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Long-lasting disruption of spatial memory by $GABA_B$ receptor antagonist induced seizures

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ABSTRACT

The objective of this project was to test whether a drug-induced model of temporal lobe seizures, namely seizures induced by a gamma aminobutyric acid ($GABA_B$) receptor antagonist, CGP35348, result in long-term disruption of hippocampal memory function. Seizures were induced in experimental rats by intracerebroventricular (i.c.v.) injection of CGP35348 (0.64 μmol in 3 μL) for three consecutive days; control rats received no injection. Rats were first trained to criterion on an open radial arm maze (RAM) with 4 of the 8 arms baited, then received seizure and control treatment, and tested again on the RAM during the first week (days 1–5) and fourth week (days 22–29) after the last injection. An initial i.c.v. CGP35348 injection induced a mean of 4.4 seizures in the hippocampus, often accompanied with stages 3–5 convulsions, and sometimes with jumping; three daily CGP35348 injections induced 10.4 ± 1.8 (n = 7 rats) seizures in total. In two separate experiments, seizure-treated rats performed worse than control rats in working memory (WM) during both the 1st and 4th weeks after seizures. Reference memory (RM) deficit during the 1st week after seizures was observed in only one experiment in which RM was acquired >2 weeks ago. The memory deficits were not accompanied by gross neuronal loss in the hippocampus. In conclusion, i.c.v. injection of a $GABA_B$ receptor antagonist in adult rats induced brief, multiple, focal hippocampal seizures that induced deficits in spatial memory for up to 4 weeks.

1. Introduction

A $GABA_B$ receptor antagonist has been shown to induce focal seizures in animals, typically arising from the limbic system [1,2]. There are similarities between the hippocampal seizure induced by a $GABA_B$ receptor antagonist and that induced by electrical stimulation, including low-frequency (2–6 Hz) onset of the afterdischarge (AD), brief seizure duration (<2 min), rebound AD after a primary AD, and postictal increase in hippocampal 30–80 Hz gamma activity [2]. However, the readiness of hippocampal ADs to develop into convulsive seizures involving the fore- and hind limbs was a distinctive feature of the $GABA_B$ receptor antagonist-induced seizure [2], compared with electrical kindling [3]. In addition, a single injection of a $GABA_B$ receptor antagonist induced several brief seizures in adult rats, without resulting in major neuronal loss (present study). The brief seizures and lack of neuronal loss are different from the status epilepticus model of temporal lobe epilepsy (TLE) using pilocarpine [4] or kainic acid [5].

Memory dysfunction is a major comorbidity of TLE [6], and some memory impairment may result from a cluster of recurrent seizures [7]. Temporal lobe seizure activity also likely contributes to the syndrome of transient epileptic amnesia. Other than a brief amnesia, patients with transient epileptic amnesia also show accelerated forgetting during interictal periods, accompanied by poor recall of remote autobiographical memories [8,9].

This study was intended to investigate the spatial memory effects of seizures induced by repeated administration of a $GABA_B$ receptor antagonist in adult rats. We hypothesize that repeated seizures induced by CGP35348 will induce long-term deficits in hippocampally mediated spatial memory. We contend that a model of drug-induced seizures is different from that induced by electrical stimulation (specific to one structure) and from the commonly used status epilepticus models that induced extensive brain damage. In previous studies, hippocampal ADs induced by electrical kindling were found to induce long-lasting (4–6 weeks) deficits of spatial memory retention in an open radial arm maze (RAM) [3,10–12]. Hippocampal kindling-induced performance deficits were also reported for other spatial tasks [13,14], and some deficits were more severe after kindling to generalized seizures [3,15–18].

2. Animals and methods

Twenty-two adult male Long–Evans rats were used for two separate maze experiments, with 16 used for the first experiment, and 6 others for the second one (Fig. 1). At 8–10 weeks old, rats were trained daily

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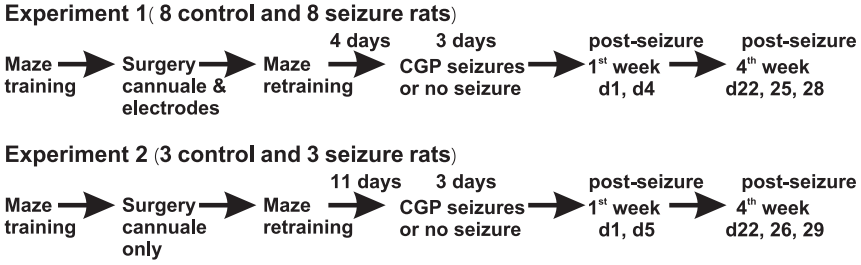

Fig. 1. Time course of procedures in two different experiments in the present study.

on an 8-arm open RAM [12]. Rats were kept at ~85% of its expected ad libitum weight. The first 6 training sessions placed food pellets all over the maze (3 sessions), and then along each arm (3 sessions). Starting at session 7, 4 randomly selected arms (out of 8 arms) were baited for each rat, with two 45 mg Noyes pellets of rat chow available only in the wells at the end of each baited arm; this set of 4 arms remained the same through the remaining days of training and testing. A rat was permitted to remain on the maze until all four baited arms were entered, 16 choices were made, or 5 min had elapsed. A reference memory (RM) error was defined as a selection of an unbaited arm, and a working memory (WM) error was defined as a revisit of any previously entered arm. Working memory errors were categorized as going to never baited arms or baited arms. The time of completing the maze was also measured. Two trials were run per day, with the trials separated by at least 3 h, 5 days/week, until the performance of the rats reached a criterion of an average total error of <1/day over 5 days, with total error being the sum of RM and WM errors. Maze runs were then paused for surgery. Sodium pentobarbital (65 mg/kg intraperitoneal (i.p.)) was used as anesthetic for surgery, and bilateral guide cannulae made from 23-gauge tubing (12 mm long) was inserted at P0.8, L1.4 above the lateral ventricle (atlas of Paxinos and Watson [19]). Rats used for the 1st maze experiment also had electrodes (125 μm Teflon-coated steel wires) placed bilaterally in hippocampal CA1 stratum radiatum (P4.5, L3.0) at 3.1 mm below skull surface. No electrodes were placed for rats in the 2nd maze experiment.

Rats were retrained after surgery. After reaching criterion for 5 consecutive sessions, a pair of rats of adjacent rank in maze acquisition was randomly selected as control and experimental (seizure) rats. Seizure rats were given three daily intracerebroventricular (i.c.v.) injections of CGP35348 (detailed below), and control rats were handled but not given i.c.v. injection. Saline i.c.v. injections would have made a more rigorous control group but could not be done because of time constraint, since the experimental design required all rats to undergo seizure/control treatment on the same day. For the 1st maze experiment (8 control and 8 seizure rats), seizure/control treatment started 4 days after the last training session, such that there was 1 week of rest on the maze. After seizure/control treatment, twice-a-day maze trials were resumed on posttreatment days 1 and 4 (1st week) and then again on posttreatment days 22, 25, and 28 (4th week) (Fig. 1). For the 2nd maze experiment, seizure/control treatment started 11 days after the last training session to give 2 weeks of rest on the maze. Maze trials, twice a day, were run on the 1st week (days 1 and 5) and the 4th week (days 22, 26, and 29) after seizure/control treatment (Fig. 1).

An experimental (seizure) rat was given i.c.v. CGP35348 (0.64 μmol in 3 μL saline) through a 26-gauge cannula that extended 1 mm beyond the guide cannulae, and 3 μL was infused through Hamilton syringe in over 1 min. After injection, rats with implanted hippocampal electrodes had their electrical activity recorded for 1 h, while connected by an electrical cable. Thereafter, the cable was disconnected and only behavioral seizures of the rat were scored for another 2 h, using direct observations and videotaped records. Stages 3, 4, or 5 seizures [20] and repeated jumping (considered stage 6 seizure) were scored. Nonconvulsive electrographic seizures would be missed during the last 2 h, but the procedure was necessitated by the limited electrical recording capacity in the laboratory. No behavioral seizure was observed at 3–6 h after an i.c.v. injection of CGP35348 in the present and a previous study [2].

At the end of experimentation, the rats were anesthetized by 80 mg/kg i.p. sodium pentobarbital and perfused through the heart with saline followed by 4% formaldehyde. The brain was removed, fixed in formaldehyde, and sectioned into 40 μm coronal sections and stained by thionin. Location of the placement of electrodes and cannulae was confirmed. Experiments were conducted in accordance with the guidelines established by the Canadian Council on Animal Care and approved by the local Animal Use Committee.

3. Results

3.1. Seizures induced by i.c.v. CGP35348

A dose of 0.64 μmol of CGP35348 i.c.v., which reliably induced ADs, was used in the present study. The latter dose of CGP35348 induced ADs typically arising from the hippocampus, and occasionally from the neocortex [2]. The hippocampal AD, especially after the first one, was often accompanied by stage 3 (forelimb clonus), stage 4 (rearing), or stage 5 seizure (rear and fall, or with other hind limb involvement). Repeated jumping of the rat was precipitated by low-intensity sound or tactile stimulus, or normally nonthreatening visual stimulus (e.g., moving experimenter's hand near the rat); vigorous jumping was shown to be accompanied by hippocampal paroxysmal activity [2]. One of 8 experimental rats in the 1st maze experiment lost its headcap after the first injection, and was removed from analysis. For the 7 remaining rats, each rat was electrically recorded for 1 h and then videotaped for another 2 h, and the total seizures for each rat were estimated by the sum of electrographic seizures in the first hour and the behavioral seizures (stages 3–5 and repeated jumps, considered to be stage 6) for the next 2 h. Following the first i.c.v. CGP35348 injection, an average of 2.2 electrographic seizures were observed in the first hour and an average of 2.2 convulsive (stages 3–6) seizures in the next 2 h (Fig. 2A inset). No additional behavioral seizures were observed at 3–6 h postinjection. The total number of ADs, including those with behavioral convulsions, over 3 days of CGP35348 injection was 10.4 ± 1.8 (n = 7 rats). The total number of ADs per day decreased during the 3 days of injection (Fig. 2A inset), as confirmed by a Friedman Analysis of variance (ANOVA) by ranks ($\chi^2(2) = 7.14$, $P = 0.028$). For the 3 rats injected i.c.v. CGP35348 in the 2nd maze experiment, the total number of stages 3–6 seizures also decreased with injection day, and the 3-day total was 8.3 ± 0.3 seizures (n = 3 rats).

3.2. RAM performance in the first maze experiment

The first maze experiment consisted of 7 seizure rats and 8 control rats. For the 10 trials before seizure/control treatment, average WM errors (the number of revisits to an arm) and RM errors (the number of entries into nonbaited arms) were not different between the two groups (Fig. 2A). This was confirmed by a lack of group effect on the pretreatment WM errors in a two-way (group × time) repeated measures ANOVA [$F(1,13) = 0.033$, $P = 0.86$]. After 3 days of seizure and control treatment, WM errors in 10 posttreatment trials (2 trials per day on days 1, 4, 22, 25, and 28) were higher in the seizure than the control

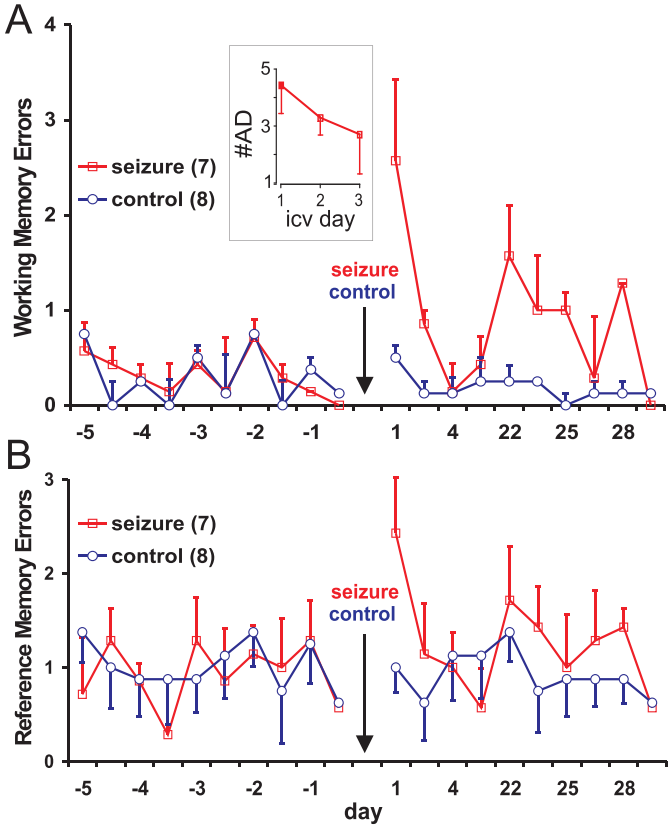

Fig. 2. Performance errors on the radial arm maze (RAM, 4 of 8 arms baited) before and after seizure treatment and control treatment in the 1st maze experiment. Seizure rats (n = 7) were injected with i.c.v. CGP35348 while control rats were not injected. A. Working memory errors plotted with test days. On the time axis, −5 to −1 correspond to the last 5 days of training before seizure or control treatment; two trials were run per day. Days 1, 4, 22, 25, and 28 were after seizure/control treatment. Working memory errors show a significant group effect between seizure and control groups. Inset shows the number of seizures/afterdischarges (#AD) induced in the seizure rats during the 3 injection days. B. Reference memory errors plotted with training and test days. Reference memory errors did not show a significant group effect.

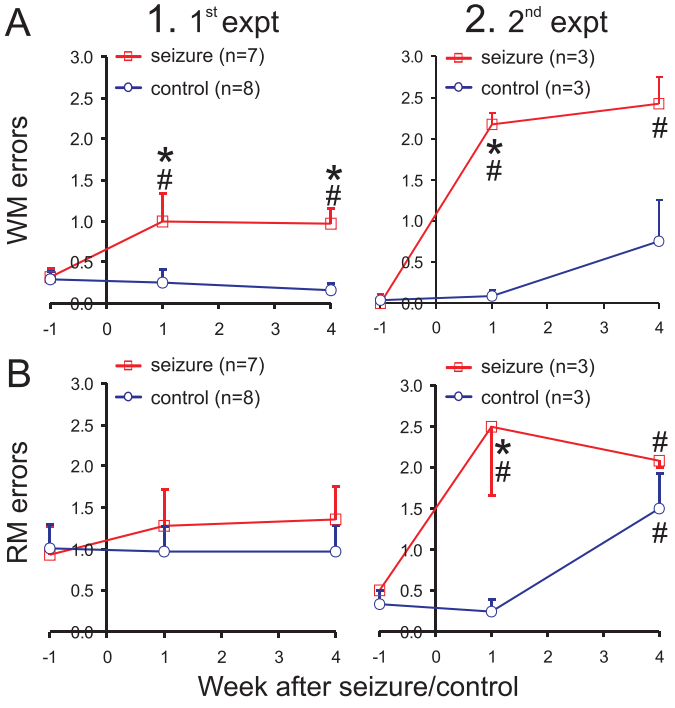

Fig. 3. Average working memory (WM) and reference memory (RM) errors per trial before treatment (week −1) and at 1st and 4th weeks after seizure/control treatment; two different maze experiments (columns 1 and 2, respectively) were run using slightly different procedures detailed in the text. A. Working memory errors were similar during week 1 and week 4, for both experiments. *P < 0.05, difference between seizure and control groups, post hoc Newman–Keuls test; # P < 0.05, difference with pretreatment values, post hoc Newman–Keuls; post hoc tests applied only after a significant two-way (group or group × time) ANOVA. B. Reference memory (RM) errors (two-way ANOVA) gave significant group and time effects only for experiment 2, and not experiment 1, with significant Newman–Keuls post hoc tests indicated.

group. Two-way repeated measures ANOVA showed a significant group effect [$F(1,13) = 12.71$, $P = 0.0035$] without a significant time or group × time interaction effect. To summarize the change in WM errors with time, the average errors during pretreatment period (average of 10 trials), the 1st week (average of 4 trials, 2 each on days 1 and 4), and the 4th week after treatment (average of 4 trials, 2 each on days 22 and 25) were calculated. The weekly average WM errors showed a significant group effect [$F(1,13) = 7.62$, $P < 0.02$] and group × time interaction effect [$F(2, 26) = 4.72$, $P < 0.02$], and post hoc Newman–Keuls test showed that the WM errors of seizure group increased at both 1st and 4th weeks compared with pretreatment, and compared with the control group (Fig. 3A).

Reference memory errors were not different between seizure and control groups before treatment, as confirmed by two-way repeated measures ANOVA [$F(1,13) = 0.037$, $P = 0.85$]. After treatment, the RM errors appeared higher in the seizure than control group, but two-way repeated measures ANOVA (2 groups × 10 times) revealed no significant group effect [$F(1,13) = 0.60$, $P = 0.45$]. Average RM errors within the 3 periods (pretreatment, 1st week, and 4th week posttreatment) also did not give a significant group [$F(1,13) = 0.26$, $P = 0.62$], time, or group × time interaction effect ($P > 0.55$).

3.3. RAM performance in the second maze experiment

A second group of rats (3 control and 3 seizure rats) was run, to confirm the changes in RM/WM errors. The 2nd group of rats was younger, and on day 1 posttreatment, weighed 236 ± 3 g, as compared with 302 ± 2 g for rats in the 1st experiment. The rats in the 2nd maze experiment also achieved lower WM and RM errors during the pretreatment period as compared with those in the 1st experiment (Fig. 3, column 2). The period from the last pretreatment maze trial to the onset of seizure/control treatment was increased to 11 days for the 2nd experiment, compared with 4 days for the 1st experiment (Fig. 1). The average WM errors during the three periods of pretreatment (10 trials), 1st week (4 trials, days 1 and 5), and 4th week posttreatment (4 trials, days 22 and 26) showed a significant group effect [$F(1,4) = 15.9$, $P < 0.02$] and time effect [$F(2, 8) = 7.5$, $P < 0.02$] but no significant group × time effect. Post hoc Newman–Keuls test showed that the WM errors of the seizure group increased at both 1st and 4th posttreatment weeks compared with pretreatment, but the seizure group was significantly different from the control groups only at the 1st week posttreatment, partly because of increased WM error of the control group at the 4th week (Fig. 3A2).

The average RM errors showed a similar trend as the average WM errors. There were significant group [$F(1,4) = 14.3$, $P < 0.02$], time [$F(2, 8) = 22.8$, $P < 0.001$], and group × time interaction effects [$F(2, 8) = 13.9$, $P < 0.003$]. Post hoc Newman–Keuls test revealed increased RM errors of the seizure group at both 1st and 4th posttreatment weeks, but the seizure group was only significantly different from the control group at the 1st week posttreatment (Fig. 3B2), because of increased RM error of the control group at the 4th week.

3.4. Histological assessment

The inner cannuale were confirmed to penetrate the lateral ventricle in all the seizure rats. Electrodes were located in hippocampal CA1. Based on a blinded assessment of the thionin-stained sections, there

was no difference in the gross morphology of the brain between seizure and control rats, including the dorsal hippocampus (dentate gyrus, CA3c, CA3b, and CA1), posterior cingulate cortex at ~P3.5, and the piriform cortex at ~P 1.

4. Discussion

The present study showed that spatial memory deficits of up to 4 weeks were found after repeated seizures induced by a $GABA_B$ receptor antagonist CGP35348. Both maze experiments showed a robust deficit in WM while only one experiment showed a deficit in RM. The results confirmed that a small number of hippocampal seizures (mean of 10) resulted in spatial memory deficits of up to 4 weeks.

4.1. CGP35348 induced seizures

The present study confirmed that CGP35348 induced hippocampal seizures, which quickly progressed to convulsive seizures of stages 3–5, as reported previously [2]. The present study only provided a rough estimate of the number of hippocampal seizures. Since electrical recordings were not made after the first hour, some purely electrographic seizures could be missed. In addition, i.c.v. CGP35348 also induced neocortical ADs (that may not be recorded) and jumping seizures that were included. It was noted that the number of ADs induced by CGP35348 decreased with the three daily injections. The latter may indicate a seizure-induced decreased efficacy of GABA on $GABA_B$ receptors [21], similar to that induced by repeated application of $GABA_B$ receptor agonist baclofen [22]. Early-life seizures induced by a $GABA_B$ receptor antagonist were proposed to cause a long-lasting decrease in $GABA_B$ receptor efficacy in adults and contribute to "seizures beget seizures" [23].

Three daily injections of CGP35348 did not induce gross histological damage to the dorsal hippocampus, the posterior cingulate cortex, or the piriform cortex. Histological assessment in a different study using repeated injections of $GABA_B$ receptor antagonists also indicated that the ventral hippocampus and entorhinal cortex did not show gross histological damage (data not shown). Detailed cell counts had not been done. However, the lack of gross pathology after several injections of CGP35348 was clearly distinct from the cell loss in hippocampal CA3 and/or piriform cortex induced by kainic acid or pilocarpine status epilepticus [4,5].

4.2. Spatial memory deficits following hippocampal seizures

The number of hippocampal seizures (mean of 10) that induced spatial memory deficit in the present study is consistent with a previous study, which reported that 10 but not 5 hippocampal ADs induced spatial memory deficit of >1 week [12]. The duration of spatial memory disruption of ~4 weeks is also consistent with previous studies of partially kindled rats performing on the RAM [10]. While a more rigorous control group of vehicle injection was not done, the effect of seizures was apparent from the difference between postseizure and baseline of the seizure group alone. The present control groups performed similarly on the RAM as previous control groups [10,12].

There were, however, differences between the present study using drug-induced seizures as compared with previous studies using electrical kindling of the hippocampus. The drug, CGP35348 (i.c.v.), induced hippocampal seizures, often accompanied by stages 3–5 (generalized) seizures, suggesting that the progression of seizure stages (epileptogenesis) could be achieved quickly in the presence of CGP35348. No spontaneous seizures were observed in the rats of the present study. However, in another study, 3 of 11 rats given 2–5 i.c.v. injection of $GABA_B$ receptor antagonist were shown to manifest 2 or more spontaneous seizures after 1 month (data not shown). Electrical stimulation could induce postictal long-term potentiation at the same CA3 to CA1 synapses that were stimulated [24] while CGP35348-induced seizure was followed by postictal depression of CA3 to CA1 synapses [2]. The relation of postictal depression of CA3 to CA1 synaptic transmission to subsequent spatial memory performance is unclear. Similar spatial memory retention deficits were found after full kindling (i.e., evoking stage 5 seizures) as compared with partial kindling (no convulsive seizures) of the hippocampus [3].

In the present study, CGP35348 induced a robust deficit in WM errors, with inconsistent RM errors. In the 2nd experiment, a rest period (free of maze trials) of 2 weeks was imposed between the end of training and retest 1st week after seizures, as compared with a 1-week rest period in the 1st experiment. The longer pause in maze runs likely contributed to a more fragile RM that could be disrupted by CGP35348-induced hippocampal seizures. A more fragile memory was indicated by a significant increase in RM errors in control animals at the 4th posttreatment week for the 2nd (Fig. 3B2), but not the 1st, maze experiment (Fig. 3B1). Using procedures similar to the 1st maze experiment (7–8 days of rest), 10 hippocampal-kindled ADs were shown to induce robust RM errors [11,12], but no WM errors [12], or only transient (day 1) WM errors [11]. Reference memory errors were cited as the main deficit after hippocampal kindling with different training and test protocols [15,16].

Reference memory is associated with long-term memory while WM is short-term (within trial) memory. Different hippocampal/entorhinal areas may contribute to WM and RM errors [25]. The electrophysiological correlates of poor spatial memory after CGP35348-induced seizures have not been studied. Both WM and RM errors may arise because seizure animals were deficient in spatial discrimination in the maze, distorted by aberrant synaptic transmission in the hippocampus [12], or by poorly tuned hippocampal place cells in a pilocarpine TLE model [26]. However, the animals showed a deficient spatial performance only for tasks acquired within ~6 weeks before the seizures [10,14], suggesting a prolonged retrograde amnesia effect of hippocampal seizures, comparable in duration with that induced by hippocampal lesion [27] or electroconvulsive seizures [28].

Given the present results, a cluster of temporal lobe seizures is expected to disrupt hippocampus-dependent memory in humans. There were apparently few studies of memory loss following a bout of seizures in otherwise healthy humans, which may be different in patients with TLE with a neurological history and/or existing pathology (such as mesial temporal sclerosis). Halgren et al. [7] reported verbal and nonverbal memory deficit in two patients with TLE at 1 day but not 2 weeks after a bout of seizures. Accelerated forgetting and patchy deficit of autobiographical (long-term) memories in transient epileptic amnesia [8,9] may also suggest a prolonged interference of memory by temporal lobe seizures in humans. Understanding the mechanisms of seizure-induced memory in animals may offer insights into epilepsy-associated memory deficits and their possible treatment.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgments

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