RESEARCH ARTICLE

Sodium valproate suppresses abnormal neurogenesis induced by convulsive status epilepticus

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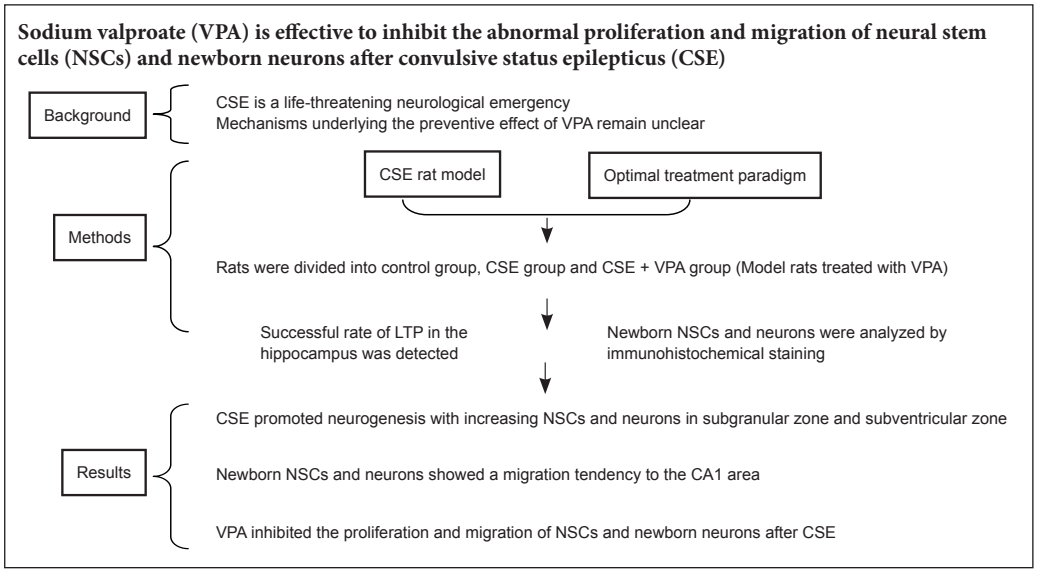
Graphical Abstract



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Abstract

Status epilepticus has been shown to activate the proliferation of neural stem cells in the hippocampus of the brain, while also causing a large amount of neuronal death, especially in the subgranular zone of the dentate gyrus and the subventricular zone. Simultaneously, proliferating stem cells tend to migrate to areas with obvious damage. Our previous studies have clearly confirmed the effect of sodium valproate on cognitive function in rats with convulsive status epilepticus. However, whether neurogenesis can play a role in the antiepileptic effect of sodium valproate remains unknown. A model of convulsive status epilepticus was established in Wistar rats by intraperitoneal injection of 3 mEq/kg lithium chloride, and intraperitoneal injection of pilocarpine 40 mg/kg after 18–20 hours. Sodium valproate (100, 200, 300, 400, 500, or 600 mg/kg) was intragastrically administered six times every day (4-hour intervals) for 5 days. To determine the best dosage, sodium valproate concentration was measured from the plasma. The effective concentration of sodium valproate in the plasma of the rats that received the 300-mg/kg intervention was 82.26 ± 11.23 μg/mL. Thus, 300 mg/kg was subsequently used as the intervention concentration of sodium valproate. The following changes were seen: Recording excitatory postsynaptic potentials in the CA1 region revealed high-frequency stimulation-induced long-term potentiation. Immunohistochemical staining for BrdU-positive cells in the brain revealed that sodium valproate intervention markedly increased the success rate and the duration of induced long-term potentiation in rats with convulsive status epilepticus. The intervention also reduced the number of newborn neurons in the subgranular area of the hippocampus and subventricular zone and inhibited the migration of newborn neurons to the dentate gyrus. These results indicate that sodium valproate can effectively inhibit the abnormal proliferation and migration of neural stem cells and newborn neurons after convulsive status epilepticus, and improve learning and memory ability.

Key Words: *nerve regeneration; status epilepticus; sodium valproate; long-term potentiation; neural stem cells; neurogenesis; migration; subgranular zone; subventricular zone; neural regeneration*

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Introduction

Status epilepticus (SE) is a medical emergency that requires immediate and effective treatment (Logroscino et al., 2005). Aborting ongoing symptoms of SE and preventing the recurrence are the main goals of treatment (Rabinstein, 2005). First-line drugs such as benzodiazepines and phenytoin/fosphenytoin have been effective in approximately 60% of all episodes (Knake et al., 2009). However, there are still a great portion of patients suffering from SE.

Sodium valproate (VPA) has become a competitive drug that is widely used to treat SE (Peters and Pohlmann-Eden, 2005). A previous study showed that intravenous VPA could reach a high concentration in the brain and led to rapid anticonvulsant activity through its efficient penetration of

the central nervous system (Hönack and Löscher, 1992). Additionally, VPA has been reported to be safe and has no potential major adverse cardiovascular side effects, such as cardiac arrhythmia or hypotension (Trinka, 2007). The efficacy and safety of intravenous VPA in controlling SE has been demonstrated in both adults and children (Malamiri et al., 2012). Thus, VPA can be used as a first-line antiepileptic drug for SE with good seizure control. However, the mechanism underlying this effect remains unclear.

Using rodent models of mesial temporal lobe epilepsy, several studies have demonstrated that SE can induce neurogenesis of dentate granule cells in the hippocampus (Parent et al., 1997, 1998; Gray and Sundstrom, 1998). In separate studies, dentate gyrus cell proliferation was increased by 5- to 10-fold within 3 days after drug-induced SE (Parent et al., 1997; Gray and Sundstrom, 1998). Additionally, another study reported that neurogenesis was correlated with hippocampus-dependent learning and memory, suggesting that mice lacking hippocampal neurogenesis displayed a learning impairment in trace fear conditioning, a specific hippocampal-dependent learning paradigm (Doetsch and Hen, 2005). We confirmed that VPA significantly improved the spatial cognitive dysfunction in the rat model of convulsive status epilepticus (CSE) in our previous study (Wu et al., 2016). Whether neurogenesis plays a role in the antiepileptic effect of VPA remains unknown. The current study aimed to investigate the role of neurogenesis in SE treatment with VPA.

Materials and Methods

Animals

Specific-pathogen-free male Wistar rats (aged 35 days and weighing 60–80 g) were purchased from the Animal Center of Chongqing Medical University in China (Animal certificate number: SYXK [Yu] 20040001). All animal procedures conformed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1985). Rats were housed in a standard laboratory at 25 ± 2°C, 60 ± 5% humidity, a 12-hour light/dark cycle, and free access to food and water.

Establishment of CSE models

To establish the CSE model (Patwardhan, 2006), rats were intraperitoneally given 3 mEq/kg lithium chloride (Sigma-Aldrich, St. Louis, MO, USA), followed by intraperitoneal injection of pilocarpine (40 mg/kg body weight; Sigma-Aldrich) after 18–20 hours. All CSE rats reached Class IV and were treated with diazepam (10 mg/kg body weight; Tianjin Jinyao Amino Acid Co., Ltd., Tianjin, China) by intraperitoneal injection 30 minutes after CSE onset. If CSE did not occur within 30 minutes after pilocarpine injection, additional pilocarpine (10 mg/kg body weight) was injected. If Class IV CSE did not occur, the rat was removed from the study (Shehata et al., 2009).

VPA administration

Initially, 35-day-old rats (normal: n = 36; CSE: n = 36) were divided equally into 6 subgroups (n = 6) and VPA (Shanghai pharmaceutical group Co., Ltd., Shanghai, China) was administered orally, with each of the 6 subgroups receiving a different dosage (100, 200, 300, 400, 500, or 600 mg/kg). VPA was administered 6 times daily (once every 4 hours) for 5 days. After the 5 days of treatment, plasma concentrations of VPA were measured to determine the optimal VPA treatment paradigm.

Other rats were further divided into a control group (normal rats treated with 0.9% saline, n = 6), a CSE group (model rats, n = 6), and a CSE + VPA group (model rats treated with the optimal VPA paradigm, n = 6). Rats were sacrificed by intraperitoneal injection of 10% chloral hydrate (Meilunbio Company, Dalian, China) 5 days after CSE model establishment, and brain slices were obtained for long-term potentiation (LTP) and immunohistochemical analyses.

Electrophysiological recording of LTP

Extracted brains were put into oxygenated slice liquid at 0–4°C for 1–2 minutes. The bilateral hippocampus was separated rapidly and hippocampal slices (400 μm) were prepared. The slices were incubated with oxygenated (95% O_2, 5% CO_2) artificial cerebrospinal fluid at 35°C for 30–45 minutes. The temperature was decreased to 24°C and hippocampal slices were incubated again for at least one hour. Hippocampal slices were directly incubated at 24°C. They were then moved to the recording bath, with continuous perfusion of oxygenated recording solution (124 mM NaCl, 2.8 mM KCl, 1.5 mM NaH_2PO_4, 24 mM $NaHCO_3$, 2 mM $CaCl_2$, 2 mM $MgSO_4$, 2 mM ATP-Mg, 0.4 mM vitamin C, 2 mM sodium pyruvate, and 10 mM glucose; pH 7.3–7.4, 1.5 mL/min, 35°C), and a bipolar tungsten stimulation electrode (Axon Instruments, Foster City, CA, USA) was placed on the Schaffer collateral pathway in the hippocampal CA3 zone. Stimulus intensity was 0.1–0.25 mA, and field excitatory postsynaptic potentials (fEPSPs) were recorded using a glass microelectrode (Axon Instruments) placed in CA1 (filled with 2 M NaCl, 10 mM hydroxyethyl piperazine ethanesulfonic acid, and 10 mM ethylene glycol tetraacetate; impedance 1–2 MΩ, pH 7.3–7.4). The data were collected and analyzed by pCLAMP 9.2 software (Axon Instruments). The basic stimulus was set to 50% of the stimulation intensity that yielded the maximum fEPSP, and LTP was induced by high-frequency stimulation after baseline stabilization for 30 minutes. If the fEPSP slope increased by at least 20% and lasted more than 30 minutes, LTP was considered to have been successfully induced.

Immunohistochemical staining

5-Bromo-2-deoxyuridine (BrdU, 50 mg/kg body weight; Sigma-Aldrich) was intraperitoneally injected twice per day on day 5 after the start of VPA administration. Rats were sacrificed 24 hours after intraperitoneal injection of BrdU. For immunohistochemical staining, brain tissue was fixed by 4% paraformaldehyde and dehydrated by sucrose. Brains were sectioned in the coronal plane (6 μm, 1-in-5 series) from 2 mm after visual acuity to the posterior ventricle angle on a cryostat. Staining for BrdU and doublecortin (DCX) was performed according to standard protocol using primary antibodies against BrdU (mouse monoclonal anti-BrdU, 1:250; Sigma-Aldrich) and DCX (mouse monoclonal anti-DCX, 1:250; Sigma-Aldrich), separately at 4°C overnight. Fluorescein isothiocyanate (FITC)-labeled rabbit anti-mouse

secondary antibodies (1:250; Sigma-Aldrich) were used at room temperature for 2 hours. Images were captured on a fluorescence microscope (Olympus, Tokyo, Japan). Under the fluorescence microscope (100×), five fields were randomly selected from each slice, and the number of positive cells was counted. The average value was calculated. The number of BrdU-positive cells was counted.

Statistical analysis

All data were analyzed with SPSS 19.0 (IBM Corp., Armonk, NY, USA) and are presented as the mean ± SEM. Data were analyzed by one-way analysis of variance followed by a least significant difference test. $P < 0.05$ was considered statistically significant.

Results

A treatment paradigm that allows adequate maintenance of VPA levels

The CSE model was established by intraperitoneally injection of pilocarpine. The evaluation of convulsions was based on previous methods (Patwardhan, 2006). According to a previous study, the effective plasma concentration of VPA in rat was 50–100 μg/mL (Löscher, 2007). To obtain the optimal VPA treatment paradigm, we drew blood and measured the plasma concentration of VPA in rats that received varying doses of VPA.

As shown in **Table 1**, normal rats exhibited effective VPA levels (64.98 ± 10.69 μg/mL and 96.91 ± 20.36 μg/mL) when treated with 300 mg/kg or 400 mg/kg of VPA, respectively. CSE rats treated with 300 mg/kg of VPA also demonstrated an effective VPA level (82.26 ± 11.23 μg/mL). Thus, we selected the 300 mg/kg VPA treatment paradigm to treat the CSE rats in subsequent experiments.

VPA intervention remarkably improves the induced success rate of LTP after CSE

The success rate for LTP induction was calculated after high-frequency stimulation of the hippocampal slices for five minutes (**Figure 1**). Compared with the rats in the control group, CSE obviously inhibited LTP in the CSE group ($P < 0.001$). Compared with the CSE group, the rate of LTP induction was significantly improved in the CSE + VPA group ($P < 0.05$). Thus, VPA intervention improved facilitated LTP induction after CSE. Because LTP is the most reliable electrophysiological index for learning and memory ability in rats, the finding suggests that VPA intervention can dramatically improve learning and memory ability of rats after CSE. based on the effect that VPA has on nerve regeneration in the hippocampus, this further suggests these benefits of VPA might be derived from regulating nerve regeneration and migration after CSE.

We also analyzed how long LTP lasted once it was induced. In the control group, the fEPSP slope showed no change from 60 minutes. However, in the CSE group it decreased 120% beneath baseline after 90 minutes. In the CSE + VPA group, VPA prolonged the duration of induced LTP to 140 minutes. VPA also significantly improved the fEPSP amplitude in rats of the CSE + VPA group relative to the CSE group ($P < 0.05$).

Table 1 Plasma concentrations of VPA in control and CSE rats after gastric administration of VPA

Dosage (mg/kg)	Control group	CSE group
100	13.52±6.58 (μg/mL) ($n = 6$)	26.83±8.47 (μg/mL) ($n = 6$)
200	35.26±10.11 (μg/mL) ($n = 6$)	46.64±9.64 (μg/mL) ($n = 6$)
300	64.98±10.69 (μg/mL) ($n = 6$)	82.26±11.23 (μg/mL) ($n = 6$)
400	96.91±20.36 (μg/mL) ($n = 6$)	129.65±28.33 (μg/mL) ($n = 6$)
500	2 rats drowsiness ($n = 4$)	3 rats drowsiness ($n = 3$)
600	2 rats drowsiness ($n = 4$)	1 rat died ($n = 5$)

VPA: Sodium valproate; CSE: convulsive status epilepticus. Data are expressed as the mean ± SEM.

Effect of VPA on nerve regeneration in the hippocampus after CSE

To assess the effect of VPA on neurogenesis after CSE in rats, the number of regenerated neural stem cells (NSCs) was calculated *via* immunohistochemical analysis (Figure 2A). NSCs were primarily found in the subgranular zone (SGZ) of the hippocampus. Analysis showed that the number of regenerated NSCs in the SGZ was significantly higher in the CSE and CSE + VPA groups than in the control group ($P < 0.05$). However, VPA significantly blocked the effect of CSE, and the number of BrdU-positive cells was significantly lower in the CSE + VPA group than in the CSE group ($P < 0.05$).

Meanwhile, the number of NSCs in the subventricular zone (SVZ) also increased after CSE (**Figure 2A**). BrdU-positive cell number was significantly higher in the CSE and CSE + VPA groups than in the control group ($P < 0.05$). Additionally, this effect was mitigated by VPA; NSCs regeneration was significantly less in the CSE + VPA group than in the CSE group ($P < 0.05$; **Figure 2B**).

Effect of VPA on migration of newborn neurons after CSE

Newborn cells present with normal function only after migrating to specific locations and properly connecting with neighboring cells. DCX is a vital microtubule-associated protein found in the cytoplasm and axons of neurons, and which has been used as a marker for mature or migrating cells (Dellarole and Grilli, 2008). To investigate the effect of VPA on newborn neurons after CSE, newborn neurons were examined by immunostaining that visualizes DCX-positive cells (**Figures 3** and **4**). The results demonstrated that newborn neurons in the SGZ increased along with NSC propagation after CSE (**Figure 3**). The number and newborn neurons and the length of their axons were greater after CSE. In the CSE + VPA group, VPA intervention mitigated these changes. Normally, the newborn neurons in the SGZ migrate to the granular cell layers to form granular cells. Our results showed that after CSE, newborn neurons tended to migrate to the dentate gyrus. Interestingly, some newborn neurons in CSE rats did not extend axons, but had short and thick lpseudoly dendritic structure (**Figure 4A**). Additionally, the number of newborn neurons in the SVZ was greater after CSE, and these neurons tended to migrate to the CA1 area (**Figure 4B**).

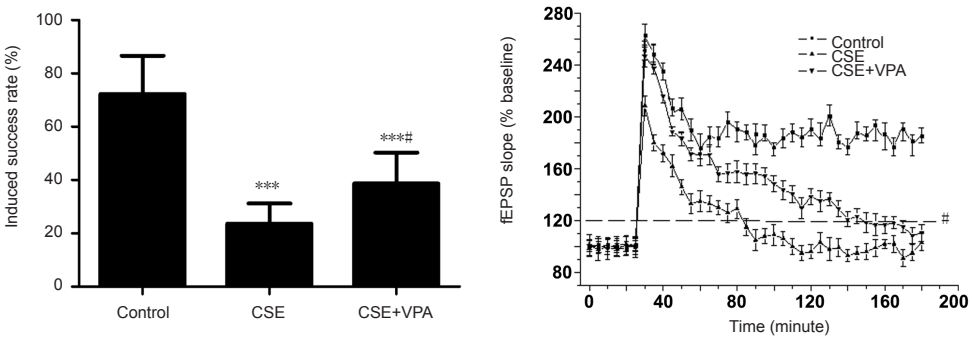

Figure 1 Success rate of inducing LTP and the fEPSP slopes in CSE rats after VPA intervention.
Data are expressed as the mean ± SEM. ***P < 0.001, *vs*. control group; #P < 0.05, *vs*. CSE group (one-way analysis of variance followed by the least significant difference test). LTP: Long-term potentiation; fEPSP: Field excitatory postsynaptic potential; CSE: convulsive status epilepticus; VPA: sodium valproate.

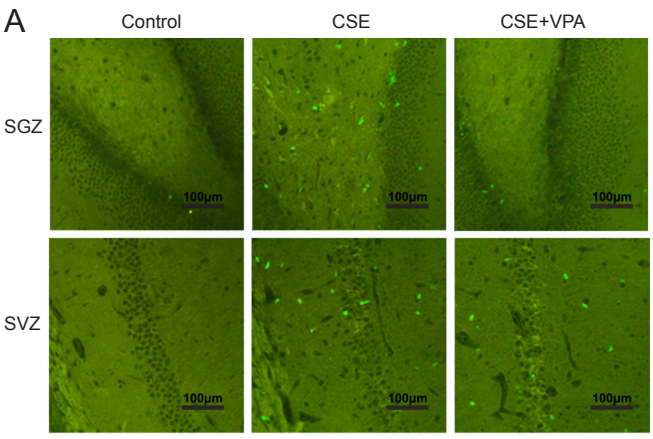

Figure 2 Number of BrdU-positive cells in 35-day-old CSE rats after VPA intervention.
(A) The SGZ of the dentate gyrus and the SVZ: Sections were counterstained with FITC after BrdU immunostaining. Bright green indicates BrdU-positive cells. Scale bars: 100 μm. (B) Number of BrdU-positive cells. Data are expressed as the mean ± SEM. *P < 0.05, *vs*. control group; #P < 0.05 *vs*. CSE group (one-way analysis of variance followed by the least significant difference test). CSE: Convulsive status epilepticus; VPA: sodium valproate; SGZ: subgranular zone; SVZ: subventricular zone; FITC: fluorescein isothiocyanate; BrdU: 5′-bromo-2-deoxyuridine.

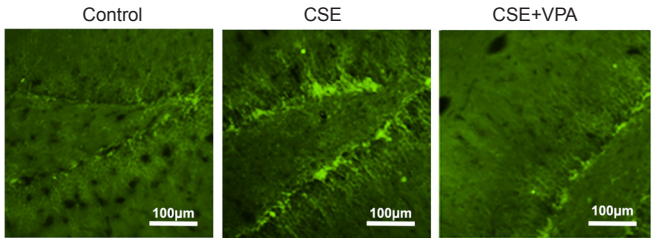

Figure 3 Distribution of DCX-positive cells in the subgranular zone of 35-day-old CSE rats after VPA intervention.
Sections were counterstained with FITC after DCX immunostaining. Bright green indicates DCX-positive cells. Scale bars: 100 μm. CSE: Convulsive status epilepticus; VPA: sodium valproate; DCX: doublecortin; FITC: fluorescein isothiocyanate.

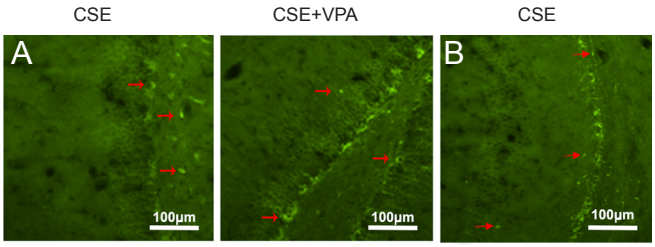

Figure 4 Migration of newborn neurons in 35-day-old CSE rats after VPA intervention.
(A) Abnormal migration in the subgranular zone; (B) migration in the subventricular zone. Sections were counterstained with FITC after DCX immunostaining. Bright green indicates DCX-positive cells. Arrows point to newborn neurons in migration. Scale bars: 100 μm. CSE: Convulsive status epilepticus; VPA: sodium valproate; FITC: fluorescein isothiocyanate; DCX: doublecortin.

Discussion

In this study, VPA intervention remarkably increased the induced success rate of LTP after CSE. Meanwhile, CSE increased the number of newborn cells, but induced abnormal migration patterns and morphology of newborn neurons. VPA intervention effectively prevented neurogenesis induced by CSE in the SGZ and SVZ. Our findings suggest adult neurogenesis appears to be a potential mechanism underlying VPA treatment.

The hippocampus plays an important role in learning and memory, and lesions to the hippocampus lead to dysfunction of cognition (Tulving and Markowitsch Hans, 1998). Studies have demonstrated that neurogenesis is involved in hippocampus-dependent learning and memory (Doetsch and Hen, 2005; Zhu et al., 2017). Adult neurogenesis mainly occurs in the SGZ of the hippocampus (Seri et al., 2001; Bortolotto and Grilli, 2017; Kandasamy and Aigner, 2018). Newborn neurons replace dead neurons and maintain their specific functions. The changes in number or function of newborn neurons may result in neurological disease.

After brain damage, including epileptogenic brain insults and seizures, neurogenesis increases in the SGZ of adult rodents. The newborn neurons in response to such stimuli have displayed abnormal function in connecting with neigh-

boring cells (Kokaia, 2011; Parent and Kron, 2012; Bielefeld et al., 2013). This is consistent with our results that CSE induced NSCs proliferation with the increased number of newborn cells in the SGZ and SVZ. However, the migration and morphology of newborn neurons after CSE were abnormal. Additionally, our previous study demonstrated that CSE rats exhibited deficits in hippocampus-dependent spatial learning and memory (Wu et al., 2016). Together, these results suggest that adult neurogenesis in the hippocampus is also involved in CSE.

As a treatment for SE, VPA is a short-chain fatty acid that possesses anticonvulsant properties and is associated with a low incidence of adverse events (Trinka, 2007; Liu et al., 2012). Our previous study showed that VPA markedly improved spatial cognitive dysfunction in CSE rats. In the present study, we investigated the effect of VPA on hippocampal LTP and neurogenesis. Our results confirmed that VPA improved the success rate of inducing LTP and alleviated the effects of neurogenesis caused by CSE.

This study has several limitations. Owing to the big difference between human and animals in learning and memory, it is essential that these findings be confirmed in large-scale prospective clinical studies. Whether VPA inhibits the maturation of newborn neurons after CSE still needs further study. Additionally, this study does not address whether long-term treatment of VPA after CSE can improve cognitive function or whether it aggravates the existing cognitive dysfunction. This issue and the inherent mechanisms underlying the effect of VPA need to be further investigated.

In summary, our findings demonstrate that neurogenesis is a pivotal regulatory element during CSE in rats. VPA is effective in inhibiting the abnormal proliferation and migration of NSCs and newborn neurons induced by CSE.

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