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Delayed treatments with pharmacological modulators of pre- and postsynaptic mGlu receptors rescue the hippocampus from kainate-induced neurodegeneration

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HIGHLIGHTS

- Microinjection of kainic acid into dorsal hippocampus results in neurodegeneration.
- Kainic acid leads to various changes in expression of mGlu receptors.
- Modulation of mGlu receptors activity is capable of reducing kainate excitotoxicity.
- Delayed combined treatment with MPEP and LY354740 decrease cell death.

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ABSTRACT

Gene expression of mGluR2, mGluR3 and mGluR5 was evaluated in the hippocampus and frontal cortex in Wistar rats in 1 and 4 weeks after bilateral microinjection of kainic acid into the dorsal hippocampus. The time-course of the receptors' expression suggested their adaptive role in response on the induction of excitotoxicity. It was assumed that the decrease of kainate-induced neurodegeneration could be achieved through simultaneous activation of presynaptic mGluRs and inhibition of mGlu postsynaptic receptors. Both negative allosteric modulator of mGluR5, MPEP, and agonist of mGluR2, LY354740, were administered intraperitoneally 5 days after microinjection of kainic acid. As shown by histochemical studies with cresyl violet and Fluoro-Jade, kainate induced significant damage of hippocampal neurons in the CA3 and CA1 fields. Pharmacological treatment with the negative modulator of mGlu5 receptors in common with the agonist of mGluR2 decreased kainate-induced neurodegeneration in dorsal hippocampus.

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1. Introduction

Excitotoxicity occurs in the nervous system as a result of excessive stimulation of glutamate receptors is associated with cell death observed in ischemia, brain trauma, some neurodegenerative diseases including epilepsy, Parkinson's disease and Alzheimer disease [1,2]. Cellular mechanisms of excitotoxicity are generally known: Ca^{2+} overflow occurs in neuron cytoplasm as a result of excessive activation of glutamate receptors; and subsequent activation of enzymes produce degradation of the cytoskeleton, membranes, and components of protein synthesis system. However, blockers of ionotropic glutamate receptors or calcium channels proved to be unsuitable as protectors for clinical use because of their low efficacy or side effects [2,3]. It was found that metabotropic glutamate receptors (mGluRs) might be promising targets for the neuroprotection against glutamate excitotoxicity [4]. There are eight types of mGluRs divided into three groups: group I (mGluR1, mGluR5), group II (mGluR2, mGluR3), group III (mGluR4, mGluR6, mGluR7, mGluR8). The role of mGluRs in synaptic transmission is determined by several factors: the source of glutamate, time-course of glutamate release into the extracellular space, receptor affinity for glutamate and subcellular localization of the receptor [5,6]. For example, receptors of group I mGluR1 and mGluR5 in hippocampus are localized predominantly at postsynaptic membranes. Both

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mGluR1 and mGluR5 are expressed in the pyramidal neurons of CA3, but CA1 neurons predominantly express mGluR5 [5–7]. Pharmacological blockade of mGlu5 receptors is able to reduce neurodegeneration, as shown in experiments *in vitro* and *in vivo* [4,8]. Stimulation of group II receptors, localized predominantly at presynaptic membranes, also possesses a neuroprotective effect that is shown for alcohol-induced neurodegeneration [9].

Microinjection of kainic acid into the brain leads to epileptic events and neuronal death, especially in the hippocampus [8,10,11]. Kainic acid injected into the hippocampus alters the expression of a large number of genes, in particular, those of glutamate receptors, in the injured hippocampus and in some other areas of the brain [12–15]. The time-course of mGluRs expression is complex: the expression level can be upregulated, as well as downregulated at different stages of degeneration. Therefore, we assessed the expression of the mGluRs, localized in the hippocampus predominantly presynaptically (mGluR2, mGluR3) and postsynaptically (mGluR5), in order to use these results for subsequent pharmacological modulation of the receptor activity with aim to find an effective treatment for kainate-induced neurodegeneration.

2. Materials and methods

Twenty eight male Wistar rats weighting 200–220 g were used in the study. Experiments were carried out in accordance with the guidelines of the Institutional Animal Care and Use Commission of ITEB RAS and the Council of the European Community (EC Directive of 1986). Rats were kept on a 12/12 h light/dark schedule with free access to water and food.

2.1. Kainic acid microinjection

Animals were anaesthetized with tiletamine/zolazepam (Virbac) and xylazine (De Adelaar) injected intraperitoneally (i.p.) at doses of 12.5/12.5 mg/kg, and 12 mg/kg, respectively. Kainic acid (Sigma) was dissolved in sterile saline and injected bilaterally into the dorsal hippocampus (AP: −3.0 mm; ML: ±3.0 mm; V: −3.0 mm [16]) at dose of 0.2 μg, in volume of 1 μl, in each side. Saline was injected into the hippocampus in rats of control group. After the treatment with kainate or saline, the rat was under attentive care for 6 h, and then returned in home cage. Within 2–4 h after microinjection of kainic acid transient limbic convulsions (the head and

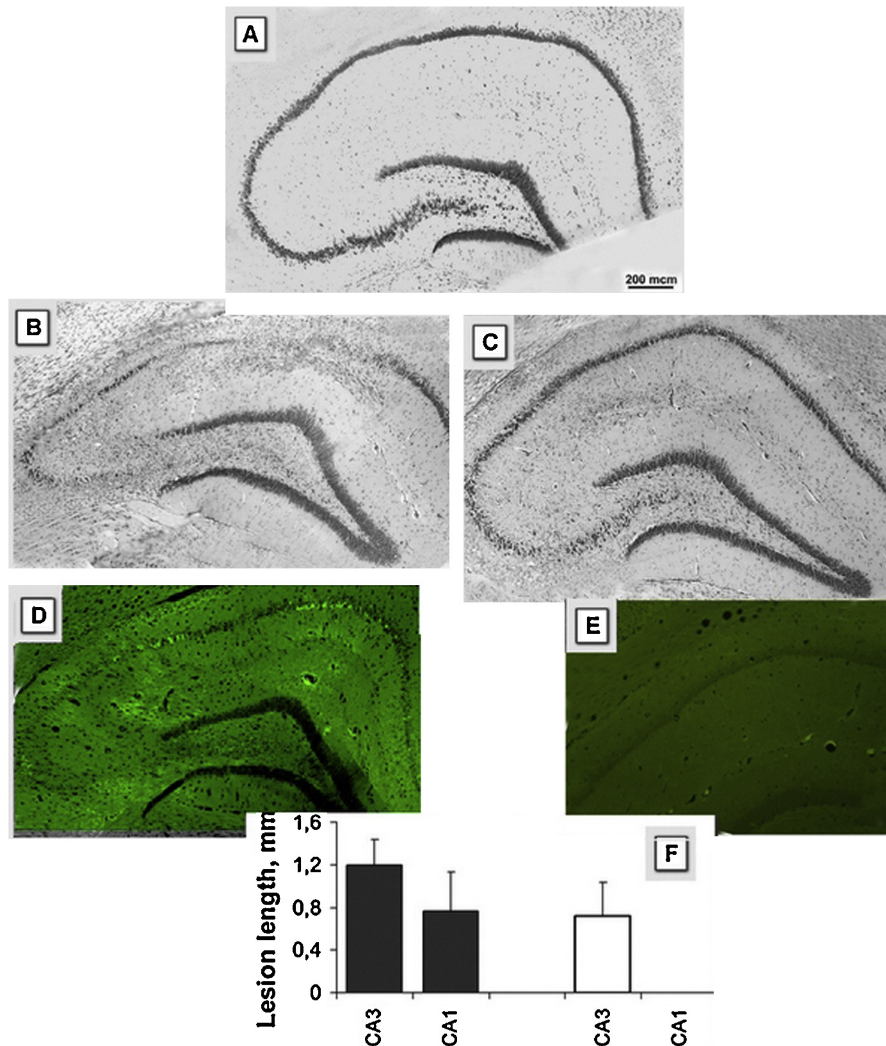

Fig. 1. (A) Hippocampal section of control rat; (B and D) sections of kainate-treated rat in 4 weeks after microinjection of 0.2 μg kainic acid into the hippocampus; (C and E) sections of rat in 4 weeks after kainic acid microinjection and subsequent treatment with the MPEP (5 mg/kg, i.p., once a day, 5 and 6 days after kainate), and LY354740 (2 mg/kg, i.p., once a day, 5–9 days after kainate); (F) CA1 and CA3 lesions in rat hippocampi 4 weeks after kainate microinjection (black bars, $n = 5$) and in 4 weeks after kainate microinjection additionally treated with MPEP and LY354740, as pointed above (white bars, $n = 5$). CA1 and CA3 lesion was calculated on equally located sections using the program ImageJ. Hippocampal sections were stained with cresyl violet (A–C) or Fluoro-Jade (D and E).

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