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·Original Article·

Serotonin 1A receptor inhibits the status epilepticus induced by lithium-pilocarpine in rats

Yi Yang*, Yi Guo*, Yifang Kuang, Shan Wang, Yan Jiang, Yao Ding, Shuang Wang, Meiping Ding
Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China
*These authors contributed equally to this work.
Corresponding author: Meiping Ding. E-mail: dingmeiping@tom.com

ABSTRACT

Status epilepticus (SE) is a life-threatening neurological emergency associated with a high mortality rate. The serotonin 1A (5-HT_{1A}) receptor is a possible target for the treatment of SE, but its role in animal models and the precise area of brain involved remain controversial. The hippocampus is a candidate site due to its key role in the development of SE and the existence of a high density of 5-HT_{1A} receptors. Therefore, we investigated the effects of subcutaneous and intrahippocampal activation of 5-HT_{1A} receptors in lithium-pilocarpine-induced SE, and tested whether the hippocampus is a true effector site. We developed SE in male Sprague-Dawley rats by giving lithium chloride (LiCl; 3 meq/kg, i.p.) 22–24 h prior to pilocarpine (25 mg/kg, i.p.), and found that 8-OH-DPAT, a 5-HT_{1A} receptor agonist administered subcutaneously (s.c.) at 0.5 or 1.0 mg/kg 1 h before pilocarpine injection increased the latency to the first epileptiform spikes, the electrographic SE, and the behavioral generalized seizures (GS), while reducing the total EEG seizure time (P <0.01). The duration of GS was shortened only by 1.0 mg/kg 8-OH-DPAT s.c. (P <0.05). All these effects were inhibited by combined administration of WAY-100635 (1.0 mg/kg, s.c.) (P <0.05), an antagonist of the 5-HT_{1A} receptor, but WAY-100635 alone and low doses of 8-OH-DPAT (0.01 and 0.1 mg/kg) did not alter seizure activity. Furthermore, intrahippocampal 8-OH-DPAT only shortened the GS duration (P <0.05). These findings imply that the 5-HT_{1A} receptor is a promising therapeutic target against the generation and propagation of SE, and hippocampal receptors are involved in reducing the seizure severity.

Keywords: status epilepticus; serotonin 1A receptor; 8-OH-DPAT; WAY-100635; lithium; pilocarpine

INTRODUCTION

Status epilepticus (SE) is a common, life-threatening neurological emergency with a high mortality rate of 20%[1]. Prolonged SE can cause permanent neurological damage that contributes to severe cognitive and behavior impairments[2, 3]. The fundamental mechanisms involve persistent, excessive excitation and the failure of inhibitory recruitment from areas adjacent to the epileptogenic zone, which normally isolate and stop seizure activity spontaneously[4, 5].

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter that mediates many physiological and pathological conditions[6]. The potential link between serotonin and the inhibition of epilepsy was first proposed by Bonnycastle in 1957[7]. More recently, Trindade-Filho *et al.* reported that depletion of serotonin increases the incidence of SE induced by pilocarpine[8]. Moreover, a number of studies have suggested that the anticonvulsant effect of serotonin is mediated *via* the serotonin 1A receptor (5-HT_{1A} receptor)[9-13], which might be a target for the treatment of SE. Despite the theoretical inhibitory effect of the 5-HT_{1A} receptor against seizures, the effects of its activation in animal models of SE remain controversial. Activation of the 5-HT_{1A} receptor by its agonist 8-hydroxyl-

2-(di-n-propylamino)tetralin HBr (8-OH-DPAT) has anticonvulsant effects in SE induced by kainic acid (KA)[5, 12, 14], but does not reduce the severity of seizures induced by pilocarpine (400 mg/kg, intraperitoneal, i.p.) at a relatively high dose (1.0 mg/kg)[15]. It is interesting that a high dose of 8-OH-DPAT (1.0 mg/kg) has an anticonvulsant effect, while a low dose (0.01 mg/kg) has a pro-convulsant effect in a KA model[12]. These opposing effects could be attributed to the differences in types and locations of 5-HT_{1A} receptor activated.

Further, it remains unclear which parts of the brain are involved in the anti- or pro-convulsant effects of 5-HT_{1A} receptors in SE. The hippocampus is a candidate site, due to its important role in the generation and maintenance of SE[4, 16, 17]. Furthermore, the hippocampus has a high density of 5-HT_{1A} receptors in the stratum radiatum of CA1 and the granule cell layer of the dentate gyrus, and a moderate level in the CA3 area. In a rat model of seizures induced by KA, activation of the 5-HT_{1A} receptor distributed adjacent to the focal hippocampal epileptogenic lesion has an inhibitory effect, which adds to the claim that the hippocampus may be a true effector site[14]. However, no further evidence from other SE models supports this hypothesis.

Compared with KA, untreated lithium (Li)-pilocarpine-induced SE is associated with high rates of mortality and an early onset of damage at 2.5 h after the beginning of SE in broad regions of brain, the neocortex, hippocampus, entorhinal cortex (EC), amygdala, and hypothalamus[16, 18-20]. Therefore, the Li-pilocarpine-induced model of SE might be appropriate as it mimics the severe damage caused by prolonged SE in humans. Therefore, in this study, we used the Li-pilocarpine rat model to investigate whether the activation of 5-HT_{1A} receptors has an inhibitory effect on SE.

The main aim of this study was to investigate the effect of 5-HT_{1A} receptor activation on Li-pilocarpine-induced SE, to test whether different doses of agonist have opposite effects, and to assess whether the 5-HT_{1A} receptors in the hippocampus may be a target for SE therapy.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (280–300 g) were provided by the Zhejiang Academy of Medical Sciences, China. All experiments were approved by the Zhejiang University Animal Experimentation Committee and were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experimental Groups

To assess the effects of subcutaneous 8-OH-DPAT administration, the rats were divided into seven groups and received the following treatment 1 h prior to pilocarpine injection: phosphate-buffered saline (PBS), 8-OH-DPAT (Sigma, St. Louis, MO) (0.01, 0.1, 0.5, or 1.0 mg/kg), WAY-100635 (a specific antagonist of the 5-HT_{1A} receptor; Sigma) (1.0 mg/kg), or WAY-100635 (1.0 mg/kg) immediately after 1.0 mg/kg 8-OH-DPAT.

To assess the effects of intrahippocampal 8-OH-DPAT administration, the rats were divided into two groups. One group received intrahippocampal injection of 8-OH-DPAT bilaterally (1 μg in 1 μL PBS, infused over 2 min) 15 min before pilocarpine injection *via* Micro4™ (World Precision Instruments, Sarasota, FL). The other received PBS (1 μL) at the same site as the control.

Stereotaxic Surgery

After rats were anesthetized with pentobarbital sodium (45 mg/kg, i.p.; Sigma) and mounted on a stereotaxic apparatus (512600; Stoelting, Wood Dale, IL). They were implanted with a guide cannula (62003; RWD Life Science, Shenzhen, China) on each side (AP = –3.5 mm, L = ±2.5 mm, and V = –2.9 mm)[14] for the intrahippocampal infusion of drugs. Stainless steel screws were placed over the frontal cortex bilaterally and connected to a miniature receptacle for electroencephalogram (EEG) recordings. The rats that received the subcutaneous drugs were only implanted with stainless-steel screws. All animals were housed individually after surgery and were allowed to recover for 7–10 days.

Status Epilepticus and EEG Recordings

Animals received an i.p. injection of lithium chloride (LiCl, 3 meq/kg, Sigma), followed by pilocarpine (25 mg/kg, i.p., Alfa Aesar) 22–24 h later. Methylscopolamine bromide (1 mg/kg, i.p., Sigma) was injected 30 min before the pilocarpine injection to limit its peripheral effects. Diazepam (5 mg/kg, i.p., Sigma) was given 90 min after the onset of SE. Seizure severity was classified according to the Racine scale[21]. The incidence of SE, the latency to and duration of generalized seizures (GS; bilateral forelimb clonus, rearing,

and falling) were recorded. The acute mortality rate was defined as the proportion of rats that died within the first 24 h after SE onset.

EEG was continuously recorded (RM-6240B; Chengdu Instrument Factory, Chengdu, China) for 2.5 h, beginning from 30 min before pilocarpine administration. The following parameters were recorded[5]: the latency to the first epileptiform spike (amplitude >2-fold of baseline and duration >3 s), the latency to the onset of electrographic SE (continuous high-amplitude polyspike activity), and the total time of seizure activity according to the EEG (total EEG recording time minus interictal time).

Statistical Analysis

All data are presented as mean ± SEM. All tests were two-sided and statistical significance was assigned as P <0.05. The χ^2 test was used to compare the incidence of SE and acute mortality rate between groups. Data on the effect of subcutaneous administration of 8-OH-DPAT were analyzed with one-way analysis of variance (ANOVA) followed by Tukey's HSD test. Data on the effect of intrahippocampal administration of 8-OH-DPAT were analyzed by a nonparametric Mann-Whitney U-test. In other comparisons, one-way ANOVA was used.

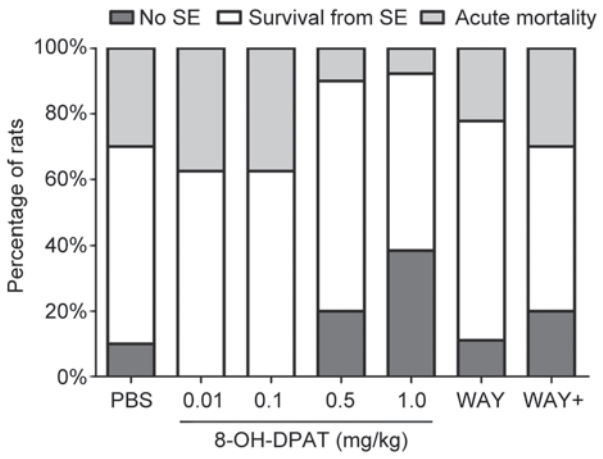

Fig. 1. Global outcome of lithium-pilocarpine-induced status epilepticus (SE). The bar graphs represent the percentage of rats that did not develop SE (dark grey), that died from SE (acute mortality, light grey), and that survived SE (white) in the seven groups (n = 10 in the PBS, 0.5 mg/kg 8-OH-DPAT, and WAY+ group; n = 8 in the 0.01 and 0.1 mg/kg 8-OH-DPAT groups; n = 13 in the 1.0 mg/kg 8-OH-DPAT group, n = 9 in the WAY group). No differences in the incidence of SE (P = 0.122) and the acute mortality rate (P = 0.756) were found. WAY, 1.0 mg/kg WAY-100635; WAY+, 1.0 mg/kg 8-OH-DPAT + 1.0 mg/kg WAY-100635.

RESULTS

Effect of Subcutaneous Administration of 8-OH-DPAT and WAY-100635

Rats were motionless 5–10 min after pilocarpine administration, and subsequently presented oro-facial movements, eye-blinking, and twitching of the vibrissae. Following discontinuous seizures, they displayed forelimb clonus, rearing, and falling, and finally developed SE. The SE incidence and acute mortality rates are shown in Fig. 1. No significant differences were found in these two parameters (P >0.05).

In the PBS group, the first epileptiform spike occurred at 18.8 ± 1.1 min and SE at 26.8 ± 1.8 min on the EEG recordings (Fig. 2). The total duration of the EEG seizure activity was 99.1 ± 1.2 min. Li-pilocarpine induced the first GS at 20.9 ± 1.4 min after pilocarpine injection and lasted 611.1 ± 65.6 s.

In contrast to the PBS group, 8-OH-DPAT had an inhibitory effect on the development of SE. 8-OH-DPAT at 0.5 and 1.0 mg/kg increased the latency to the first epileptiform spike and delayed the onset of electrographic SE (P <0.01, Figs. 2 and 3A) and decreased the total seizure duration on the EEG (P <0.01, Fig. 3B). 8-OH-DPAT also increased the latency to the first GS (Fig. 3C) at 0.5 (P <0.05) and 1.0 mg/kg (P <0.01), and the duration of GS at 1.0 mg/kg (P <0.05, Fig. 3D). Rats pretreated with 0.01 or 0.1 mg/kg 8-OH-DPAT showed no significant differences from the PBS group in any parameters.

The 5-HT$_{1A}$ receptor antagonist WAY-100635 prevented the effects of 1.0 mg/kg 8-OH-DPAT on the latency to discharge (P <0.01, Figs. 2 and 3A), total seizure time (P <0.01, Fig. 3B), GS latency (P <0.05, Fig. 3C), and GS duration (P <0.05, Fig. 3D). However, WAY-100635 administration alone did not cause any significant changes.

Effect of Intrahippocampal Administration of 8-OH-DPAT

Among the 24 rats administered pilocarpine, 3 out of 15 rats in the 8-OH-DPAT group failed to develop SE, whereas all the 9 rats in the control group developed SE (P >0.05). Among the 21 rats with SE, 4/12 in the 8-OH-DPAT group

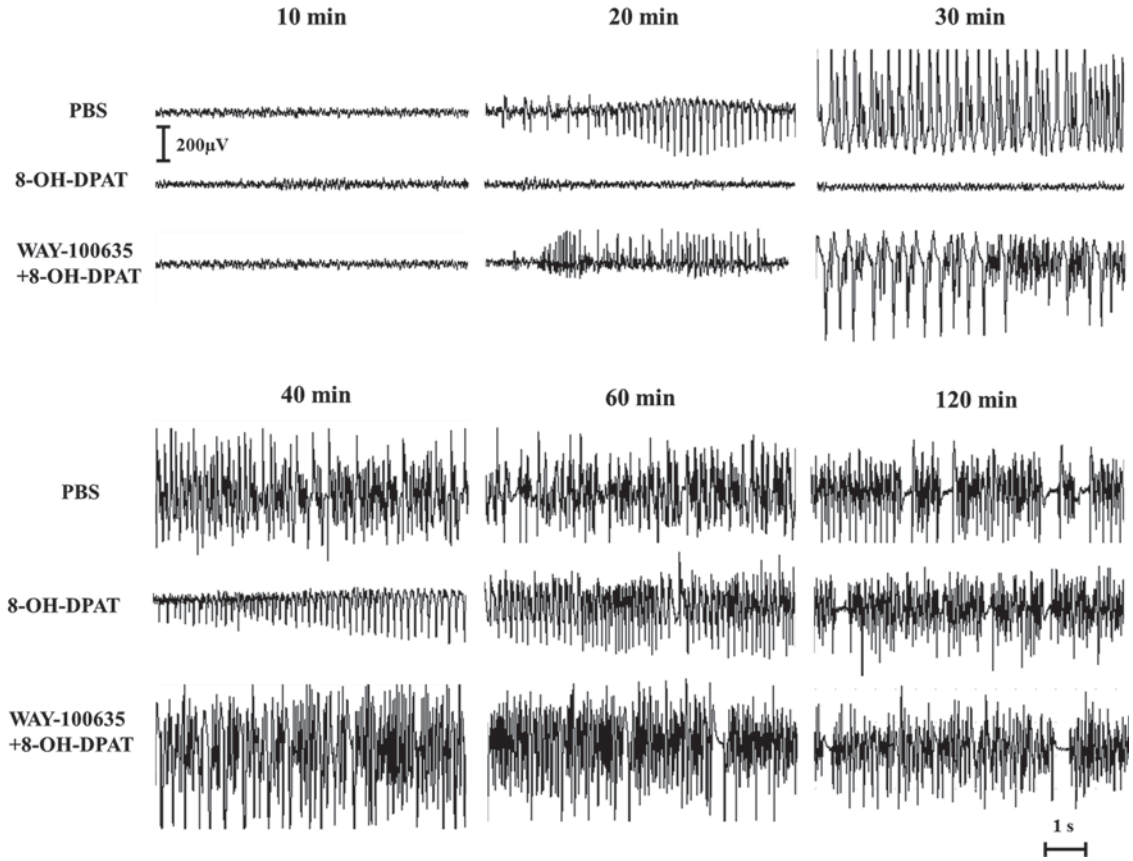

Fig. 2. EEG recordings from the PBS, 1.0 mg/kg 8-OH-DPAT and 1.0 mg/kg 8-OH-DPAT + 1.0 mg/kg WAY-100635 groups obtained at 10, 20, 30, 40, 60, and 120 min after pilocarpine injection. Note that the epileptiform discharges first appeared within 20 min after pilocarpine injection, while the onset of electrographic SE was detected within 30 min in the PBS group. 8-OH-DPAT markedly delayed the onset of the first epileptiform discharge and electrographic SE. These effects were inhibited by the combined administration with WAY-100635 (*n* = 9 in the PBS group, *n* = 8 in others groups).

Table 1. Effect of intrahippocampal administration of 8-OH-DPAT on electrographic seizure activity in Li-pilocarpine-induced status epilepticus

Groups	Latency to first spike (min)	Latency to SE (min)	Total seizure time (min)
PBS	16.5 ± 1.8	25.6 ± 2.3	110.9 ± 1.6
8-OH-DPAT	16.5 ± 1.6	22.6 ± 2.1	113.9 ± 0.9

Data are presented as mean ± SEM (*n* = 8). No significant difference was found between 8-OH-DPAT and PBS groups.

and 1/9 in the PBS group were excluded from the study after sacrification as they had developed a hippocampal hemorrhage or the position of the guide cannula was inaccurate. Thus, data from the remaining 16 rats were analyzed.

In contrast to the PBS group, 1 μg 8-OH-DPAT decreased the duration of GS during SE (P <0.05, Fig. 4A). However, it did not have any significant effect on the latency to behavioral GS (Fig. 4B) or EEG seizure activity, or the total seizure time (Table 1).

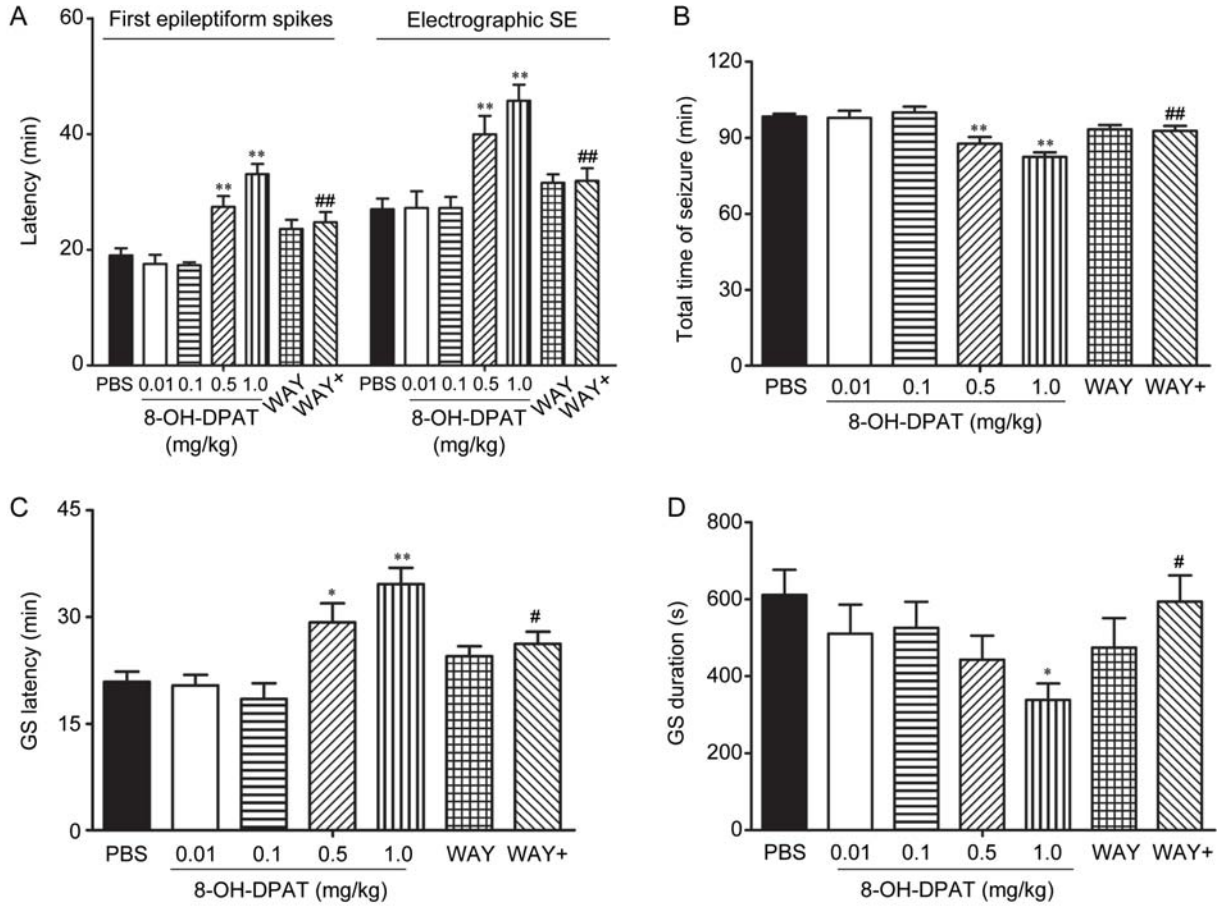

Fig. 3. Effects of subcutaneous administration of 8-OH-DPAT on the EEG seizure activity and generalized seizures (GS) in Li-pilocarpine-induced SE (*n* = 9 in PBS group, *n* = 8 in other groups). A: Latency to the first epileptiform spike (left) and the onset of electrographic SE (right). B: Total seizure duration on EEG. C: Latency to the first GS. D: Duration of GS. Values are mean ± SEM. The data were analyzed by one-way ANOVA followed by the Tukey's HSD test. **P* <0.05, ***P* <0.01 *vs* PBS; #*P* <0.05, ##*P* <0.01 *vs* 1.0 mg/kg 8-OH-DPAT. WAY, 1.0 mg/kg WAY-100635; WAY+, 1.0 mg/kg 8-OH-DPAT + 1.0 mg/kg WAY-100635.

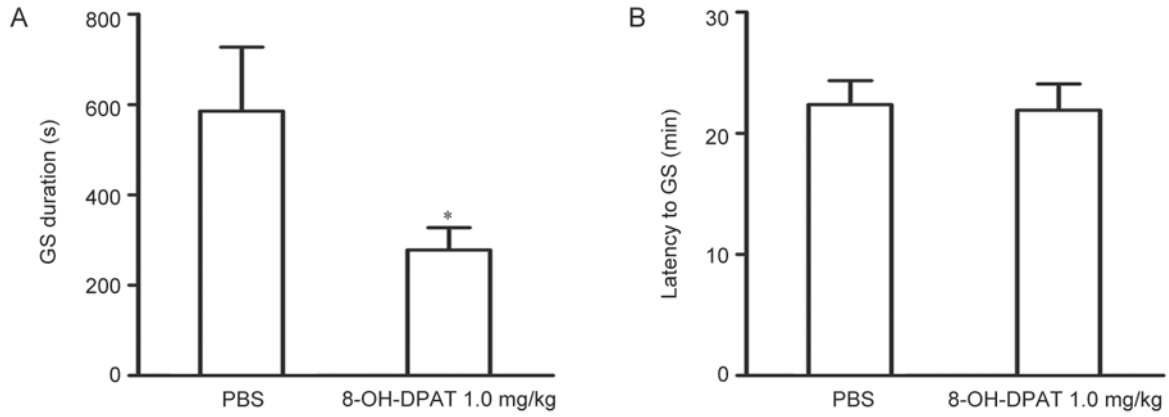

Fig. 4. Effect of intrahippocampal administration of 8-OH-DPAT on behavioral seizure activity in Li-pilocarpine-induced SE; duration of general seizures (GS) (A) and latency to the first GS (B). Values are mean ± SEM (*n* = 8 for both groups), and were analyzed by one-way ANOVA followed by the Tukey's HSD test. **P* <0.05.

DISCUSSION

In the present study, subcutaneous 8-OH-DPAT delayed the onset of both EEG and behavioral seizure activity and shortened the duration of GSs in a Li-pilocarpine-induced rat model of SE, and these effects were prevented by WAY-100635. These findings support the hypothesis that the activation of 5-HT_{1A} receptors induces an inhibitory effect on seizure activity[22-24]. These inhibitory effects on both the generation and severity of SE are consistent with previous reports in KA-induced models of SE[5, 12, 14]. However, these results differ from previous findings in the pilocarpine model of SE (400 mg/kg, i.p.) where 1.0 mg/kg 8-OH-DPAT did not reduce the severity of seizures or change the tolerance to pilocarpine (ED_{50} value). A possible explanation is the addition of lithium to the model. Both short-term (24 h) and chronic (14–21 days) Li treatment enhance the responsiveness of postsynaptic 5-HT_{1A} receptors, while the chronic effects of Li attenuate the effects of presynaptic 5-HT_{1A} receptors and increase the release of 5-HT[25, 26]. Hence, the inhibitory effect of 5-HT_{1A} receptors might be more evident in the Li-pilocarpine model than in the high-dose pilocarpine-only model. Compared with the GSs in SE models, however, the activation of 5-HT_{1A} receptors does not affect the GSs in fully amygdaloidal kindled rats[12, 27]. This difference suggests that 5-HT_{1A} receptors are more effective in seizure generation.

In the present study, low doses of 8-OH-DPAT (0.01 and 0.1 mg/kg) did not alter the seizure activity in SE, differing from the effects of different doses of 8-OH-DPAT in the KA model of SE[12]. A similar situation was found for WAY-100635 administration, which increased the discharge duration at 0.1 mg/kg in hippocampal kindling rats, but reduced subsequent discharges at 0.3 and 1.0 mg/kg[28]. The different effects induced by high and low doses of agonist or antagonist may be associated with the activation or inactivation of different types or locations of 5-HT_{1A} receptor. 5-HT_{1A} receptors are located presynaptically in the raphe nuclei (RN), are postsynaptically abundant in the frontal cortex, hippocampus, EC and lateral septum, and are present at moderate levels in the amygdaloid nucleus and piriform cortex[6, 29, 30]. Low doses of 8-OH-DPAT (0.1 mg/kg) were found to activate only the pre-synaptic receptors, whereas high doses (1.0 mg/kg) activate both the pre- and the post-synaptic receptors in a study of psychotic-like behavior[31]. Therefore, the present results indicate the possible involvement of post-synaptic receptors in the anticonvulsant effects of this treatment.

It is worth noting that the intrahippocampal administration of 8-OH-DPAT reduced the severity of SE by shortening the GS duration, indicating that hippocampal 5-HT_{1A} receptors may contribute to the inhibitory effect. Activation of 5-HT_{1A} receptors reduces the bursts in the hippocampal CA1 area *in vitro*[32]. This inhibitory effect might be primarily correlated with its ability to activate G protein-coupled inward-rectifying potassium channels, which enables them to induce hyperpolarizing currents that suppress neuronal firing and excitability[6, 33]. Besides, diminished glutamate release induced by the activation of 5-HT_{1A} receptors may also be involved in the anticonvulsant effects of 8-OH-DPAT[14, 34].

However, intrahippocampal activation of 5-HT_{1A} receptors fails to delay the development of SE in both the Li-pilocarpine and KA models. Subcutaneous 8-OH-DPAT administration in KA-induced SE only suppresses spike frequency in the frontal cortex, but not in the hippocampus[5], which indicates that a delayed propagation of seizure discharges might occur on the way from the limbic regions to the cortex. 5-HT_{1A} receptors are also distributed in several important extra-hippocampal sites of the limbic system that are involved in the development of SE, including the EC, the pyriform cortex and the amygdaloid nucleus[6, 18, 35]. The inhibitory effect on seizure propagation could be attributed to the activation of 5-HT_{1A} receptors within these sites. However, more studies focusing on the direct activation of receptors in these sites are needed to test this hypothesis.

In addition, 8-OH-DPAT may have non-specific effects mediated by activation of 5-HT_7 receptors and α1-adrenergic receptors[23, 24]. Although WAY-100635 is regarded as a specific antagonist of 5-HT_{1A} receptors, it also affects the dopamine system[36-38]. Therefore, further experiments are required to explore the possible involvement of these receptors in the effects of 8-OH-DPAT and WAY-100635 on seizure activity.

In conclusion, the activation of 5-HT_{1A} receptors has an anticonvulsant effect on Li-pilocarpine-induced SE in rats. 5-HT_{1A} receptors located in the hippocampus are involved in reducing seizure severity, while receptors located in the extra-hippocampal regions may contribute to delayed

seizure propagation. These findings suggest that the 5-HT_{1A} receptor is a promising therapeutic target against the generation and propagation of seizures in SE.

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