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# Sodium valproate at the therapeutic concentration inhibits the induction but not the maintenance phase of long-term potentiation in rat hippocampal CA1 area

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ABSTRACT

Sodium valproate (VPA) is currently one of the major antiepileptic drugs and has been reported to impair the induction of long-term potentiation (LTP) in rat hippocampal. However, there are discrepancies when used at therapeutic dose and few researches to study the effects of VPA on the maintenance of LTP. Here we investigated the effects of VPA at therapeutic concentration on two LTP phases: induction and maintenance in CA1 region. We found (1) VPA inhibited field excitatory postsynaptic potentials (fEPSPs) without modifying paired-pulse facilitation (PPF) solely occured presynaptically as a form of synaptic plasticity. (2) Pretreatment with VPA before high-frequency stimulation (HFS) decreased the fEPSPs slope. (3) There were no significant changes in fEPSPs slope with VPA applied in maintenance phase of LTP. These results indicate that VPA inhibited the induction of LTP postsynaptically without modifying presynaptic neurotransmitter release and had no significant influence on the two maintenance phase of LTP.



Adverse effects of antiepileptic drugs (AEDs) are common and cognitive impairment is one of the most common side effects including slowing of central information processing, impairment of short-term (working) memory and language disturbances such as anomia and dysphasia. Even modest effects can have significant impact on the functioning and lives especially for patients who are engaged in demanding activities such as schoolwork or employment that require focused attention and novel learning [1,2]. Among the traditional AEDs, sodium valproate (VPA) is currently one of the major antiepileptic drugs with a wide spectrum of anticonvulsant activity [3] and also used to prevent panic attacks or as a mood stabilizer in bipolar disorder [4]. In patients with epilepsy and/or normal volunteers, valproate has been reported to adversely affect cognition with a extent similar to carbamazepine and phenytoin, although the magnitude of the effects of these three drugs appears to be less than that of barbiturates and benzodiazepines [5–8]. Animal behavior studies have also shown that VPA exposure significantly impairs learning and memory in rats [9,10].

AEDs adversely affect cognition by suppressing neuronal excitability or enhancing inhibitory neurotransmission [11,12]. Long-term potentiation (LTP) in hippocampus refers to a long-lasting enhancement in efficacy of synaptic transmission, which is extensively studied as a synaptic model of learning and memory [13]. So VPA could suppress the expression of LTP via several different mechanisms to elicit its potent anticonvulsant effects. Analogous to learning and memory storage, LTP is divided into two phases: induction, triggering the synaptic potentiation rapidly (within seconds), and maintenance, sustaining the potentiation for hours in vitro and days in vivo [14]. Several researches have studied the effects of VPA on the induction of LTP and it possible mechanisms, but when used at therapeutic dose there are some discrepancies among these studies [15–18]. Moreover, there is no research to study the effects of VPA treatment on the LTP maintenance phase. In the present study, we investigated the effects of VPA at therapeutic dose on two LTP phases: induction and maintenance in the CA1 region of hippocampal slices, respectively. We conclude that VPA inhibits the induction of LTP through postsynaptic mechanisms without modifying presynaptic neurotransmitter release parameters and has no significant influence on the maintenance phase of LTP at therapeutic concentration.

## Materials and methods

*Animals.* Male Wistar rats (Chong Qing Medical University Animal Care Center), on postnatal 33–40 days, were used in this study.

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Upon arrival, the rats were allowed for a 7-day recovery from transport before they were used in the experiment. Rats were housed six in a cage in a temperature controlled (23 °C) colony room and maintained on a 12-h light/dark cycle with food and water ad libitum. Efforts were made to minimize both the suffering and the number of animals used. The experiments were carried out in accordance with the guidelines of the Local Institutional Animal Care and Use Committee.

*Preparation of hippocampal slices.* All animals were lightly anesthetized with ethyl ether, transcardially perfused within 30 s with 100 ml ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM) 120 NaCl, 3 KCl, 1.8 $NaH_2PO_4$, 26 $NaHCO_3$, 2 $CaCl_2$, 2 $MgCl_2$ and 10 D-glucose (pH 7.3–7.4) which were saturated with 95% $O_2$–5% $CO_2$. Then the rat was decapitated and the brain was quickly removed and placed in ice-cold oxygen saturated ACSF for approximately 1–2 min. Two hippocampi were rapidly dissected out and glued to the cutting stage of a vibratome (Vibroslice NVSLM1, WPI, USA) filled with ice-cold oxygen saturated cutting solution containing (in mM) 2.8 KCl, 1 $CaCl_2$, 1 $MgCl_2$, 2 $MgSO_4$, 1.5 $NaH_2PO_4$, 24 $NaHCO_3$, 0.4 vitamin C, 2 pyruvate-Na, 2 ATP-Mg, 10 D-glucose and 198 sucrose (pH 7.3–7.4), bubbled continuously with 95% $O_2$/5% $CO_2$. This low-sodium, low-calcium and high-magnesium solution is routinely used to reduce cellular damage promoted by calcium influx during slicing. Five to six transversely sectioned hippocampal slices (400 μm) were collected and placed on a nylon net within an interface chamber (BPC-PC, Warner, USA) filled with oxygen saturated recording solution containing (in mM) 124 NaCl, 2.8 KCl, 1.5 $NaH_2PO_4$, 24 $NaHCO_3$, 2 $CaCl_2$, 1 $MgSO_4$, 0.4 vitamin C, 2 pyruvate-Na, 2 ATP-Mg and 10 D-glucose (pH 7.3–7.4), bubbled continuously with 95% $O_2$–5% $CO_2$. The slices were first kept in recording solution at 35 °C for 30–45 min and then incubated in recording solution at 24 °C for at least 60 min. The longest time period between tissue preparation and recording was approximately 6 h.

*Stimulation and recording.* Slices were transferred to an immersion recording chamber placed on the stage of an upright microscope (Nikon E600FN, Tokyo, Japan) and perfused (1.5 ml/min) with oxygen saturated recording solutions at 35 °C. Extracellular field excitatory postsynaptic potentials (fEPSPs) were recorded deeply into the CA1 region of the stratum radiatum using glass microelectrodes filled with 2 M NaCl (resistance 1–2 MΩ) and amplified by an MultiClamp 700B amplifier (Axon Instruments, Foster City, CA, USA). A bipolar tungsten stimulating electrode was pressed against the surface of the Schaffer/Commissural fibers using a micromanipulator (MX160L, SD, USA), kept about 500 μm from the recording electrode. fEPSPs were evoked by a single test stimulus (0.1-ms duration at 0.05 Hz) using a constant current stimulus isolator (ISO-Flex, AMPI, Israel). Test stimulus current intensity was adjusted to evoke fEPSPs of approximately half of the maximal amplitude and then established a steady baseline (⩾30 min) before drug or tetanic stimulation was applied. For paired-pulse facilitation (PPF) induction, two pulses were delivered at test stimulus current intensity (50-ms interval). To elicit LTP, high-frequency stimulation (HFS) consisting of two trains of 100 stimuli at 100 Hz (30-s interval) were delivered at a current intensity set to produce 50% of the maximal fEPSP response, then recording continued for a minimum of 30 min to determine the effects of the HFS.

*Drug administration.* VPA (Sigma, final concentration: 70 μg/ml, a therapeutically attainable concentration [19]) were added to recording solution, which was perfused across the slices using standard delivery techniques as above. To study the effects on the induction phase of LTP, VPA was applied before HFS; to study the effects on the maintenance phase of LTP, VPA was applied after LTP had been successfully induced.

*Data analysis and statistics.* Data are expressed as the mean ± SD, unless otherwise noted. Statistical evaluation of data was performed using Student's *t*-tests. Probabilities less than 0.05 were considered statistically significant.

## Results

### *The effect of VPA on fEPSPs*

To analyse the effects of VPA on synaptic transmission, we first investigated its effect on fEPSPs at therapeutic dose, which were thought to participate in information coding at the cellular level. Recording solution containing 70 μg/ml VPA was superfused onto the slices after establishing a steady baseline of fEPSPs (⩾30 min) and the magnitude of the effect was quantified for 30 min. Compared with the data before drug application, VPA at therapeutic dose induced a progressive reduction (13.55 ± 11.24% of baseline fEPSPs; 60 min; $n = 6$; $p < 0.05$) of the fEPSPs amplitude (Fig. 1A and B). In control group without VPA, the fEPSPs amplitude remained stable for 1 h (100.02 ± 14.18% of baseline fEPSPs; 60 min; $n = 8$) (Fig. 1B). So VPA could significantly inhibit the excitatory synaptic transmission.

### *The effect of VPA on PPF*

Most excitatory synapses in the hippocampus exhibit PPF, which is defined as an increase in the size of the synaptic response to a second pulse delivered within a short interval of time following the first pulse and maximal at short (e.g., 50 ms) interstimulus intervals. PPF in the hippocampus is a well-established purely presynaptic phenomenon [20] and often used to monitor for presynaptic changes during LTP [21]. The PPF index was calculated from the expression $R2/R1$, where $R1$ and $R2$ were the peak amplitudes of the first and second fEPSPs, respectively. Compared with the data before drug application, $R1$ and $R2$ were both significantly reduced 10 min after VPA superfusion ($n = 6$; $p < 0.05$) and recovered 15 min after VPA clearation (Fig. 2A), but the PPF index ($R2/R1$) had no significant difference among the data before, during and after VPA superfusion ($n = 6$) (Fig. 2B). The above results imply that VPA reduces fEPSPs through postsynaptic mechanisms without modifying presynaptical neurotransmitter release.

### *The effect of VPA on the induction phase of LTP*

To explore the effect of VPA at therapeutic concentration on the induction phase of LTP, it was applied 30 min before HFS and perfused throughout all the experiment period. The data recorded before HFS application served as baseline controls. In VPA-treated group the mean slope of fEPSPs immediately after HFS was greatly lower than control group (202 ± 18% of baseline, 30 min, $n = 9$, VPA; 287 ± 16% of baseline, 30 min, $n = 8$, Con, $p < 0.05$) and progressively decreased (138 ± 16% of baseline, 60 min; 47 ± 12% of baseline, 120 min, $n = 9$, VPA, $p < 0.05$) while kept steady in control group from 30 min after HFS (183 ± 17% of baseline, 60 min; 191 ± 15% of baseline, 120 min, $n = 8$, Con) (Fig. 3).

### *The effect of VPA on the maintenance phase of LTP*

The maintenance phase of LTP in hippocampus can be divided into two phases, that is, early-phase (1–3 h) and later-phase (>3 h) [14]. To test whether VPA also affects the two maintenance phases of LTP, the drug was applied 30 min after successful LTP induction and perfused throughout the remaining experiment period. The data recorded before the drug application served as self-control in the VPA-treated group. There was no significant effect

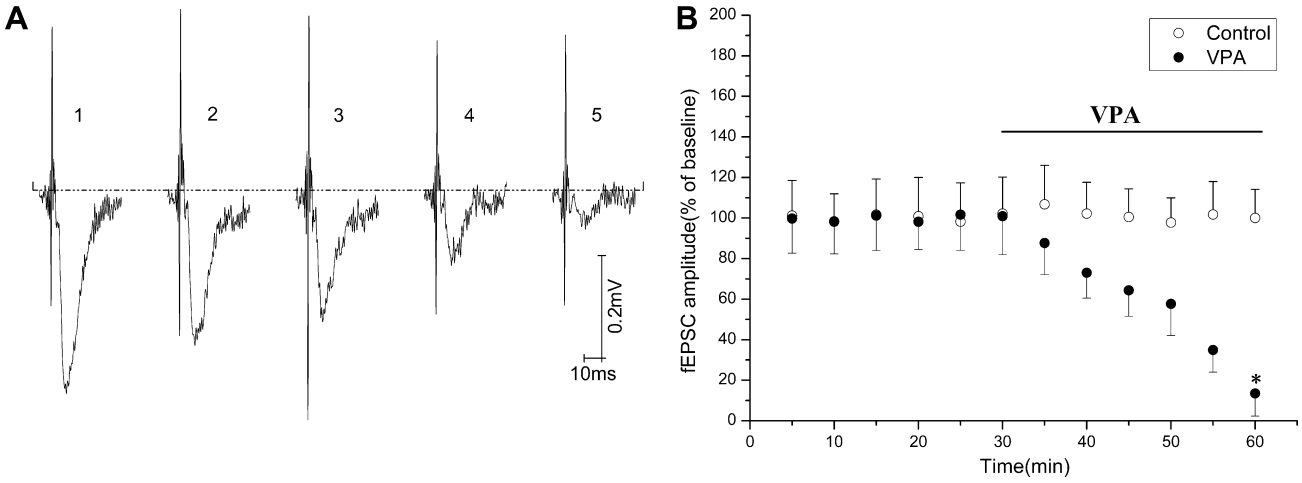


**Fig. 1.** VPA induced a progressive fEPSPs amplitude reduction. (A) Sample traces of extracellular fEPSPs recorded before (trace 1) and 5, 10, 20, 30 min (trace 2–5) after VPA application. (B) 70 μg/ml VPA induced a progressive reduction (13.55 ± 11.24% of baseline fEPSPs; 60 min; $n = 6$; $^{*}p < 0.05$) of fEPSPs amplitude but there were no significant changes in the control group (100.02 ± 14.18% of baseline fEPSPs; 60 min; $n = 8$). The horizontal dark bar in the graph indicates the time during drug application occurred in the VPA group.

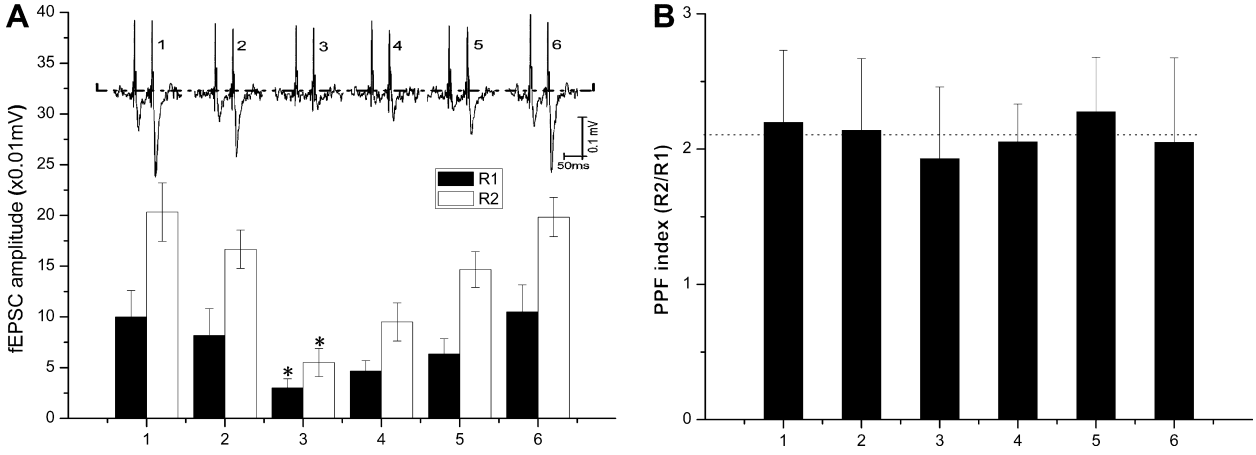


**Fig. 2.** VPA did not inhibit PPF. (A) VPA at therapeutic dose induced a reversible *R*1 and *R*2 reduction. Gradually reduced *R*1 and *R*2 before (1) and 5, 10 min (2, 3) after drug application and progressively recovered *R*1 and *R*2 5, 10, 15 min (4, 5, 6) after drug washout were represented in graph. Above were the sample traces of PPF recorded before, during and after drug application. $^{*}p < 0.05$, significant difference between 1 and 3. (B) The averaged PPF index (*R*2/*R*1) before, during and after VPA superfusion, which had no significant difference in above six time points. The numbers below the graph represent the same as in graph (A).

of VPA on fEPSPs slope compared with its self-control and the control group (191 ± 13% of baseline, 360 min, $n = 7$, VPA; 189 ± 23% of baseline, 60 min, $n = 7$, self-Con; 179 ± 19% of baseline, 360 min, $n = 6$, Con) (Fig. 4). The results show that VPA (70 μg/ml) have no outstanding effects on both maintenance phases of LTP although VPA significantly blocked the induction of LTP when applied before HFS.

## Discussion

In the present study, we used hippocampal brain slices to investigate the effects of VPA on the induction and maintenance phases of LTP at therapeutical dose. Our results indicate that VPA inhibits the induction of LTP postsynaptically without modifying presynaptic neurotransmitter release parameters but has no significant influence on the maintenance phase of LTP.

LTP of synaptic transmission in the hippocampus refers to an increase in the size of the fEPSPs and is the leading experimental model for the synaptic changes that may underlie learning and memory [13,22]. The hippocampal synapses that exhibit LTP use the neurotransmitter glutamate. Glutamate is released from the presynaptic cell with each action potential, and binds to receptors on the postsynaptic cell. It has been shown that VPA might interfere with excitatory synaptic transmission and decrease the quantal content of endplate potentials [23,24]. In our present studies, VPA at therapeutic concentrations 70 μg/ml induced a dramatic decrease of fEPSPs, which was induced by presynaptic or postsynaptic activity. PPF is a purely presynaptic phenomenon and is often used to control or monitor for presynaptic changes during LTP experiments [20]. To determine whether the effects of VPA on fEPSPs were exerted presynaptically or postsynaptically, we further estimated the changes of PPF after VPA (70 μg/ml) superfusion and found that although VPA significantly reduced *R*1 and *R*2 amplitude, the PPF index had no significant changes. Therefore we conclude that VPA reduced fEPSPs by suppressing postsynaptical signal transduction without reducing presynaptical excitatory neurotransmitters release, which was consistent with one previous research [17]. However, there were some discrepancies in our study compared with Zhang's study which had reported that VPA of 0.6 mM, 1 mM had no effects on fEPSPs but significantly decreased the PPF index [15], that maybe due to the differences in rats age and components of the recording solution.

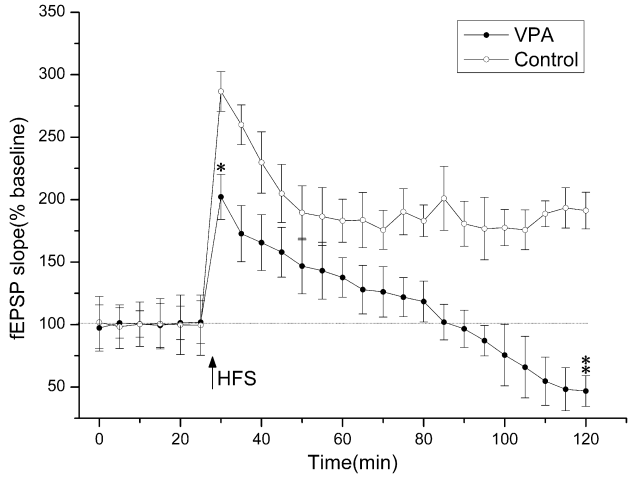


**Fig. 3.** The effect of VPA on the LTP induction phase. LTP was induced by HFS 30 min after VPA perfusion, which was delivered at the time point indicated by an arrow. In the control group, fEPSPs slope recorded immediately after HFS was 287 ± 16% of baseline ($n$ = 8, 30 min); in the VPA group, the fEPSPs slope with the same HFS protocol was 202 ± 18% of baseline ($n$ = 9, 30 min). In the VPA-treated slices the slope of fEPSPs measured 90 min after HFS was only 47 ± 12% of baseline compared to 191 ± 15% of baseline in the control group slices. $^{*}p < 0.05$, significant difference between the control group and the VPA group at 30 min; $^{**}p < 0.05$, significant difference between the data recorded at control group and the VPA group at 120 min.

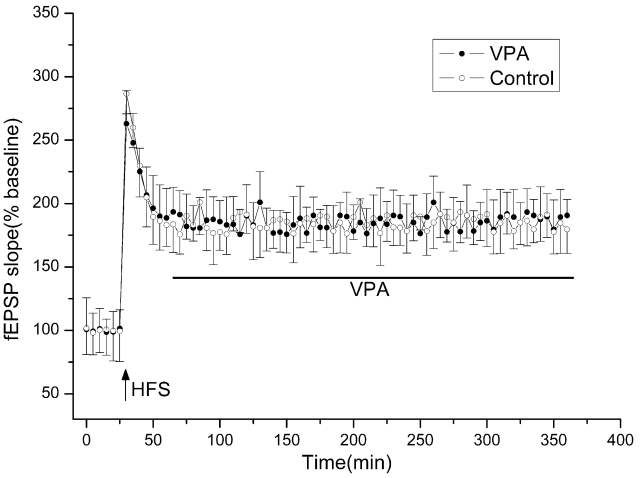


**Fig. 4.** The effect of VPA on the LTP maintenance phase. VPA was applied 30 min after the successful induction of LTP and perfused throughout all the experiment period. HFS (indicated by an arrow) of the Schaffer collaterals resulted in both early and late-phase of the LTP maintenance. The mean fEPSPs slope at 60 min in VPA group and control group were, respectively, 189 ± 23% ($n$ = 7), 183 ± 17% ($n$ = 6), and at 360 min they were, respectively, 191 ± 13% ($n$ = 7), 179 ± 19% ($n$ = 6). There was no significant effect of VPA on fEPSPs slope compared with its self-control and the control group in both early and late-phase of the LTP maintenance.

LTP in the hippocampus is considered to be important for elucidating the molecular mechanism of learning and memory and divided into induction and maintenance phases analogous to learning and memory storage [25]. Since VPA could reduce fEPSPs and LTP is characterized by a persistent increase in the size of fEPSPs, the LTP expression might be impaired by VPA at therapeutical dose. Therefore we further explored the effects of VPA on LTP expression. We first investigated the effects of VPA on the induction phase of LTP and found that VPA (70 μg/ml) significantly blocked the induction of LTP with a progressive decrease of the fEPSPs slope. The critical event leading to the induction of LTP is approved to be the influx of calcium ions into the postsynaptic spine, and the elevation of postsynaptic calcium concentration is necessary and sufficient for the induction of hippocampal LTP [13]. Meanwhile there are some reports that contributing to the anticonvulsant action VPA reduced the T-type $Ca^{2+}$ currents [11,26,27]. Therefore maybe VPA suppressed LTP induction through inhibiting $Ca^{2+}$ diffusing into the postsynaptic neurons. Although the induction of LTP in Schaffer collaterals-CA1 synapses is NMDA dependent, NMDA activation alone does not induce LTP. The calcium release from intracellular stores augments the NMDA-receptor-mediated calcium influx [28]. Thus, further studies are needed to determine whether VPA has any effects on calcium release from intracellular stores.

Although triggered rapidly, LTP can last for hours in vitro and days in vivo [29,30]. The NMDA-receptor-mediated $Ca^{2+}$ elevation of postsynaptic neurons during LTP induction can activate $Ca^{2+}$/calmodulin-dependent protein kinases II (CaMKII), which is the final step in the induction phase of LTP and makes CaMKII persistently autophosphorylated for at least one hour [22]. An important property of CaMKII is that when autophosphorylated on Thr286 its activity is no longer dependent on $Ca^{2+}$ entry even the $Ca^{2+}$ concentration has returned to baseline, and it is necessary for the maintenance of LTP and plays a critical role in the early-phase (1–3 h) of the LTP maintenance phase [31,32]. Our present study showed that when applied 30 min after successful triggeration, VPA (70 μg/ml) had no outstanding effects on the LTP maintenance during the first three hours (data not shown). The result suggests that VPA was not likely to inhibit the autophosphorylation of CaMKII. The switch from the early-phase to the late-phase (>3 h) of LTP maintenance requires gene transcription and new proteins synthesis. There are many evidences of newly synthesized proteins in the extracellular medium 3 h after the induction of LTP and LTP can be inhibited by the protein synthesis inhibitors [32–34]. In our study, the maintenance of LTP lasted for 5 h without significant suppression throughout all the experiment period with VPA application 30 min after the successful triggeration of LTP. The results indicate that the acute application of VPA at therapeutical dose after LTP was triggered successfully had no greatly effects on the new protein synthesis occurred in LTP maintenance phase.

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