Effect of Sodium Valproate on Cognitive Function and Hippocampus of Rats After Convulsive Status Epilepticus

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Background: The aim of this study was to explore the effect and possible mechanism of sodium valproate (VPA) on the cognitive function and the hippocampus of rats after convulsive status epilepticus (CES).

Material/Methods: A rat model of CES was established and the Morris water maze was used to observe changes in the cognitive function of the rats after the administration of VPA. Acute hippocampal slices were made to detect field excitatory postsynaptic potential. Western blot analysis was used to test for the expression of CaMKII and p-CaMKII.

Results: (1) CSE caused no spatial reference memory (SFM) or spatial working memory (SWM) damage to 15-day-old (P15) rats, but caused significant SRM and SWM damage to 35-day-old (P35) rats. VPA damaged the SRM and SWM of P15 rats in both the CSE and control groups. However, VPA improved the memory damage caused by CSE in P35 rats. (2) VPA treatment in vivo increased the induced success rate and the sustainable time of long-term potentiation (LTP) in P35 rats, and also inhibited the expression of CaMKII and p-CaMKII in both P15 and P35 rats.

Conclusions: VPA significantly improved spatial cognitive dysfunction in a CSE model of P35 rats, and damaged the spatial memory of normal P15 and P35 rats. Improvements after administration of VPA were closely related to the increase of induced success rate and the prolongation of the sustainable time of LTP. VPA treatment in vivo, which inhibited expression and phosphorylation of CaMKII, showed no obvious inhibition on LTP, which may be related to the elution effect of VPA.

MeSH Keywords: Epilepsies, Partial • Epilepsy, Generalized • Valproic Acid • Vipoma

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Background

Status epilepticus (SE) is a common neurological emergency in childhood and associated with significant morbidity and mortality, with morbidity rates of 10–73/100,000 (135–156/100,000 among children under 2 years old) and mortality rates of 0–7% [1]. SE can be divided into two categories: convulsive (CSE) and nonconvulsive (NSE) [2]. CSE presents with a regular pattern of contraction and extension of the arms and legs and may cause the loss of neurons in the hippocampus, causing serious brain damage [3]. In addition, some patients with severe CSE can suffer from long-term cognitive impairment and abnormal behavior, such as decreases in intelligence, memory, and attention; CSE is associated with depression, anxiety, and other mental symptoms, which can have serious impacts on a patient’s quality of life [4]. The studies of various kindling models and gene models have found that CSE can cause a significant decrease of hippocampus-dependent spatial learning and memory ability in rats. At present, the research on CSE is mainly focused on the pathogenesis of secondary epilepsy with less focus on the specific mechanism of cognitive dysfunction.

In order to prevent recurrent attacks of secondary epilepsy after CSE, long-term treatment with antiepileptic drugs (AEDs) is currently advocated, and sodium valproate (VPA) has become the first choice for treatment of children due to its wide clinical use [5]. However, most clinical studies of VPA have found that while VPA controlled occurrence of epilepsy it also caused different degrees of attention and memory loss and unusual emotional behavior that had a negative impact on patients’ quality of life, such that many patients did not want to continue treatment with VPA [6].

In neuroscience, long-term potentiation (LTP) is a persistent strengthening of synapses based on recent patterns of activity. These patterns of synaptic activity produce a long-lasting increase in signal transmission between two neurons [7]. Previous studies found that the hippocampus is part of the limbic system and plays an important role in the consolidation of information from short-term memory to long-term memory, and also affects spatial navigation. Harm to the hippocampus in human and animal experiments can result in loss of memory acquisition abilities. Also, the hippocampus has a clear hierarchical structure with three synapses. The best-studied form of LTP occurs at synapses. Therefore, LTP in the hippocampus is an ideal model and electrophysiological index to use to study the mechanism of learning and memory. Moreover, a large number of studies have found that calcium/calmodulin-dependent protein kinase II (CaMKII) can remain active by phosphorylation (p-CaMKII) and can act as a molecular switch for memory [8]. Thus, CaMKII is likely a key protein molecule in the mechanism of LTP formation.

Human studies of VPA’s effect on the cognitive function and efficacy for managing long-term drug withdrawal among patients with CSE is difficult to carry out, making animal studies important proxies. In this study, CSE models of rats at different ages were used, and rats was administered VPA. Electrophysiological indexes related to hippocampus-dependent spatial learning and memory ability were observed and key protein molecules in the LTP formation mechanism were tested to look for a key therapeutic target that could promote the improvement of cognitive function in epilepsy patients.

Material and Methods

Grouping of experimental animals

Wistar rats were provided by the animal center of Medical University of Chongqing; the experimental animals’ use license was SYXK(Yu) 20040001. The rats were 15 days old (P15) and 35 days old (P35). The two groups are shown in Table 1. Feeding was under general laboratory environmental conditions. P15 and P35 rats were orally administered VPA at 5 mg/kg (12 times/day) and 350 mg/kg (6 times/day), respectively, for five days. In addition, a positive control group was used in experiments looking at the expression of CaMKII and p-CaMKII.

Establishment of CSE model

Each rat was injected with 3 mEq/kg lithium chloride intraperitonally and after 18–20 hours with pilocarpine (30 mg/kg for P15 rats and 40 mg/kg for P35 rats). If no convulsions happened within 30 minutes, additional pilocarpine of about 1/4 of the original dose was injected. According to the evaluation

Table 1. Names of animal groups.

|         | P15                      |          | P35                      |          |
|---------|--------------------------|----------|--------------------------|----------|
|         | With CSE  | n         | Without CSE  | n         | With CSE  | n         | Without CSE  | n         |
| NS*     | CSE group  | 12        | Control group  | 12        | CSE group  | 11        | Control group  | 12        |
| VPA     | CSE+VPA group  | 10        | VPA group  | 12        | CSE +VPA group  | 10        | VPA group  | 12        |

* NS stands for normal saline, the commonly-used term for a solution of 0.91% w/v of NaCl.
tests were place navigation tests. A semi-random method was adopted. Latency was recorded and rats stayed on the platform for 60 seconds every time. If a rat could not find the platform within 60 seconds, it would be taken to the platform and left on the platform for 60 seconds. The time interval of the first three tests was 30 seconds. The last time was the probe trial test; the time interval between the probe test and the third or last navigation test was 15 seconds. The time periods for the rats to first cross the original platform and swim the distance in the target quadrant within 60 seconds were recorded. The platform was placed semi-randomly in a different quadrant during the following five days; other steps were the same as with the first day.

**Detection of SRM**

Place navigation experiments began on the fifth day after the administration of VPA. Each rat was tested four times per day and for five days. Latency was recorded. If latency was more than 60 seconds, the rat was taken to the platform and left for 15 seconds, and latency of this test was recorded as 60 seconds. The probe trial experiment was conducted 24 hours after the place navigation experiment was completed. The time of first crossing of the original platform and the ratio of swimming distance in the target quadrant and the total swimming distance within 60 seconds were recorded.

**Detection of SWM**

SWM was detected from the fifth day after the administration of VPA and this lasted for six days. Rats who were included in SRM experiments were excluded from the SWM experiments. Each rat was tested four times per day; the first three tests were place navigation tests. A semi-random method was adopted. Latency was recorded and rats stayed on the platform for 60 seconds every time. If a rat could not find the platform within 60 seconds, it would be taken to the platform and left on the platform for 60 seconds. The time interval of the first three tests was 30 seconds. The last time was the probe trial test; the time interval between the probe test and the third or last navigation test was 15 seconds. The time periods for the rats to first cross the original platform and swim the distance in the target quadrant within 60 seconds were recorded. The platform was placed semi-randomly in a different quadrant during the following five days; other steps were the same as with the first day.

**Electrophysiological recording of LTP**

Rats were anaesthetized with ether on the fifth day after the administration of VPA. After heart perfusion with 50 mL ice-cold oxygenated artificial cerebrospinal fluid (ACSF), the head was removed and the brain was extracted and put into oxygenated slice liquid (0–4°C) for 1–2 minutes. The bilateral hippocampus was rapidly separated from the inside and hippocampal slices were placed in the recording solution containing 95% O$_2$ and 5% CO$_2$, and incubated at 35°C for 30-45 minutes. Then the temperature was decreased to 24°C and hippocampal slices were incubated again for at least one hour. Hippocampal slices of P15 rats were directly incubated at 24°C. When the hippocampal slices were moved to the recording bath, with continuous perfusion of oxygenated recording solution (1.5 ml/min, 35°C), the data of field excitatory postsynaptic potential (fEPSP) began to be recorded. Software pCLAMP9.2 was used to process and preserve data.

**Expression of CaMKII and p-CaMKII**

Protein in the bilateral hippocampus was extracted. Bicinchoninic acid was used for quantitative analysis. Electrophoresis was done with 10% polyacrylamide gel. Transmembrane was used with polyvinylidene fluoride (PVDF). The membrane was blocked with TTBS (NaCl 150 mM, Tris 25 mM, pH 7.6), and then probed with β-actin (1:500 in blocking solution for 14–16 hours at 4°C, Kangchen Bio-tech, Shanghai, China). The secondary antibody IgG (Cell Signaling, USA) was applied for two hours with slow shaking at room temperature. After each incubation, the membrane was thoroughly washed with TTBS, and then the membrane was treated with an ECL kit (Pierce, USA) and by Western blot.

**Statistical analysis**

Software SPSS 19.0 was used to analyze data. All data were expressed by mean ±SEM. Data between the two groups were compared with t-test. One-way ANOVA was used in SRM and SWM analysis. A p value less than 0.05 was considered significant.
**Results**

**Effect of VPA on SRM and SWM of rats after CSE**

The results of SRM are shown in Table 2. In the place navigation test of P15 rats, time of latency was the shortest on the third day in the CSE group and the control group (p>0.05) and was maintained at this level, which indicated that the rats’ learning ability had not been obviously damaged in the CSE group. Except for the first day, the time of latency was prolonged in the VPA group and the CSE+VPA group (p<0.05), and this showed a downward trend during the five days. In the probe test, the CSE group showed the same result compared to the control group (p>0.05), which further suggests that the onset of CSE had no effect on the SRM of P15 rats, while VPA treatment alone caused obvious damage to SRM in the control group and CSE group. However, swimming distance of the VPA group and CSE+VPA group in the target quadrant was significantly shorter than that of the control group and CSE group (p<0.05). In the place navigation test of P35 rats, the time of latency began to decrease from the second day in the control group (p<0.05), but there was no significant difference until the fifth day in the CSE group (p>0.05), which suggests that the onset of CSE caused significant damage to the SRM of P35 rats, but that this damage could be lessened by VPA treatment. Time of latency presented a slow shortening trend from the first day to the fifth day for the CSE+VPA group compared to the CSE group (p<0.05). Compared to the CSE group, the time of first crossing to the original platform was significantly shortened in the CSE+VPA group and the control group (p<0.05), and the ratio of swimming distance in the target quadrant and the total swimming distance within 60 seconds was increased significantly (p<0.05).

The results of SWM are shown in Figure 2. Except for the time of first crossing to the original platform on the third day, there was no statistical difference in the other days, and the indexes indicated that the onset of CSE had no effect on the SWM of P15 rats, while VPA caused damage to the control group and the CSE group (p<0.05). Compared to the control group, the time of latency in the CSE group was prolonged and the ratio of swimming distance in the target quadrant was significantly decreased (p<0.05), which suggests the onset of CSE caused damage to the SWM of the P35 rats. However, VPA appeared to improve the situation of the SWM in the CSE group. The time of latency was shortened and the ratio was increased in the CSE+VPA group (p<0.05).

**Effect of VPA treatment in vivo on fEPSP and LTP**

In order to detect the effect of VPA on synaptic transmission, ACSF of P15 and P35 rats were isolated and the same intensity of electrical stimulation was applied. The fEPSP amplitudes and slopes for each group are shown in Figure 3A and 3B.

| Experiment       | Control group | VPA group | CSE group | CSE+VPA group |
|------------------|---------------|-----------|-----------|---------------|
| **P15 rats**     |               |           |           |               |
| Place navigation | Day 1 (s)     | 49.38±3.22 | 49.46±4.30 | 48.55±7.43    | 46.62±5.39    |
|                  | Day 2 (s)     | 27.75±4.49 | 41.88±6.24 | 37.28±7.44    | 39.39±4.46    |
|                  | Day 3 (s)     | 16.95±2.39 | 38.71±6.63 | 19.15±4.57    | 28.64±4.25    |
|                  | Day 4 (s)     | 20.01±4.88 | 35.50±4.78 | 17.47±3.55    | 34.43±5.04    |
|                  | Day 5 (s)     | 17.50±3.23 | 26.61±5.30 | 18.82±3.05    | 25.05±2.62    |
| Probe trial      | Distance (%)  | 46.20±4.18 | 34.96±3.07 | 43.42±4.37    | 33.10±3.00    |
|                  | Time (s)      | 16.62±4.83 | 32.42±5.13 | 18.70±5.38    | 31.24±7.41    |
| **P35 rats**     |               |           |           |               |
| Place navigation | Day 1 (s)     | 48.49±4.15 | 45.33±4.89 | 55.32±1.79    | 52.22±1.79    |
|                  | Day 2 (s)     | 19.56±4.17 | 32.03±3.13 | 51.56±2.93    | 43.51±6.87    |
|                  | Day 3 (s)     | 16.56±3.06 | 14.56±6.69 | 44.20±5.04    | 40.82±7.44    |
|                  | Day 4 (s)     | 9.07±2.01  | 16.87±3.09 | 48.05±4.42    | 23.94±8.47    |
|                  | Day 5 (s)     | 4.82±0.73  | 4.93±0.47  | 41.03±3.72    | 20.34±7.61    |
| Probe trial      | Distance (%)  | 4.50±1.68  | 50.71±4.19 | 23.45±2.43    | 33.21±5.08    |
|                  | Time (s)      | 4.82±0.73  | 5.68±1.35  | 38.08±8.21    | 19.84±8.62    |

Table 2. Performance of P15 and P35 rats in spatial reference memory after VPA treatment.
respectively. These results showed that the changes of fEPSP in the hippocampal slice from the CSE model had the opposite trend in P15 and P35 rats. VPA significantly improved the fEPSP amplitude in the CSE group of P35 rats (p < 0.05), whereas no significant difference appeared in the P15 rats.

The induction period of LTP was studied after the hippocampal slices were stimulated by high frequency stimulation (HFS) for five minutes. The slope increase for the P35 rats was significantly higher than that of the P15 rats (p < 0.05); similar results were seen in the induced success rate of LTP (Table 3). These results indicate that CSE and VPA caused no obvious damage on the induction period of LTP, but the elution effect of ACSF to VPA during incubation was eliminated. VPA advanced the induced success rate in the CSE group of P35 rats (p < 0.05) but had no effect in the control group (p > 0.05). The sustainable period of LTP was also studied, and our results demonstrated that CSE and VPA caused no obvious damage in this period in the P15 rats except for the elution effect of ACSF to VPA during incubation. The fEPSP slope showed no change from 60 minutes in the control group, but decreased to 120% of baseline in the CSE group at 105 minutes (p < 0.05), which demonstrated that VPA prolonged the sustainable time of LTP in the CSE+VPA group of P35 rats to 140 minutes (p < 0.05).

The absorbance ratio of CaMKII or p-CaMKII with β-actin was set as one in P15 and P35 rats. Expression of CaMKII was not affected by CSE (p > 0.05) but decreased significantly with VPA-treated P15 rats (p < 0.05), as shown in Figure 4. Expression of p-CaMKII was the same as expression of CaMKII. VPA treatment in vivo had an inhibitory effect on expression and phosphorylation of CaMKII in P15 rats. Expression of p-CaMKII in each group was not changed markedly, which may be due to the difference in expression of CaMKII, which was decreased more in the VPA groups and CSE+VPA groups. The expression of CaMKII in the four groups of P35 rats was higher for all groups than the expression of CaMKII in the positive control group (p < 0.05), although there was no difference between groups (p > 0.05). A comparison of expression of p-CaMKII in the VPA group to that of the positive control group found no difference. However, data from the other three groups were all higher than the data from the positive control group (p < 0.05) and there was no difference between groups (p > 0.05).
Discussion

Classification of learning and memory

Learning and memory are physiological activities of advanced nerve activity in the brain. Learning is the act of acquiring new, or modifying and reinforcing, existing knowledge, behaviors, skills, values, or preferences, and may involve synthesizing different types of information. Memory is the process by which information is encoded, stored, and retrieved. The term “working memory” was coined by Miller, Galanter, and Pribram [10,11] and was used in the 1960s in the context of theories that likened the mind to a computer. Along with the continuous study of learning and memory, the Atkinson-Shiffrin model was first proposed in 1968 by Richard Atkinson and Richard Shiffrin [12], which changed the progress and direction of research about learning and memory. This model asserts that human memory has three separate components: a sensory register, a short-term store, and a long-term store. What we now call working memory was referred to as a “short-term store” or short-term memory [13]. Animal memory is relatively simple, and is divided into short-term memory

Table 3. Induced success rate of LTP in P15 and P35 rats.

|                | Control group | VPA group | CSE group | CSE+VPA group |
|----------------|---------------|-----------|-----------|---------------|
| P15 rats       | 35.27±4.36    | 31.63±7.59| 38.73±2.54| 29.58±7.33    |
| P35 rats       | 68.34±1.54    | 62.98±4.65| 33.68±6.37| 51.89±5.42    |

![Figure 3. (A) fEPSP amplitudes in each group. (B) fEPSP slopes in each group.](image-url)
and long-term memory, corresponding to working memory and reference memory in humans [14].

Learning and memory are different not only in forms of expression, but also in the memory system of structure and function, which involves different information processings, extraction methods, and neural mechanisms. At least four structural systems are involved in the regulation of learning and memory, including the hippocampus, amygdala, cerebral cortex, and cerebellum [15], of which the hippocampus is the most important; its loss will result in the complete absence of spatial learning and memory [16]. At present, test methods for learning and memory have been established for different brain regions. The Morris water maze was used in this study to research hippocampus-dependent spatial learning and memory, which is the most widely method in neural pharmacology.

**Age difference in effect of VPA on spatial learning and memory ability after CSE**

In rats, P15 and P35 are considered the equivalent ages of human infants and adolescents, respectively [17]. In our study, we found that the effect of CSE on spatial learning and memory ability was age-dependent. Significant damage appeared in P35 rats, while no damage appeared in P15 rats; similar results have been reported in other studies. The reason may be related to differences in the tolerance of the brain to damage at different ages. The incidence of convulsions in children is higher than that of adults, and children are more prone to present with the incidence of CSE in clinical practice. However, the mortality and disability caused by convulsive seizures in children is still lower than in adults [18], which may indicate that children have a relative tolerance to brain damage. Animal experiments have proved that a convulsive attack can cause the death of neurons in the hippocampus, and the loss of hippocampal neurons in an immature brain has been found to be significantly lower than that in the mature brain [19]. In our study, VPA significantly improved spatial learning and memory ability after CSE in P35 rats, which may be related to the decreased discharge of secondary epilepsy after CSE and the apoptosis of neurons.

**Mechanism of LTP**

LTP was first observed by Terje Lømo in 1966 in the laboratory of Per Andersen in Oslo, Norway [20]; Lømo proposed that LTP may be a synaptic model of memory. LTP has a persistent strengthening effect on synapses based on recent patterns of activity and is a type of information storage method. The enhancement of synaptic transmission efficiency after receiving a certain amount of reinforcing stimulus is mainly expressed as the enhancement of fEPSP [21]. In recent years, it has been confirmed that LTP in the hippocampus is the basic functional electrophysiological mechanism of learning and memory. Behavioral training can induce the appearance of LTP, while the inhibition of LTP can damage learning and memory ability, as has been established in experimental animals. Studies have found that the hippocampus is the main area of convulsive
attack and neuron injury by antiepileptic drugs (AEDs), and is the basis of epilepsy discharge and cognitive impairment by AEDs. Thus, cognitive impairment after CSE is closely related to the effects of AEDs on cognitive function and LTP in the hippocampus. In the hippocampus, presynaptic neurons release excitatory amino acids which combine with receptors in the postsynaptic membrane, motivating electrophysiological signal transduction in postsynaptic neurons to generate EPSP. The mechanism of abnormal discharge of neurons in the hippocampus affected by VPA also has an antiepileptic effect by inhibiting excitatory signal transmission between synapses. Therefore, VPA may have an inhibitory effect on the transduction of excitatory electrophysiological signals in the process of LTP.

Expression of CaMKII and p-CaMKII

CaMKII is the main component in postsynaptic densities (PSD), and accounts for 20–30% of total protein in PSD. When the concentration of Ca\(^{2+}\) in neurons increases too much and for a long time, CaMKII can lead to the phosphorylation of itself, becoming p-CaMKII [8]. During the induction and maintenance of LTP, the increase of the Ca\(^{2+}\) concentration in neurons only plays a triggering role, whereas CaMKII plays a more vital role. Studies have shown that the phosphorylation of Thr286 of the CaMK protein in neurons is a necessary factor and sufficient condition for the induced success of LTP [22]. At the final stage of LTP induction, the increase of the Ca\(^{2+}\) concentration in neurons can activate CaMKII and cause the phosphorylation of Thr286, whereas p-CaMK II is a molecular switch that triggers the LTP change. Activation of CaMKII is sufficient to cause LTP. In our VPA in vivo experiments, we found that VPA had a significant inhibitory effect on the p-CaMKII in P15 and P35 rats, suggesting that VPA may inhibit the induction and maintenance of LTP by inhibiting p-CaMKII, but the inhibition effect of p-CaMKII will be lost once LTP is induced successfully. However, the expression of p-CaMK in P35 rats increased significantly after CSE, while CSE caused obvious damage to the spatial learning and memory ability of P35 rats. The probable cause was that CSE caused significant damage to P35 rats, and secondary epilepsy discharge may cause an abnormal increase of Ca\(^{2+}\) concentration in neurons, promoting the increase of p-CaMKII.

Conclusions

VPA can significantly improve the spatial cognitive dysfunction in a CSE model of P35 rats, but also can cause obvious damage to the spatial memory of normal P15 and P35 rats. Improvements by VPA were closely related to the increase of induced success rate and the prolongation of the sustainable time of LTP. VPA treatment in vivo, which inhibited expression and phosphorylation of CaMKII and showed no obvious inhibition of LTP, may be related to the elution effect of VPA.

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Competing interests

The authors declare that they have no competing interests.

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