BIOPHYSICS AND BIOCHEMISTRY

Effects of the Anticonvulsant Lamotrigine and Carbamazepine on Synaptic Transmission in the CA1 Area of Rat Hippocampal Slices

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Lamotrigine and carbamazepine (10^{-3} M) almost completely inhibit electrical activity of neurons in hippocampal slices. The effect of these drugs on signal transmission in the system of Schaffer collaterals/commissural fibers—CA1 hippocampal area pyramidal neurons shows that both anticonvulsants inhibit the excitability of the presynaptic axons and transmission efficiency in the glutamatergic synapses without any significant influence on signal transmission from a synapse to the spike generator region in the postsynaptic pyramidal neurons.

Key Words: *lamotrigine; carbamazepine; hippocamp; glutamatergic synaptic transmission*

Although lamotrigine (LT) and carbamazepine (CM) are widely used in clinics to treat epilepsy and affective disorders, the neuronal mechanisms of their anticonvulsant effects are virtually unknown [1,3]. There is evidence that LT and CM block the potential-dependent sodium channels of neuronal membranes and inhibit the release of excitatory neurotransmitter amino acids, glutamate in particular [4,5,7]. These data imply that these anticonvulsants affect signal transmission in the cerebral glutamate synapses. However, it is not clear what links in the signal transmission chain are the main targets for these drugs. The answer to this question may elucidate possible cellular mechanisms of epileptogenesis and help develop pharmacological tools to correct the seizure states.

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Our aim was to compare in hippocampal slices the effect of LT and CM on signal transmission in the system of Schaffer collateral/commissural fibers (SC/CF)-CA1 area pyramidal neurons. This transmission includes spike conduction in the membrane of presynaptic glutamatergic axons, signal transfer across the glutamate synapses and from a synapse to the spike generator region in postsynaptic pyramidal neurons.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 120-150 g. After decapitation under weak ether anesthesia, the brain was extracted and placed into oxygenated Krebs—Ringer's solution, where the left hippocamp was isolated. The hippocampal slices (340-360 μm) were prepared with tissue chopper by conventional technique [2] and superfused with Krebs-Ringer's solution (mM: NaCl 124; KCl 3; $MgSO_4$ 2; $CaCl_2$ 2; $NaHCO_3$ 26; KH_2PO_4 1.24;

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D-glucose 10; pH 7.4 was adjusted with 95% O_2, 5% CO_2; temperature 32°C). The superfusion rate was 1.2 ml/min.

Electrical stimulation of SC/CF was performed with a bipolar Nichrome electrode placed in the stratum radiatum of CA1 area. The field EPSP (fEPSP) together with the presynaptic fiber population spike (PrPS) and population spike (PS) of pyramidal neurons were recorded with two glass microelectrodes placed in the stratum radiatum and in the stratum pyramidale of the CA1 area, respectively. To stabilize the electrical activity of the neurons, the superfused slices were allowed to equilibrate in the chamber for 3 h. Then they were stimulated with rectangular electric current pulses (0.1 msec) of various amplitude. The amplitude varied from the threshold value to that which evoked the maximum PS of pyramidal neurons. The evoked responses were processed in a computer with original software based on the algorithm [6]. Both LT and CM were dissolved in the superfusion medium to final concentrations of 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M (CM was dissolved initially in dimethyl sulfoxide).

To analyze the effect of these drugs on the signal transmission in SC/CF-CA1 area pyramidal neurons system, we studied dependences of PrPS amplitude (mV) on stimulus intensity (μA), slope of the falling phase of fEPSP (mV/msec) on PrPS amplitude (mV), and PS amplitude (mV) on fEPSP slope [6]. Statistical significance of the intergroup differences was determined by analysis of variance (ANOVA).

RESULTS

Figure 1 shows the concentration dependence of LT and CM effects on PrPS and PS amplitude as well as on fEPSP slope at the stimulus intensity that evoked the maximum PS in the control.

LT (10^{-5} M) caused a statistically significant decrease in the PrPS amplitude, the effect being more pronounced at 10^{-4} M. After washing the slices from LT, the PrPS amplitude turned to the control level. The effect of LT on fEPSP manifested itself in a decrease in the slope of its falling phase. It was significant only at a concentration of 10^{-4} M. The amplitude decrement of PS of pyramidal neurons was significant for all tested LT concentrations.

In contrast to LT, CM did not produce any significant effect on the PrPS amplitude at concentrations 10^{-5} and 10^{-6} M. However, in a concentration of 10^{-4} M CM significantly decreased this index. A decrease in the fEPSP slope was significant for all tested concentrations of CM, while PS amplitude decreased significantly only at 10^{-4} M CM.

Analysis of the "input-output" functions (Fig. 2) showed that LT decreased the excitability of presynaptic glutamatergic fibers (see the dependence PrPS amplitude on stimulus intensity) and inhibited signal transmission in the glutamatergic synapses (the dependence of fEPSP slope on PrPS amplitude), but it did not affect the excitability of the postsynaptic pyramidal neurons (the dependence of PS amplitude on fEPSP slope). CM produced similar effects, but its influence on the excitability of glutamatergic fibers was revealed only at a concentration of 10^{-4} M.

In a concentration of 10^{-3} M both drugs almost completely suppressed the electrical activity of neurons in CA1 area of hippocampal slices (data not shown).

Thus, both LT and CM produced a general inhibitory effect on the excitability of neurons in CA1 area. However, their inhibitory effects on various links of signal transmission in SC/CF—CA1 pyramidal neurons system were concentration-dependent. LT inhibited the excitability of presynaptic axons in a concentration-dependent manner and,

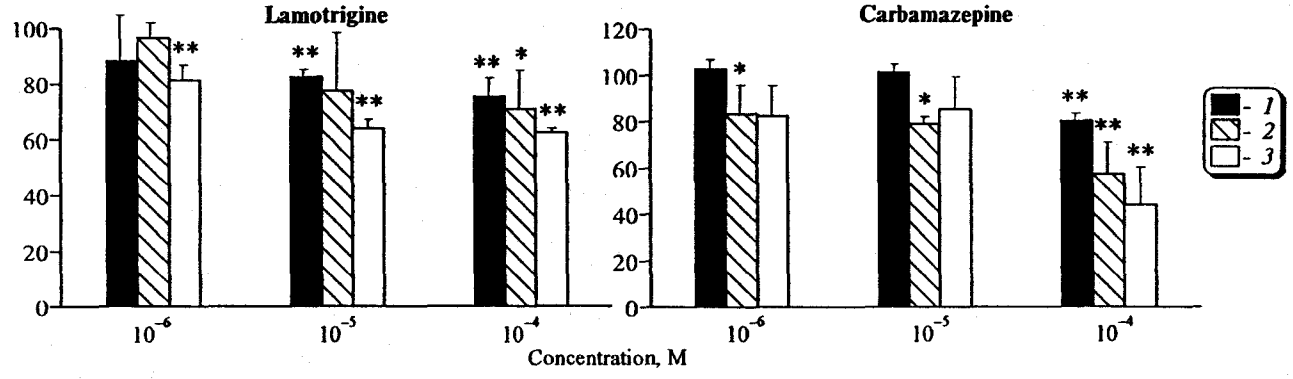

Fig. 1. Concentration-dependent effects of lamotrigine and carbamazepine on the amplitudes of population spikes of (*1*) presynaptic fibers and (*3*) pyramidal neurons and (*2*) on the slope of the falling phase of the field EPSP in a 1-msec period. Data are shown in percentage (n=4) relative to the control values of the corresponding parameters recorded prior to application of the drugs. *p<0.05, **p<0.001 in comparison with control.

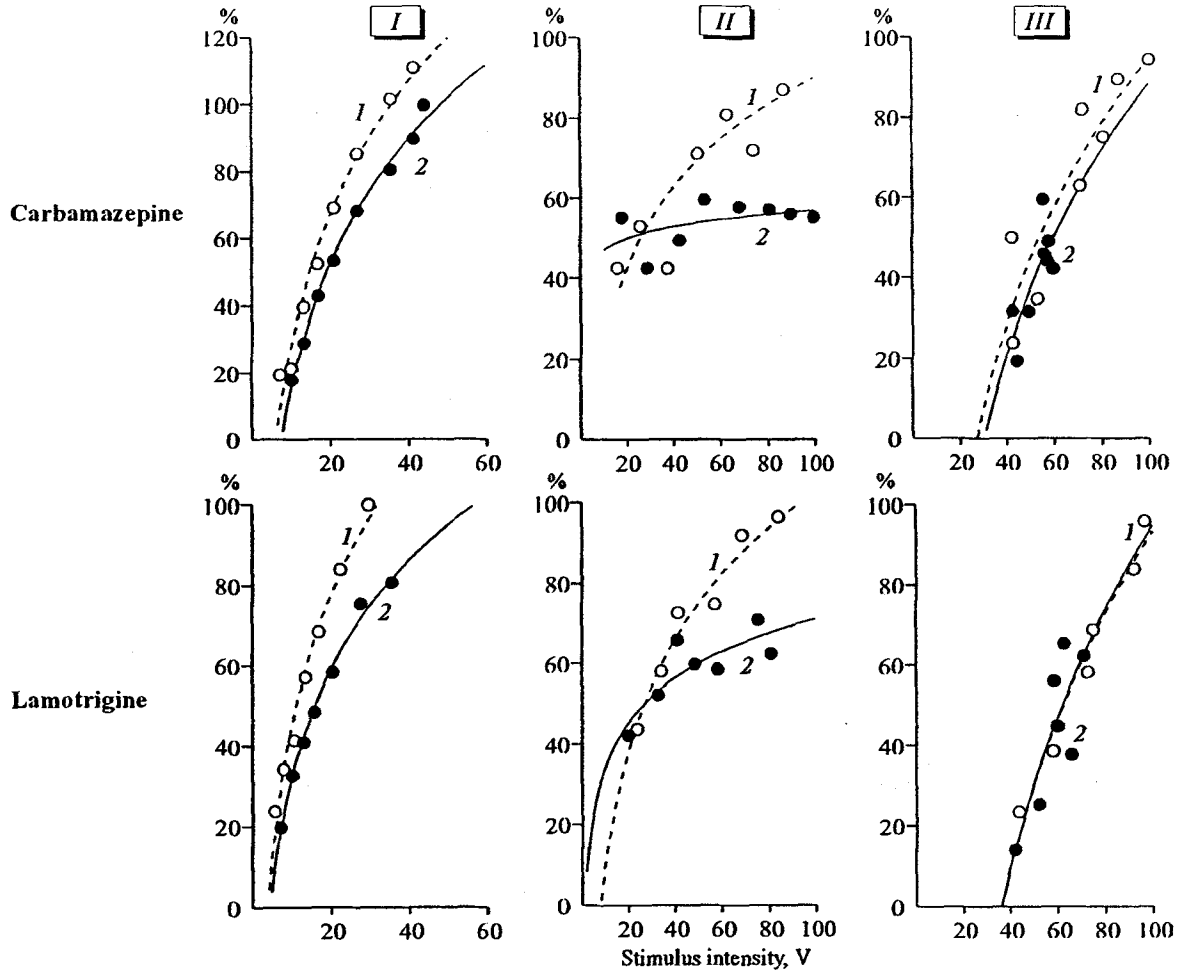

Fig. 2. Dependences of (*I*) the amplitude of presynaptic fibers population spike on stimulus intensity, (*II*) slope of the falling phase of the field EPSP (in 1 msec period) on presynaptic fibers population spike amplitude and (*III*) amplitude of population spike of pyramidal neurons on the slope of field EPSP (in 1 msec period) in (*1*) control condition and (2) under the action of a drug in concentration of 10^{-4} M. Data are shown in percentage (n=4) relative to the control values of the corresponding parameters recorded prior to commencement of application of the drugs. The stimulus intensity corresponded to the maximum amplitude of the population spike in pyramidal neurons.

although its influence on the effectiveness of synaptic transmission was statistically significant only at 10^{-4} M, the PS amplitude of pyramidal neurons decreased significantly at all tested concentrations of this anticonvulsant. When applied in the concentration range of 10^{-6}-10^{-5} M, CM significantly decreased the synaptic transmission efficacy, while it virtually did not affect the excitability of presynaptic axons. At the same time, there was no significant decrease in PS amplitude. Strong inhibition of the three stages of synaptic transmission was observed only when CM was applied in a concentration of 10^{-4} M. In a concentration of 10^{-3} M both anticonvulsants completely suppressed the evoked electrical activity of the CA1 area neurons in rat hippocampal slices. Thus, our results attest to a significant difference in the neuronal mechanisms underlying the effects of LT and CM, which agrees with the concept that LT acts predominantly at the presynaptic level [7].

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