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# New Insights into the Mechanisms and Sites of Action of Lamotrigine

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**Key Words**
CA1 · Epilepsy · Field potentials · Guinea pig · Hippocampus · Lamotrigine · Synaptic transmission

**Abstract**
This study was aimed at investigating the effects of lamotrigine (LTG) on electrically evoked field excitatory postsynaptic potentials (fEPSP) and population spikes in the CA1 hippocampal region of guinea pigs. The concentration response curves showed different actions of LTG on fEPSP and on population spikes. The data are in contrast to previous findings that suggest the drug acts primarily on presynaptic sites via a blockade of the release of excitatory amino acids. In the range of therapeutic plasma levels, synaptic transmission was not affected.



## Introduction

The new antiepileptic drug lamotrigine (LTG) has been used in the treatment of focal epilepsy with or without secondary generalization [1, 2]. Additionally, there are now several reports indicating efficacy in the treatment of bipolar affective disorders [3, 4]. LTG is believed to block presynaptic voltage-sensitive sodium channels, which results in an inhibition of the release of excitatory amino acids [5, 6]. Furthermore, antagonistic effects of LTG on calcium channels have been found in rat cortical neurons and in the CA1/CA3 hippocampal area of guinea pigs [7, 8].

## Methods

Hippocampal slices were prepared as described previously. For preparation of concentration response curves, LTG was applied for 30 min, and the maximum change was measured. Each concentration was used on one slice only. The CA1 region of the hippocampus was identified by transmission microscopy and glass microelectrodes filled with 3 *M* NaCl were used to detect population spikes and fEPSP in the pyramidal cell layer or in the dendritic region of CA1, respectively. Test stimuli were generated by isolated pulse stimulators. Field potential changes (fEPSP and population spikes) were evoked by constant stimulation ($f$ = 0.066 Hz, duration 50 μs, $I$ = 0.8–4 mA) with an insulated bipolar tungsten electrode, placed in the stratum radiatum of CA1. The intensity of test stimulation was adjusted to evoke two thirds of maximal fEPSP or population spikes, respectively.

## Results

The concentration response curves showed different actions of LTG in concentrations near therapeutic plasma levels (10 μ*M*) on fEPSP and population spikes. The initial slopes of fEPSP were not affected, whereas the ampli-

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tudes of population spikes were significantly decreased by 15.1 ± 4.2%. Higher concentrations of LTG decreased both fEPSP slopes and population spikes amplitudes; however, effects on population spikes were much stronger. Those effects were reversible after a 30-min wash-out period.

## Discussion

The release of excitatory amino acids from presynaptic sites of the synaptic cleft as well as antagonistic actions on the various glutamate receptors are possible targets for drugs modulating synaptic transmission and excitability in the CA1 region of the hippocampus. LTG is believed to block voltage-sensitive sodium channels with a resulting decrease in glutamate release [5, 6]. The measurement of fEPSP may provide some evidence for a suspected modulation of synaptic transmission by LTG. Our experiments do not show any change in the slope of fEPSP at concentrations up to 10 μ*M* LTG. Therefore, no significant influence on the neurotransmitter release can be presumed in this concentration range. However, 10 μ*M* LTG is a concentration that clearly affects amplitudes of population spikes. A concentration of 10 μ*M* LTG in our experimental setting corresponds to estimated therapeutic plasma levels of about 4–16 μ*M* in humans, especially if 55% plasma protein binding is taken into account [9]. We have found effects of LTG on neurotransmitter release only for concentrations far above the pharmacologically relevant ones. However, at these concentrations, effects of LTG on population spikes were much stronger than on fEPSP. This is in contradiction to previous reports and may be due to higher concentrations or a pharmacologically induced transmitter release in those studies [5, 10, 11].

Measurements of population spikes are important in understanding the effects of LTG on the integration of synaptic signals into a neuronal output. Possible mechanisms for the decrease of population spike amplitudes reported here are well-known inhibitions of voltage-dependent sodium channels [12–14] and antagonistic effects of LTG on calcium channels [7, 8] or modulation of transient potassium outward currents as recently reported [15]. This might explain a reduced neuronal excitability and antiepileptic effects of LTG.

In conclusion, our experiments reveal different effects of LTG on synaptic transmission and on postsynaptic neuronal sites, whereas in the range of therapeutic plasma levels, synaptic transmission was unaffected.

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