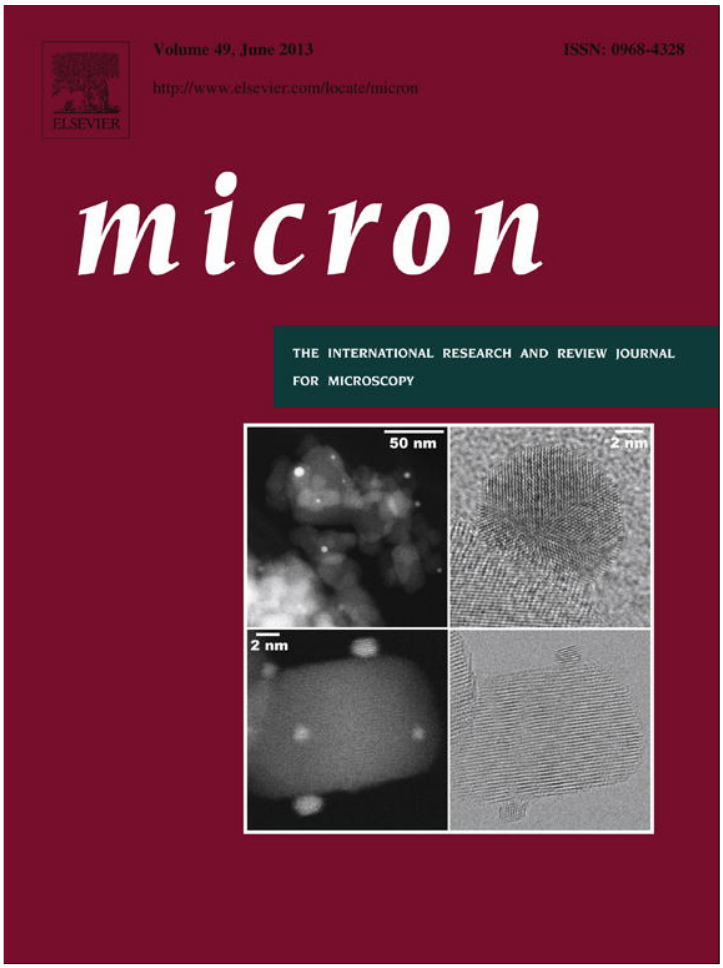

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The effect of kainic acid on hippocampal dendritic spine motility at the early and late stages of brain development

Tamar Lordkipanidze[a,b,*], Tamar Bikashvili[b], Nadia Japaridze[b], Mzia Zhvania[a,b]

[a] Ilia State University, Georgia
[b] I.Beritashvili Centre of Experimental Biomedicine, Georgia

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ABSTRACT

Dendrites and spines undergo dynamic changes in physiological conditions, such as learning and memory, and in pathological conditions, such as epilepsy. Abnormalities in dendritic spines have commonly been observed in brain specimens from epilepsy patients and animal models of epilepsy. However, the functional implications and clinical consequences of this dendritic pathology for epilepsy are uncertain. Motility of dendritic spines and axonal filopodia has been recently discovered by the advanced imaging techniques, and remains to a large degree an exciting phenomenology in search of function. Here we demonstrate the effect of kainic acid (KA), which is a structural analog of glutamate, on dendritic spine motility in hippocampal CA1 area at the different stages of brain development. In order to reveal the changes that take place in spine and filopodial motility in the epileptic model of brain, time-lapse imaging of acute hippocampal slices treated with various concentrations of KA after different incubation time points was performed. The effects of KA exposure were tested on the slices from young (postnatal day (P)7–P10) and adolescent (P28–P30) Thy1-YFPH transgenic mice. Slices were treated with either 50 μM or 100 μM of KA, for either 30 or 100 min. The results obtained in our experiments show diverse effects of KA in 2 different age groups. According to our results, 100 μM/100 min KA treatment increases spine motility at early stage of brain development (P10) by 41.5%, while in P30 mice spine motility is increased only by 3%. Our findings also indicate that effect of KA on hippocampal dendritic spine motility is predominantly time- rather than concentration-dependent.

1. Introduction

Patients with epilepsy often suffer from significant neurological deficits, including memory impairment, behavioral problems and psychological disorders, in addition to the immediate disabling effects of seizures themselves (Elger et al., 2004; Wong, 2005). The reasons for these pathological symptoms are generally multifactorial, involving biological, environmental and psychosocial issues. However, in some instances seizures themselves have been implicated in directly causing brain injury, contributing to cognitive deficits in epilepsy patients. The most evident type of seizure-induced brain injury is neuronal death. The potential behavioral and functional consequences of seizure-related neuronal death in human epilepsy are most strongly implicated in cases of mesial temporal epilepsy and hippocampal sclerosis, in which progressive epileptogenesis and memory dysfunction take place (Elger et al., 2004; Wong, 2005). Still, despite the relatively high incidence of neurological and behavioral problems in epilepsy, many patients have no clear evidence of neuronal death (Elger et al., 2004). Therefore, it was suggested, that besides cell death, there may be other mechanisms of seizure-induced brain injury, affecting neuronal brain structure and function, which might also explain cognitive deficits in epilepsy.

Human pathological specimens from the region of epileptic focus in neocortex and hippocampus have revealed a variety of dendritic abnormalities such as changes in dendritic length, shape, and branching patterns (Guo et al., 2012). The most common abnormality is the loss of dendritic spines, which may occur either in isolation or in association with varicose swelling of the dendrites. Dendritic spines – the micrometer-sized cellular structures, that are the sites of most excitatory synaptic contacts in the central nervous system, have been implicated in many forms of postsynaptic plasticity of neuronal communication (Wong, 2005). Impressive alterations in the quantity or form of spines are observed in a number of pathological brain disorders, while subtle changes in spine density, shape or motility have been related to normal cognitive behavior, learning and memory (Bourne and Harris, 2008; Wong, 2005). Although the functional consequences of these structural alterations have not been finally determined, it is strongly suggested, that the changes

* Corresponding author at: Ilia State University, Georgia. Tel.: +995 322234027.
E-mail addresses: tamar_lortkipanidze@iliauni.edu.ge, tlordkip@gmail.com (T. Lordkipanidze).

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