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Effects of Lamotrigine on Field Potentials, Propagation, and Long-Term Potentiation in Rat Prefrontal Cortex in Multi-Electrode Recording

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Lamotrigine (LTG) is an anti-epileptic drug that is widely used clinically in various neuropsychiatric disorders. Although consensus is found on the general mode of action by LTG on voltage-gated sodium current, its effect on field potential, neuropropagation, and long-term potentiation, especially in prefrontal cortex (PFC), is still not understood completely. We investigated LTG effects on synaptic response in rat prefrontal cortical slice with the aid of a novel multi-electrode dish (MED64) system. The amplitude and propagation of field excitatory postsynaptic potentials (fEPSP), presynaptic fiber volleys (PrV) were expressed dimensionally in the MED64 system. Lamotrigine (3–100 μM) inhibited the amplitude and propagation of fEPSP and PrV in a concentration dependent manner. It exerted a predominant presynaptic action, as indicated by the increment in paired-pulse facilitation. Stimulating dependency with reduction fEPSP was seen in the presence of LTG at clinically relevant concentrations as well as with PrV, both in amplitude and propagation. In addition, the depression of PrV amplitudes in the presence of LTG showed a use-dependent fashion. As to LTP in PFC, it was not fEPSP amplitude but propagation reduced by LTG. In PFC, LTG exerts its use- and concentration-dependent inhibitory effect on presynaptic action and depresses fEPSP amplitude and propagation in a clinically relevant concentration. LTP was preserved in its fEPSP amplitude but not propagation in PFC in the presence of LTG.

Key words: lamotrigine; prefrontal cortex; presynaptic fiber volleys; excitatory post-synaptic potential; long-term potentiation

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,3-trazine] (LTG), one of the newer antiepileptic drugs (AED) with broad spectrum of clinical effects, has been used widely in the treatment of partial epilepsies with or without secondary generalization and absence seizures (Messenheimer, 1995; Bialer et al., 2004). Lamotrigine has also gained increasing interest as a potential mood stabilizer in treating bipolar disorders (Calabrese et al., 1998). In general, consensus is found on the mode of action by LTG on voltage-gated sodium current (Cheung et al., 1992; Lees and Leach, 1993; Xie et al., 1995; McKee and Brodie, 1996), resulting in blockade of the release of excitatory amino acid transmitters and reduction in sustained repetitive firing. The clinical profile of LTG seems broader than would be expected based on the single mechanism, however, and many other potential mechanisms of LTG have been suggested in previous studies. It has been suggested that LTG acts primarily postsynaptically in therapeutic concentrations (Calabresi et al., 1996; Langosch et al., 2000); LTG was reported to suppress Ca^{2+}-sensing cation current in cultured hippocampal neurons (Xiong et al., 2001). In addition, it has been demonstrated that LTG could alter 5-hydroxytryptamine receptor-mediated response in rat brain (Ahmad et al., 2005). Moreover, LTG was reported previously to increase the hyperpolarization-activated cation current in the dendrites of pyramidal neurons (Poolos et al., 2002) and it is of interest that it has been shown to inhibit A-type potassium currents in our previous studies in hippocampal neurons (Huang et al., 2004). Lack of effect of LTG on the presynaptic release of GABA, acetylcholine, norepinephrine, or dopamine were reported (Leach et al., 1986).

Lamotrigine has been shown to preserve cognitive performance, especially the behavior and attention, in normal and epilepsy individuals (Marciani et al., 1996;

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Ettinger et al., 1998; Martin et al., 1999; Gillham et al., 2000; Besag, 2001; Meador et al., 2001; Brunbech and Sabber, 2002). Improvement on attentional process has been reported in some epilepsy patients (Marciani et al., 1998) with unknown mechanism, although a marginal reduction in general cerebral insufficiency was suggested in another study (Banks and Beran, 1991).

Long-term potentiation (LTP), is long-lasting enhancement of synaptic function that is induced by a brief high-frequency tetanus (Teyler and DiScenna, 1987). This phenomenon has been investigated extensively as a process that could potentially underlie learning and memory formation in vertebrates (Bliss and Collingridge, 1993). Inconsistency exists between studies regarding LTG in LTP, though absence of effect of LTG on LTP in hippocampus has been studied in several reports (Wang et al., 1997; Xiong and Stringer, 1997; Otsuki et al., 1998; Langosch et al., 2000).

Prefrontal cortex (PFC) is essential in integrating attention and executive functions (Arnsten and Li, 2005). Previous investigations regarding the effects of LTG were mainly confined to hippocampus and enough information about the effect of LTG on LTP and field potentials in PFC is still lacking. One report concerning the effect of LTG in cortical slices has been noted (Calabresi et al., 1996) and instead of presynaptic mechanism, effect on non-NMDA glutamate receptors was suggested. Additionally, the general inhibitory effect on cortical neuronal excitability and the complex effect of LTG in PFC and limbic circuits were reported in a transcranial magnetic stimulation study (Li et al., 2004). As frontal lobe seizures are the second most common in partial seizures and with the increasing awareness of frontal lobe epilepsy syndrome (Kellinghaus and Luders, 2004; Oguni, 2004) and the impact of AED on cognitive performance, especially the attention and executive function, it will be necessary to further delineate the relationships between field potential properties and LTG, the potential AED in prefrontal cortex. The present study explores the effects of LTG on field potentials, including amplitudes, propagation patterns, and LTP by recording electrically-evoked potentials in rat PFC slices with the aid of a novel multi-electrode recording.

MATERIALS AND METHODS

Preparation of Prefrontal Coronal Slices

All the experiments described in this study were carried out in accordance with the specifications of the Ethical Committee of National Cheng Kung University and met the guidelines of the responsible governmental agency. Sprague-Dawley male rats (2–3 weeks old) were used for all experiments. They were originally housed under conditions of constant temperature at 22 ± 2°C with a 12-hr light:dark cycle and were sacrificed by decapitation after halothane anesthesia. A block of the rat brain including the whole primary frontal cortex was removed rapidly. Coronal slices of prefrontal cortex (400 μM thick) were prepared by a vibrating tissue slicer (DTK-100, Dosaka, Japan). This was carried out in an artificial cerebrospinal fluid (ACSF), made up of NaCl (124 mM), KCl (3 mM), $NaHCO_3$ (26 mM), $CaCl_2$ (2 mM), $MgSO_4$ (1 mM), KH_2PO_4 (1.25 mM), and d-glucose (10 mM) saturated with 95% O_2/5% CO_2 at pH 7.4 at 4°C. Slices were hemisected with a cut down the midline and transferred to an ACSF holding chamber for equilibration at room temperature. Electrophysiological recordings were started at least 1 hr after the recovery of slices.

Preparation of Electrophysiological Recording-Multi-Electrode Dish System

The 64-channel multi-electrode dish (MED64) system (Alpha MED Sciences, Tokyo, Japan), a novel two-dimensional neuronal electro activity monitoring technique based on the methods described by Oka et al. (1999) and Shimono et al. (2000), was employed. We used MED-P530A probes (Alpha MED Sciences) with 300 μM interpolar distance of electrodes, chamber depth of 10 mm and 64 planar microelectrodes in an 8 × 8 array for determination of the propagation patterns in prefrontal cortical evoked field potentials, including presynaptic fiber volley (PrV), an indicator of presynaptic intraneuronal response and field excitatory post synaptic potentials (fEPSP), an indicator of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/glutamate receptor response and LTP. During electrophysiological recording, the individual prefrontal cortical slice was positioned on the MED64 probe where it was placed on a fine mesh net and an adequate anchorage. The probe was composed of transparent liquid crystal materials except the electrodes, thereby allowing the localization of the electrodes in the slice under a microscope. The relative position of the multi electrodes on the motor cortex is shown in Figure 1A. The probe was superfused with ACSF at 32°C at a flow rate of 2 ml/min. One single planar microelectrode with bipolar constant current pulses (60 μA, 0.1 msec) was used for stimulation on the prefrontal slice. Stimulation patterns were designed using data acquisition software (Panasonic: MED conductor) and delivered through the isolator (BSI-2: Alpha MED Sciences Co., Tokyo, Japan). These procedures of electro-evoked stimulation were controlled by a computer running Windows NT. When the signal-to-noise (S/N ratio) was >3, detectable responses were recorded. The responses in all electrodes were evaluated and compared in a centrifugal fashion from the stimulating electrode. The visually detectable signal change in the central and visually undetectable signal change in the peripheral electrodes was defined responder and non-responder, respectively. The parameter of ''propagation'' indicated the total number of electrodes that monitored the detectable responses (the responsive electrodes). The parameter of ''amplitude'' indicated the total amount of amplitude of each PrV and fEPSP recorded by all electrodes that monitored the detectable responses. The propagation area and amplitude of PrV and fEPSP were recorded with all 64 microelectrodes (Okada et al., 2003; Huang et al., 2005), as demonstrated in Figure 1B,C. Lamotrigine (donated by Glaxo SmithKline Research and Development, Hertfordshire, NY) and 6,7-dinitroquinoxaline-2,3-dione (DNQX, an AMPA/glutamate receptor inhibitor, purchased from Sigma Chemical, St. Louis, MO) were the drugs used. Lamotrigine was applied into the bath by

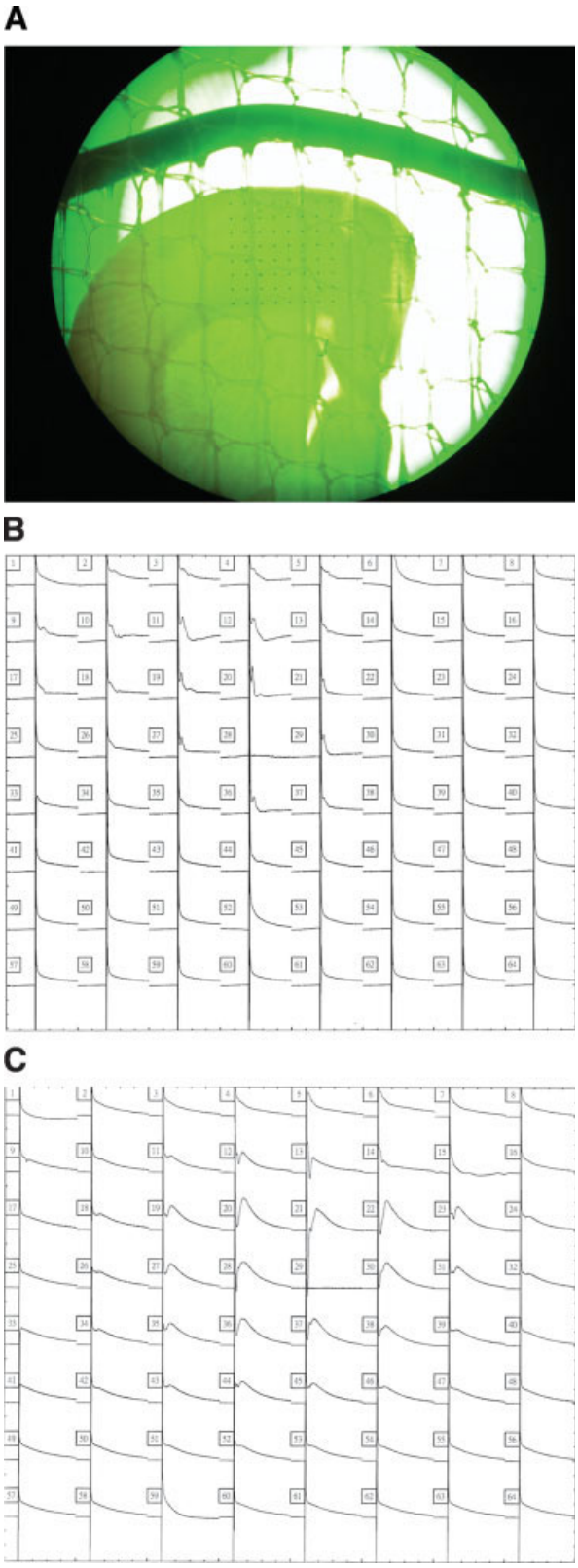


Fig. 1. The relative position of the multi-electrodes on the motor cortex of the prefrontal cortical slices (**A**). The representative figure of propagation area and amplitude of PrV (**B**) and fEPSP (**C**) recorded with all 64 microelectrodes.

dissolving it into the desired final concentration; DNQX was dissolved in dimethyl sulfoxide (DMSO) before it was added to the bath. All EPSPs were verified by the addition of DNQX.

For paired pulse facilitation two fEPSPs were evoked with twin pulses at interpulse intervals of 60 msec. A ratio of the second vs. the first potential was determined. For LTP experiments, tetanic LTP was elicited by high frequency stimulation (HFS) with a 1-sec 100-Hz volley (pulse duration = 500 msec). After the tetanic stimulation, excitatory postsynaptic potentials (EPSP) was recorded for 60 min at 1-min intervals from a slice.

Data Acquisition and Statistical Analysis

Data recorded during these experiments were analyzed by the software (MED Conductor), the Origin 6.0 software (Microcal Software, Inc., Northampton, MA) and custom-made macros in Excel (Microsoft, Redmont, WA). Data expressed as mean ± SEM. The effects of LTG on total amplitude of PrV and fEPSP responses were analyzed by repeated measurements of ANOVA. The effects of LTG on total propagation responses of PrV and fEPSP were analyzed by non-parametric Kruskal-Wallis test. The concentration of LTG required to inhibit 50% of total fEPSP amplitude was fitted to a non-linear regression. To analyze LTP data, responses were expressed as % change from pre-tetanus baseline (average = >10 min). Significance of the data was determined using ANOVA and *t*-tests (two-tailed, unpaired).The Solver subroutine built in Excel (Microsoft) was also used to fit data by a least-squares minimization procedure. A P-value < 0.05 denotes the presence of statistical significance.

RESULTS

Concentration Effects of LTG on fEPSPs on Rat PFC

The concentration effect of LTG on the total amplitude and propagation of fEPSPs were elicited. Lamotrigine was applied into the bath by dissolving it into the desired final concentration of 3, 10, 30, and 100 μM under a bipolar current pulse (stimulation intensity of 60 μA, 0.1 msec; $n = 8$). Figure 2 shows the representative inhibitory effect of PrV and fEPSP amplitude by 10 μM LTG. Figure 3 shows the relationship between the concentration of LTG and the percentage of inhibition of total fEPSP amplitude and propagation, respectively. Concentration dependent depression of fEPSPs by LTG was elicited. Evoked fEPSPs amplitude and propagation were depressed by LTG with a half maximal depression (54.2 ± 12.6%; mean ± SD, $n = 8$) occurred at 13.75 μM LTG ($P < 0.001$). The percentage of inhibition corresponding to the control and LTG concentration of 3, 10, 30, and 100 μM were 0, 16.5, 47.5, 65.9, and 87.9, respectively. The initial slope of fEPSP was also reduced by 45.8 ± 5% in the presence of 10 μM LTG. The average responsive electrodes corresponding to control and LTG 3, 10, 30, and 100 μM were 34, 28.5, 19.5, 9.5, and 5, respectively. These results indicate that LTG has a significant action on the fEPSP of the PFC, both in amplitude and propagation.

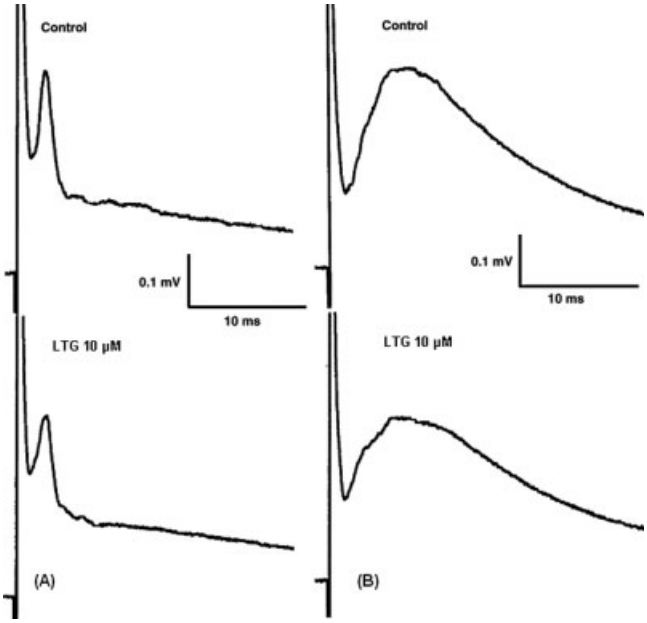


Fig. 2. Representative figure of the effect of lamotrigine (LTG) on field potentials. **A:** PrV amplitude recorded under control solution and in the presence of LTG 15 μM. **B:** fEPSP amplitude recorded under control solution and in the presence of LTG 15 μM.

fEPSP Depression Resulted From Depressed Excitatory Synaptic Input in LTG Treatment

The paradigm of paired-pulse facilitation (PPF), which has been used to differentiate the site of induction and expression of long-term potentiation (Manabe et al., 1993; Schulz et al., 1994), induces for a short time an increase in transmitter release resulting from the residual presynaptic free Ca^{2+} levels. A pair of synaptic responses was elicited with an inter-stimulus interval of 60 msec, and the ratio of the second response to the first one was monitored continuously during the experiment. In paired-pulse facilitation, LTG (15 μM) reduced the amplitude of the first EPSP but increased the EPSP2/EPSP1 ratio (Fig. 4A). The ratio of second/first EPSP response was 1.15 in control condition and 1.54 in the presence of 15 μM LTG (Fig. 4B).

Stimulating Amplitude Dependency of Total fEPSP and PrV Amplitudes and Propagation

Stimulating amplitudes with bipolar current of 20, 40, 60, and 80 μA vs. total fEPSP amplitudes and propagation in control and presence of LTG 15 μM were elicited. The presence of clinically relevant concentration of LTG (15 μM) caused stimulating dependency versus total fEPSP curves in a rightward shift (Fig. 5), on amplitudes and propagation, respectively ($n = 8$). Stimulating amplitudes of bipolar current of 20, 40, 60, and 80 μA vs. total PrV amplitudes and propagation in control and presence of LTG 15 μM were elicited. There was a significant effect of LTG on total PrV amplitude and propagation that caused stimulating dependency vs. total fEPSP curves in a rightward shift. (Fig. 6A,B; $n = 8$). fEPSP amplitude vs. PrV amplitude with

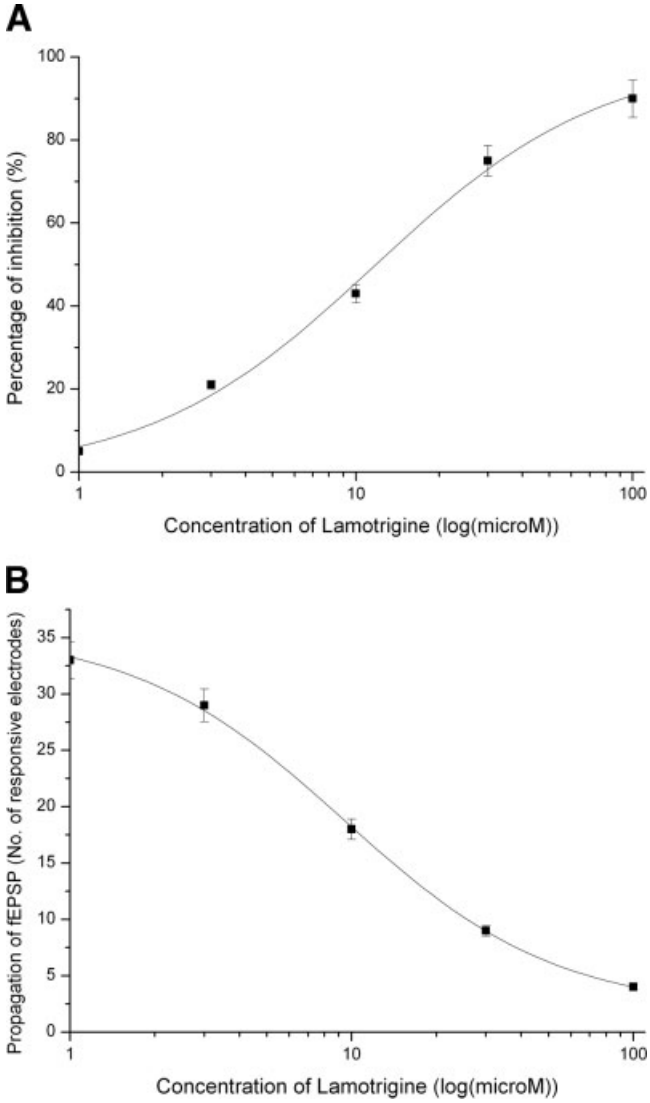
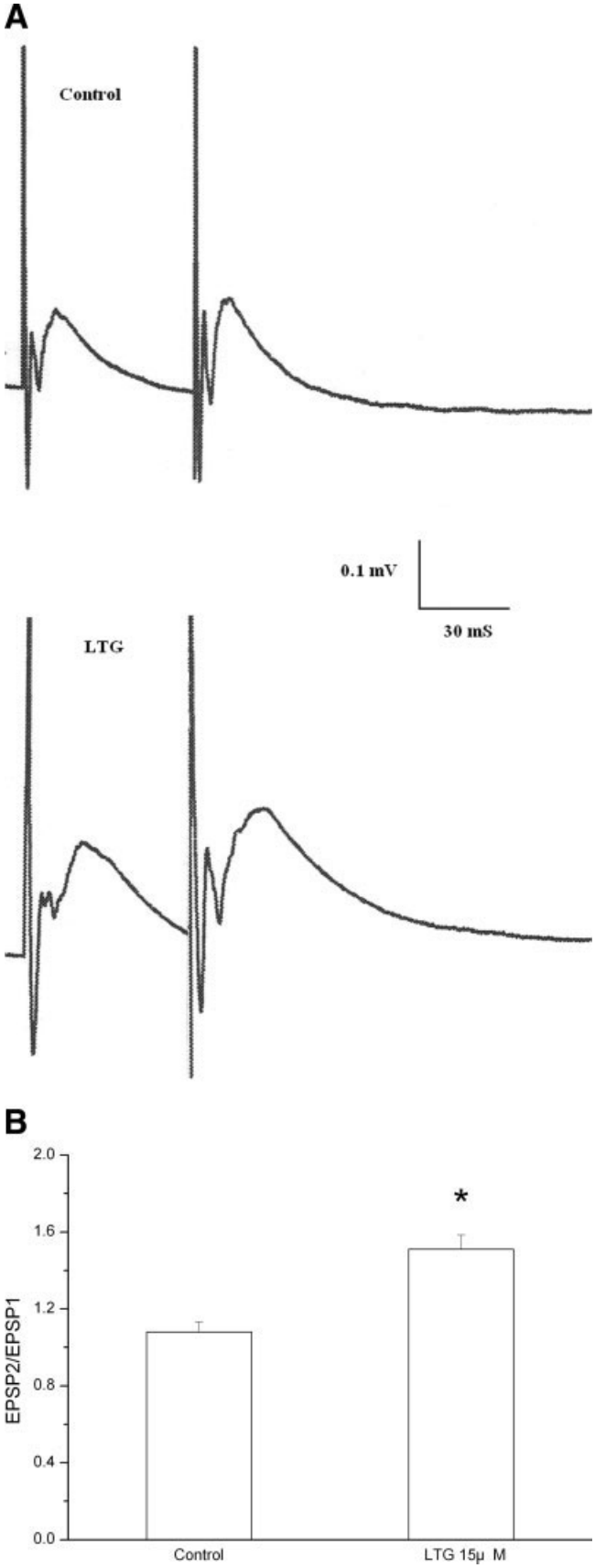


Fig. 3. **A:** Concentration-dependent inhibition of total fEPSP amplitude by LTG in rat prefrontal cortical slices. The IC_{50} value was 13.75 μM. **B:** Concentration-dependent inhibition of fEPSPs propagation by LTG in rat prefrontal cortical slices. Each point represents the mean ± SEM ($n = 8$). The smooth line represents the best logistic fit. The vertical ordinates indicate the propagation area (number of responsive electrodes).

increasing stimulus intensity is shown in Figure 6C, both values expressed as a percentage of maximum response. A best fit to the data was found to have a slope of 0.9 over the linear region.

LTG Depressed Presynaptic Fiber Volley in a Use-Dependent Manner

To determine whether LTG depressed axonal conduction, effect on isolated fiber volleys were studied. In the presence of 15 μM LTG, fiber volleys were depressed by 10 ± 2.5% for first pulse response ($P < 0.001$). The second and subsequent fiber volleys in a 30-



Hz train showed an increased in sensitivity to LTG (Fig. 7A). The second response in a train was depressed an additional 5%, and the twelfth response was depressed by a further 10% compared to the first, for a total depression of approximately 25%. The discrepancy in amplitude between the first and the last (12th) PrV was 0.0025 mV (control) vs. 0.013 mV (LTG) (Fig. 7B).

Effect of LTG on LTP in Amplitude and Propagation of Prefrontal fEPSP

Lamotrigine was induced in additional experiments. High frequency stimulation was applied in the presence of LTG 15μM and fEPSP were measured (Fig. 8A,B). Amplitude of fEPSP were not influenced by 15 μM LTG (139.5 ± 7.3%; control 148.3 ± 8.8%; 1 hr after HFS; $n = 8$) (Fig. 8C); however, the propagation of fEPSP was reduced in the presence of LTG (responsive electrodes: 33 [LTG] vs. 47 [control]) (Fig. 8D).

DISCUSSION

The main results of the study in PFC include: 1) LTG produced a potent depression of fEPSP amplitudes and propagation; 2) fEPSP depression resulted from depressed excitatory synaptic input; 3) LTG depressed presynaptic fiber volley in a use-dependent manner; 4) LTG exerts stimulating amplitude dependency of total amplitude and propagation of fEPSP and PrV in clinically relevant concentrations; and 5) LTG did not alter LTP of fEPSP amplitude but did impair its propagation in prefrontal cortex. To our knowledge, this is the first in vitro study clearly demonstrating the effect of LTG on LTP and field potentials in rat PFC. It has been shown that LTG is potent at depressing hippocampal CA 1 neuron fEPSP and population spike amplitudes (Langosch et al., 2000), consistent with the antiepileptic potency for LTG observed in vivo. In clinically relevant concentrations, LTG also exerts potent depression of fEPSP, both in amplitudes and propagation in prefrontal cortex, mainly through presynaptic inhibition. This is essentially correlated to a clinical transcranial magnetic stimulation study on LTG on concentration-dependent reduction of cortical excitability (Manganotti et al., 1999).

Lamotrigine-induced depression of prefrontal cortex seemed to result from an action at a presynaptic site to block excitatory synaptic input. As one of the newer antiepileptic drugs, LTG is also effective in preventing brain damage after recovery from cardiac arrest (Crumrine et al., 1997) and in vitro ischemia (oxygen-glucose deprivation) (Siniscalchi et al., 1998). This neuroprotec-

Fig. 4. Effects of LTG on paired-pulse facilitation. **A:** The traces show EPSPs evoked by paired stimulation in prefrontal cortical slices. Under control conditions, the amplitude of the EPSP evoked by the second stimulus was slightly higher than the amplitude of the first EPSP. LTG (15 μM) reduced the amplitude of the first EPSP but increased the EPSP2/EPSP1 ratio. **B:** Comparison between the effect of LTG (15 μM) and control on EPSP2/EPSP1. Mean ± SEM, *Significance at $P < 0.05$.

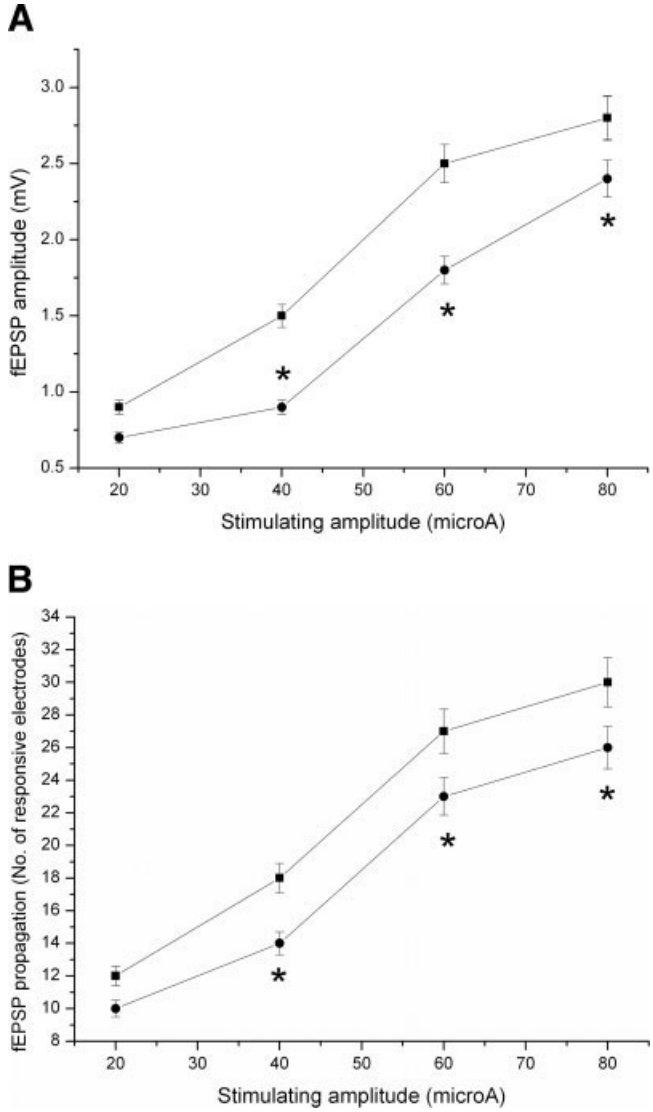


Fig. 5. **A:** Stimulating amplitude dependency of total fEPSP amplitudes in control and presence of LTG (15 μM). The presence of LTG caused stimulating dependency vs. total fEPSP amplitude curve with a rightward shift. **B:** Stimulating amplitude dependency of fEPSP propagation in control and presence of LTG. LTG (15 μM) caused stimulating dependency vs. fEPSP propagation curve with a rightward shift. Each point represents the mean ± SEM ($n = 8$). ■, control; ●, LTG 15 μM. ∗Significant difference from controls.

tive effect was suggested to result from depressed glutamate release, secondary to a block of voltage-activated sodium channels or altered function at *N*-methyl-D-aspartate receptors. In Xenopus oocytes, 31.9 μM LTG depressed rat-brain-derived Type IIA sodium channels by stabilizing inactivated channels (Liu et al., 2003). Similarly, the time course of fast recovery from inactivation was potently slowed by LTG on sodium currents in dissociated rat hippocampal granule neurons in both normal and the pilocarpine model of chronic epilepsy (Remy et al., 2003). This selective interaction of LTG

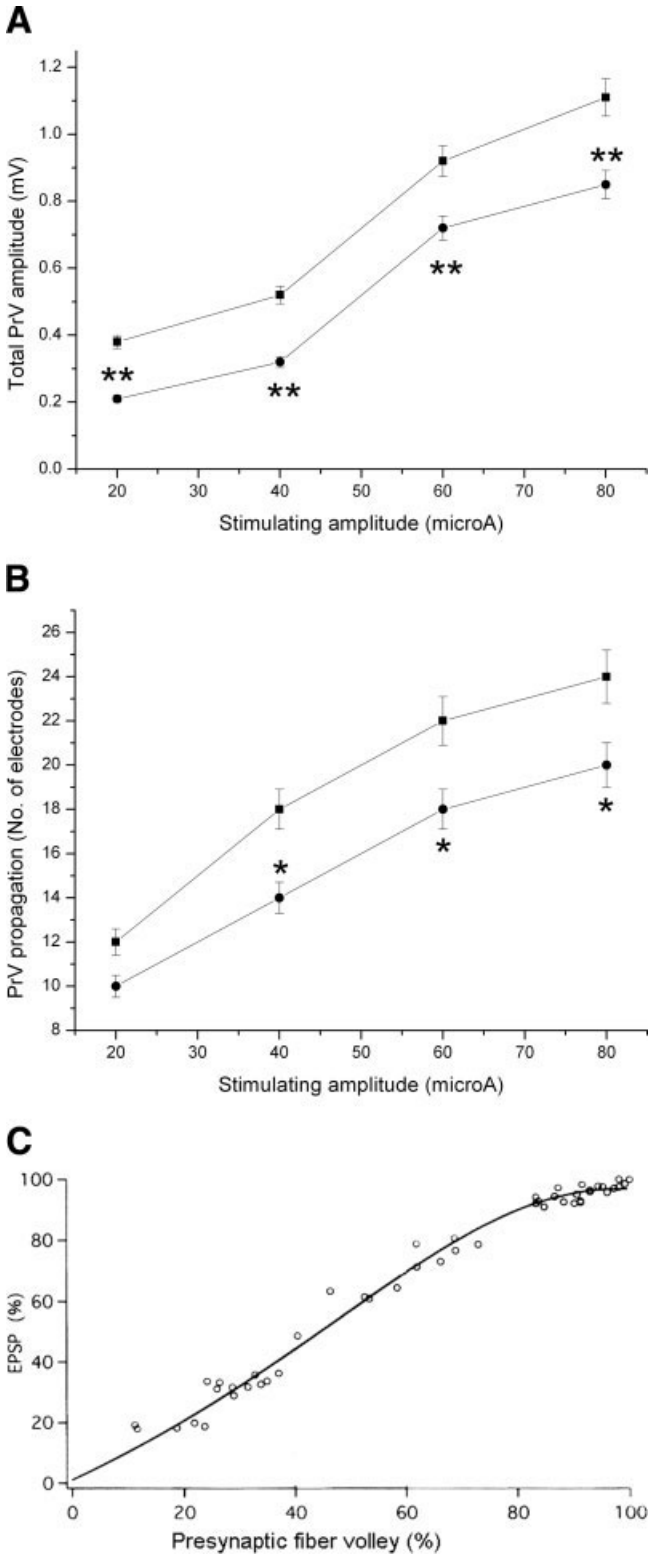


Figure 6

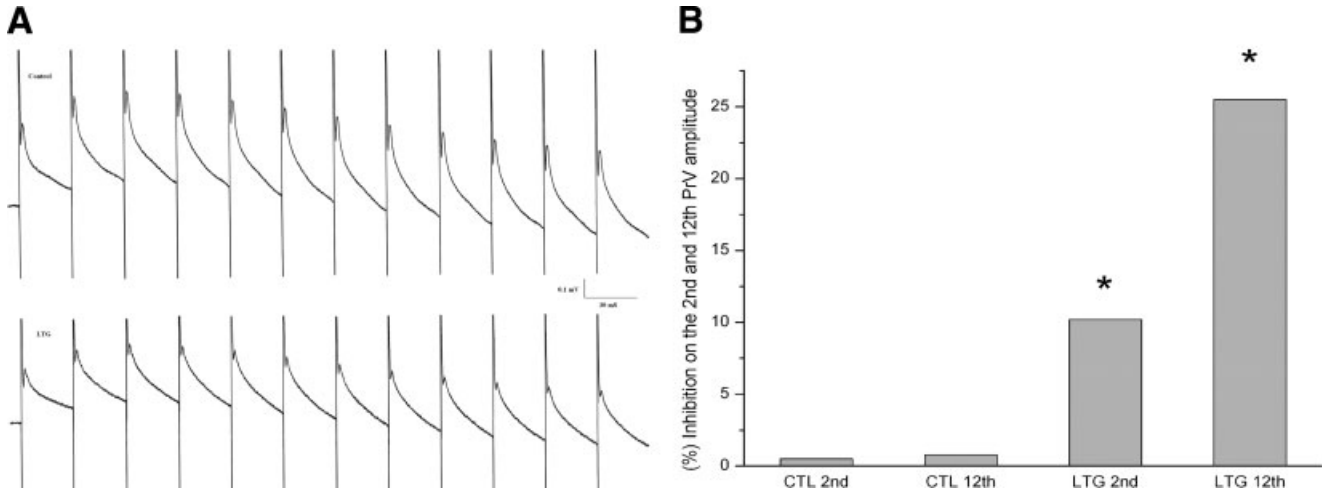


Fig. 7. Recordings of 12 consecutive PrV separated by interpulse intervals of 30 msec. **A:** Demonstrating a use-dependent decrease in amplitude produced by LTG (15 μM) compared to control group. The greater decrease in PrV amplitude produced by LTG on the last response compared to control was observed. **B:** The relative inhibition of the second and the twelfth fiber volley amplitude in both control and LTG. The discrepancy in amplitude between the first and the last (12th) PrV was 0.0025 mV (control) vs. 0.013 mV (LTG). Mean ± SEM. *Significance at $P < 0.05$.

with inactivated sodium channels could probably be related to the use-dependent depression of sodium channel-mediated conduction observed in the current study, although the detailed kinetics of sodium channels in PFC needs further investigation. Similarly, by analogy to the modulated receptor theory, these results suggest that LTG binds selectively to inactivated sodium channels. The high degree of selectivity and use-dependent fashion for LTG block of sodium channels could demonstrate the uniqueness of LTG in anti-epileptic properties.

Lamotrigine-induced depression of synaptically evoked neuron discharge in prefrontal cortex was paralleled by a reduction in EPSP and fiber volley amplitudes. Input/output analyses of fiber volley vs. EPSP relations demonstrated that depressed fiber volley amplitudes accounted for the depression of EPSP responses.

Synaptic plasticity and NMDA receptor activation as epileptogenic mechanisms as well as antagonists at NMDA receptors capable of inhibiting epileptic activity have been discussed (Mody, 1999; Leite et al., 2005). In our experimental setting, LTG had no definite influence on the induction and maintenance of LTP in the fEPSP amplitude, suggesting that, in clinical practice, cognitive performance such as attentional process of the frontal domains could be fairly preserved in the presence of LTG, both in normal individuals and in patients with epilepsy. Although the reduction of spontaneous epileptiform discharges by LTG in clinical studies could partially explain the favorable cognitive profile (Aldenkamp et al., 2003); from our study, the preserved amplitude in fEPSP after LTP would provide a more direct basis. Although in the dentate gyrus of urethane-anesthetized rats, no influence of LTG on LTP was reported (Xiong and Stringer, 1997; Otsuki et al., 1998), one report regarding LTG on tetraethylammonium-induced synaptic plasticity in the rat amygdala demonstrated the inhibitory effect of LTG on LTP and postsynaptic action site was suggested (Wang et al., 1997). The differential effects in prefrontal cortex, hippocampus, and amygdala need to be validated. Moreover, our study also suggested that in PFC, the NMDA receptor-independent pathway might be less activated because LTG would inhibit presynaptic sodium channels and calcium channels. It would also inhibit glutamate release but does not significantly affect LTP amplitude.

More recent experiments have suggested that LTP induced at one synapse may result in potentiation of nearby inactive synapses and this spreading LTP is anatomically discrete, occurring over a distance of <70 μM from the activated synapses (Engert and Bonhoeffer, 1997). The restriction of LTP to only those synapses directly activated during the tetanus, or ones located close to the activated synapses, suggests that the strength of small groups of synapses onto a neuron can be poten-

Fig. 6. **A:** Stimulating amplitude dependency of total PrV amplitude in controls and the presence of LTG (15 μM). The presence of LTG caused stimulating dependency vs. total fEPSP amplitude curve with a rightward shift. ■, control; ●, LTG 15 μM. **Significant difference from controls. **B:** Stimulating amplitude dependency of PrV propagation in controls and in the presence of LTG. Lamotrigine (15 μM) caused stimulating dependency vs. fEPSP propagation curve with a rightward shift. Each point represented the mean ± SEM ($n = 8$). ■, control; ●, LTG 15 μM. *Significant difference from controls. **C:** fEPSP amplitude vs. PrV amplitude with increasing stimulus intensity. Both values expressed as a percentage of maximum response. A best fit to the data was found to have a slope of 0.9 over the linear region.

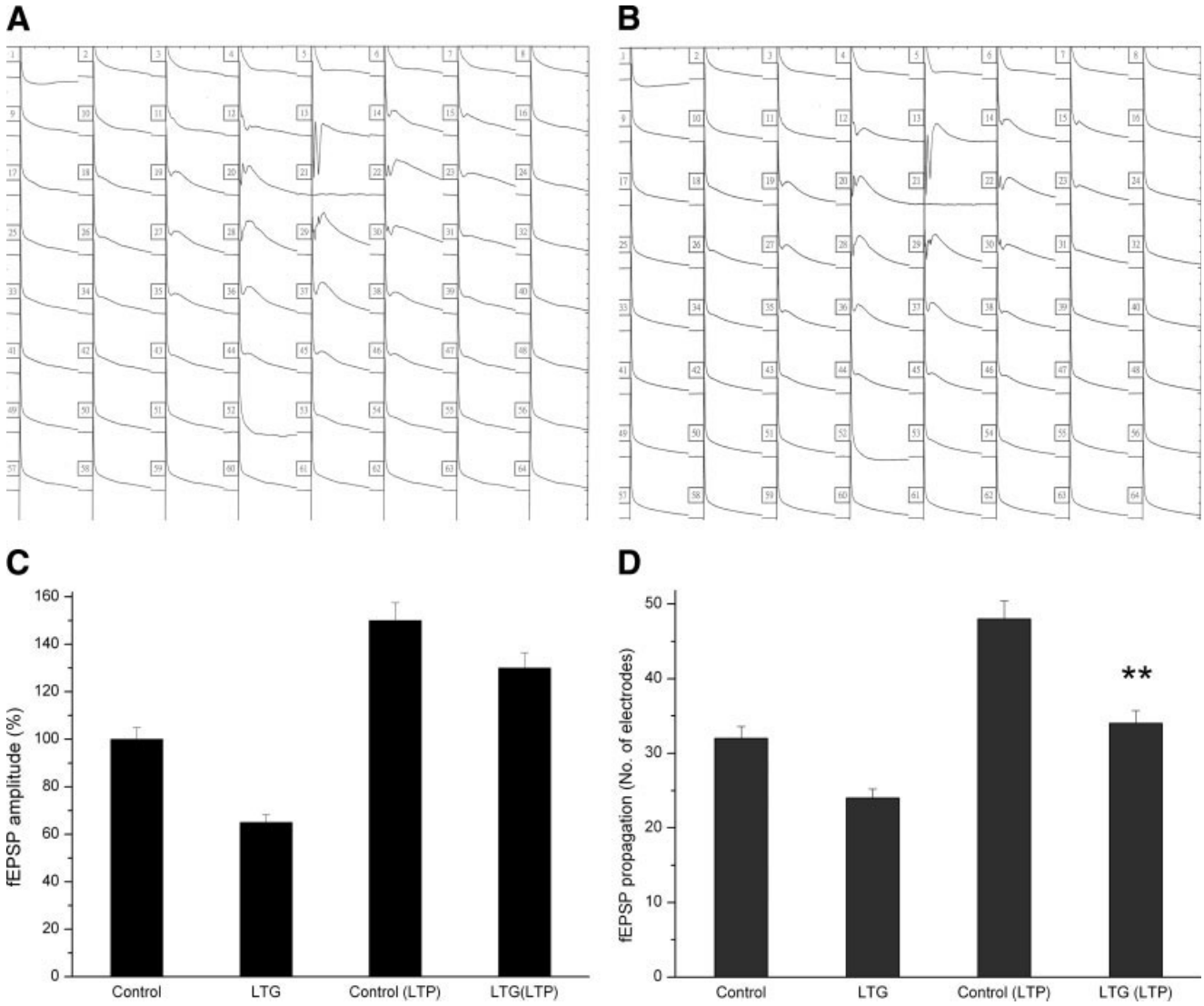


Fig. 8. High frequency stimulation was applied for LTP in the presence of LTG (15μM) and fEPSP were measured. **A:** Representative figure illustrating multi-electrode recording (MED64) of fEPSP after HFS in control and (**B**) in the presence of LTG. **C:** Amplitude of fEPSP were not influenced by 15 μM LTG (139.5 ± 7.3%; control 148.3 ± 8.8%; 1 hr after HFS; $n = 8$). **D:** The propagation of fEPSP was reduced in the presence of 15 μM LTG. The responsive electrodes were 33 in the presence of LTG and 47 in the control group. LTP: after HFS for LTP.

tiated independently. In our study with multi-electrode recording, the spreading effect (propagation) on LTP has been extensively evaluated. The interpolar distance of electrodes are 300 μM in our MED-P530A probes. It seems that the propagation effect on LTP would be wider, at least in PFC. The limited propagation effect in the presence of LTG suggested that LTP is regional specific. In addition, the reduction of propagation of fEPSP in LTP in our study might suggest an unfavorable role in more complex cognitive tasks, and this is worth considering with the clinical situation and needs further studies.

In situations of moderate to severe excitatory input, LTG exerts obvious suppression in PrV and fEPSPs with stimulating dependency. This phenomenon suggests the wide range of the effect of LTG in clinical seizures. In addition, the effects of LTG on propagation properties have been well described in our study with the aid of multi-electrode recording because all electrodes responsive for field potentials could be evaluated. Lamotrigine has been shown to prevent propagation of seizures in hippocampus (D'Arcangelo et al., 2001). From our study, LTG could inhibit the propagation activities bidirectionally either from the cortex to subcortical structures or from subcortical structures to the cortex. Clinically, LTG exerts good controllability over generalized seizures, such as absence epilepsy (French et al., 2004). In addition to antiepileptic effect, LTG has also gained evidence in treating bipolar affective and neuropathic

pain disorders, probably partially related to its antagonistic effect on N- and P-type calcium channels (Bialer et al., 2004), agonistic action on A-type potassium channel (Zona et al., 2002) and inhibitory effect on the kindling (Bialer et al., 2004). As seizures arising from the frontal lobe represent the second most common area of seizure onset in partial seizures and the increasing attention on the cognitive effect of an anti-epileptic drug, the role of LTG in frontal lobe function, especially in the epilepsy group, needs to be further investigated.

In conclusion, as a newer antiepileptic drug, LTG, exerts its use-dependent inhibitory effect on presynaptic glutamate release and further depresses fEPSP. LTG preserves LTP in fEPSP amplitude, but not its propagation in rat prefrontal cortex.

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