatment did not affect LTP generation in control slices and post-SE slices obtained at other times after SE. This form of synaptic plasticity did not require the activity of NMDARs because it was preserved, even when the NMDARs were inhibited with AP-5. It is well established that group I mGluRs modulate the generation of NMDAR-dependent LTP in multiple synapses (Abraham 2008; Anwyl 2009) and in turn their expression changes following LTP induction protocol (Manahan-Vaughan et al. 2003). However, LTP that involves only mGluRs in the CA1 hippocampus was previously observed only at excitatory synapses on interneurons (Lapointe et al. 2004; Perez et al. 2001).

The precise role of mGluR$_1$ in synaptic plasticity in CA1 synapses on pyramidal cells has been a matter of intense, controversial debate (Anwyl 1999; Ferraguti et al. 2008). Many groups have demonstrated the involvement of group I mGluRs in both LTP and LTD (Bortolotto et al. 1994, 2005; Hu et al. 2005; Neyman and Manahan-Vaughan 2008; Wang et al. 2016). However, other groups have failed to identify attenuation of either LTP or LTD after the application of specific inhibitors in vitro (Manzoni et al. 1994; Selig et al. 1995), which is in line with our results obtained in the control rats. LTP generation in CA1 synapses of knockout mice lacking mGluR$_1$ is also controversial, as different groups found LTP to be unaffected (Conquet et al. 1994) or significantly reduced (Aiba et al. 1994; Gil-Sanz et al. 2008). Subsequent studies clarified that mGluR activation played an essential modulatory and metaplastic role in the generation of LTP but that mGluR activation did not appear to be imperative for the generation of certain basic LTP under most conditions prevailing in vitro (Anwyl 2009). One proposed mechanism for the role of mGluR1 in LTP is that the activation of group I mGluRs enhances NMDA responses and alleviates the generation of LTP through PKC (Conn and Pin 1997; Fitzjohn et al. 1996) (for review see Anwyl 1999). However, in our study, this mechanism is unlikely because LTP was NMDAR-independent in 1 day post-SE slices.

In an immunocytochemical study, Lujan et al. (1996) revealed that mGluR$_5$ was the only postsynaptic group I mGluR expressed at synapses on spines of CA1 pyramidal cells. This finding indicated that mGluR$_5$ alone might play a possible role of mGluRs in LTP in the CA1 area. Our results suggest that functionally active mGlu$_1$ receptors are present in CA1 synapses after PTZ-induced SE, at least temporarily. Although we did not perform an immunohistochemistry study, previously published data point to such a possibility. Initial upregulation in mGluR$_1$ mRNA expression was found in the hippocampus of amygdala-kindled rats (Akbar et al. 1996). Furthermore, a quantitative RT-PCR analysis identified a significant rise in mGluR$_1$ gene transcript levels within the hippocampus of kainate-treated and electrical-kindled rats (Blumcke et al. 2000). The same group also reported increased immunoreactivity for mGluR1α in the dentate molecular layer in kindled and kainate-treated rats, as well as in surgical specimens from patients with temporal lobe epilepsy (Blumcke et al. 2000). However, other groups observed a reduction in mGluR$_{1a}$ immunoreactivity in the CA1 area, with this reduction lasting from 1 to 5 days post-SE rats in a kainate model of acquired epilepsy (Ong et al. 1998). In addition, downregulation of mGluR$_1$ was found in the hippocampus between 3 and 31 days after pilocarpine-induced SE in rats (Tang et al. 2001). It should be also noted that there is a tight interplay between mGluR$_1$ and mGluR$_5$ activation. For example, positive allosteric modulation of mGlu$_5$ strongly reinforces LTP (Bikbaev and Manahan-Vaughan 2017) while negative allosteric modulation of mGlu$_5$ prevents persistent ($>$ 24 h) LTP in the dentate gyrus and leads to an inhibition of mGluR$_{1a}$ receptor expression in the dentate gyrus and an enhancement of LTP in the CA1 region (Bikbaev et al. 2008).

In the present study, increased PPR in slices 1 d post-SE provided indirect confirmation of a temporary rise in postsynaptic expression of mGluR$_1$. In previous research, upon activation of mGluR$_1$, an endogenous endocannabinoid, 2-arachidonoyl glycerol, was produced from diacylglycerol by diacylglycerol lipase and released in the extracellular space from where it reached CB$_1$Rs, which, in turn, caused inhibition of transmitter release at presynapse (Maejima et al. 2001; Varma et al. 2001).

Implications for Epilepsy

The transient functional changes in the activity of mGluR$_1$ in the hippocampus following seizures could be involved in the pathogenesis of acquired epilepsy through an additional mGluR$_1$-dependent mechanism of activity-related potentiation of excitatory neurotransmission. Despite a lack of convincing evidence on the implications of mGluR$_1$ transcriptional regulation in epileptogenesis, a large body of data has identified a critical role for mGluR$_1$ in the transition of interictal bursts into ictal activity and in the maintenance of prolonged synchronized discharges (see for review Ferraguti et al. 2008). Therefore, mGluR$_1$ antagonists may have therapeutic promise for the future treatment of epilepsy syndromes.

Author Contributions TP, OZ, and AZ designed the study. TP, JE, AT, SK, and OZ performed experiments and analyzed data. TP, JE, AT, OZ, SK, and AZ interpreted data for the work. TP, JE, OZ, and AZ wrote the manuscript. TP, EJ, AT, OZ, SK, and AZ approved the final version.

Funding This study was funded by the Russian Science Foundation (project 16-15-10202) and the experiments shown in Fig. 4 by the Russian Foundation for Basic Research (project 17-00-00408).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All applicable international, national, and institutional guidelines for the care and use of animals were followed.

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