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

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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

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in spine morphology may affect the efficiency of electrical and biochemical signal in conduction of synaptic inputs (Yuste et al., 2000), thus, potentially influencing mechanisms of synaptic plasticity and learning. Given the evidence for the involvement of dendritic spines in these processes, abnormalities in dendritic spines represent a possible structural substrate for cognitive deficits (Mizrahi et al., 2004).

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. Speculations on the potential role of spine and filopodial motility have ranged from epiphenomena of the actin cytoskeleton to regulation of critical periods of facilitating synaptogenesis. The regulation of this motility by neuronal activity is controversial, since experiments manipulating synaptic activity with glutamate or electrical stimulation have produced opposing results (Chang and De Camilli, 2001; Engert and Bonhoeffer, 1999; Fiala et al., 2002; Wong et al., 2000). This controversy could be associated with a dose-dependent or developmental stage-dependent effect of glutamate or synaptic activity on filopodia or dendritic spine motility (Segal and Andersen, 2000; Wong and Wong, 2000; Yuste and Bonhoeffer, 2001). Kainic acid (KA), a structural analog of glutamate, when injected intraperitoneally, intracerebrally or intravenously, activates glutamate receptors, resulting in prolonged depolarization, and neural death. KA injections are widely used for chemically induced models of epilepsy. Human epilepsy studies and various experimental models indicate that epilepsy provokes alterations in spine number and structure.

In order to reveal the changes that take place in spine and filopodial motility in the epileptic model of brain, we decided to perform time-lapse imaging of acute hippocampal slices treated with various concentrations of KA after different incubation time points. The effects of KA exposure were tested on the slices from young (postnatal day (P)7–P10) and adult (P28–P30) Thy1-YFPH transgenic mice. Slices were treated with either 50 μM or 100 μM of KA, for either 30 or 100 min.

2. Materials and methods

2.1. Animals

All experiments were performed using Thy1-YFPH mice. All experiments were performed using Tg(Thy1-YFPH)HJrs/J mice. These mice express YFP at high levels in motor and sensory neurons, as well as subsets of central neurons. Pyramidal neurons are selectively labeled in the hippocampus. Mice were purchased from Jackson Lab. Total 40 mice were used for the experiment (8 – for control and 4 – for each experimental case). The mice were kept on regular light/dark cycles throughout the procedures. All protocols were approved by the University of Nebraska Institutional Animal Care and Use Committee.

2.2. Preparation of acute slices

P10 pups were sedated using hypothermia, and older pups – P30 were anesthetized with ketamine/dormitory (70 mg/kg, 0.5 mg/kg; respectively), before rapid decapitation. Brains were removed from the skulls immediately and the hippocampus was dissected out. Sagital 350 μm hippocampal sections were prepared with the vibratome. Slices were kept in oxygenated CMF-PBS (calcium- and magnesium-free phosphate-buffered saline) for an hour before acute slice imaging experiments. Control slices were left in PBS-SMF for the same time periods of 30 or 100 min. Slices from experimental groups were kept for 30 and 100 min in CMF-PBS containing 50 μM or 100 μM KA (Sigma, USA, K0250).

2.3. Time-lapse imaging of slices and image analysis

Imaging was conducted using multiphoton laser-scanning microscope (Movable Objective Microscope, Sutter) with a Ti-Saphire laser (Chameon Vision II, Coherent) at 920 nm. High-resolution imaging was performed with a long working distance, dipping objective 60×, N.A.1. Images were collected every 30 s for a period of 15 min at a digital zoom of 4 (yielding a pixel size of 0.08 μm × 0.08 μm). At each time point, seven to ten focal planes 0.5 μm apart were collected. Slices were perfused with oxygenated artificial cerebral spinal fluid (ACSF) at 35–37 °C, the imaging chamber was kept at 35–37 °C (Warner Instruments), and the slices were held in place using a platinum and nylon harp.

2.4. Analysis of spine dynamics

Spine motility was quantified using "Motility Index" (MI) as previously described (Dunaevsky et al., 1999). The motility index measures the overall displacement of a process. We first measure the area of a process at seven time points that differ the most from each other in a single time-lapse movie, then subtract the smallest area from the total projected or accumulated area and divide by the average area.

2.5. Statistical analysis

Data were analyzed using one-way ANOVA test. In the case of significant effect planned comparisons were carried out using student *t*-test. The level of significance was set as $p < 0.05$. All data are presented as a mean ± standard error of the mean (SEM).

3. Results and discussion

To detect the effect of KA (kainic acid) on spine dynamics we used two different mouse age groups, P10 and P30 (early and late postnatal development). Thy1-YFPH transgenic mice, in which pyramidal hippocampal neurons express green fluorescence, were used for the experiments. The effect of KA was detected by time lapse imaging of hippocampal slices, specifically of the pyramidal cells in CA1 area (Fig. 1). KA treatment was performed using different concentrations (50 μM and 100 μM) of KA and different incubation time points (30 min and 100 min). First of all we compared spine motility index in hippocampus (as it is described in Section 2; Figs. 2 and 3) during early and late postnatal development. It is known from previous studies that spine dynamic decreases in different brain regions during development; at the stage of early development spines and filopodia are highly motile (searching for presynaptic target). 80 (from 8 to 10 cells) spines were measured for each case (control and experiment). In control groups (no KA treatment), as expected, data analysis revealed significant decrease ($p = 0.01$) of spine motility in P30 mice, as compared to P10 mice. According to our results, motility index in P10 mice was 0.8780 ± 0.2196, while in P30 it was 0.7286 ± 0.2110 (Fig. 4). These data demonstrate that spine motility index is reduced by ~15% at the later stage of postnatal development, as compared to the earlier time period.

It is known from the literature that dendritic spines and filopodia show actin-based rapid motility in the time scale of seconds (Bonhoeffer and Yuste, 2002; Dailey and Smith, 1996; Dunaevsky et al., 1999; Fischer et al., 1998). This motility is downregulated during postnatal development (Dunaevsky et al., 1999; Grutzendler et al., 2002; Konur and Yuste, 2004; Lendvai et al., 2000; Portera-Cailliau et al., 2003). Phenomenologically, spines show at least two major types of motility: extensive length changes including both extension and retraction (protrusive motility) and morphological changes in their heads (head morphing) (Dunaevsky et al., 1999).

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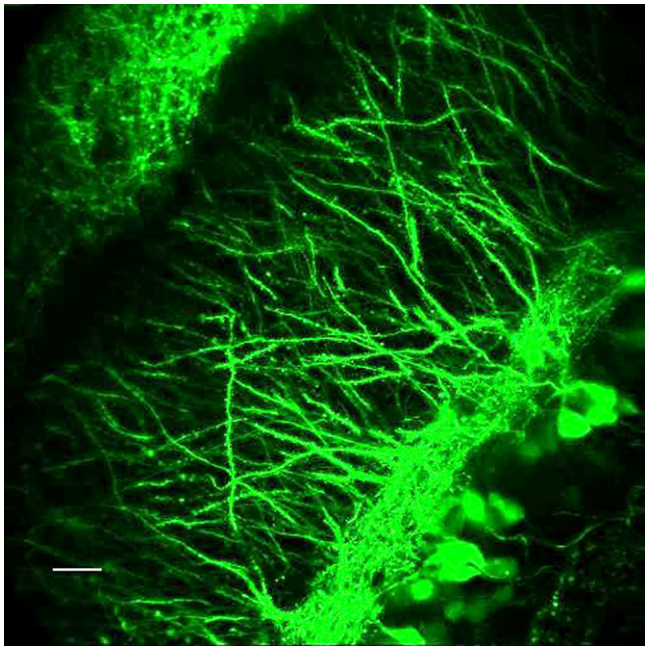

Fig. 1. Low magnification (40× objective; zoom 2) image of the dendrites in the hippocampal CA1 area from Thy1-YFPH mouse where all pyramidal neurons express YFP. Scale bar = 22 μm.

Tashiro and Yuste (2004) also showed two different types of spine motility: protrusive motility and head morphing, which are differentially regulated by Rac1 and Rho kinase. They propose that these two different types of spine motility serve different functions in synaptogenesis and synapse maturation.

Dendritic spines were highly motile in young 4- to 7-day-old cells. At this age, neurons had little spontaneous calcium fluctuation or FM4-64 labeling. Within 2–3 weeks in culture, dendritic spines were much less motile, they were associated with active presynaptic terminals. It is proposed that an active presynaptic terminal restricts motility of dendritic spines (Korkotian and Segal, 2001). Developmental decrease in spine motility is a common property of all morphological classes of spines, but not filopodia (Oray et al., 2006). Spine motility seems to be regulated by glutamate receptor activation (Fischer et al., 2000). However, the molecular mechanisms underlying spine motility are largely unknown.

KA which effects AMPA and KA receptors, may induce changes in actin cytoskeleton rearrangement resulting in spine motility modifications. The results obtained in our experiments show diverse effects of KA in 2 different age groups. We have found significant changes in spine motility in P10 mice; this effect was not only concentration- but mostly time-dependent ($p = 0.003$). The most significant increase was detected at 100 μM KA and

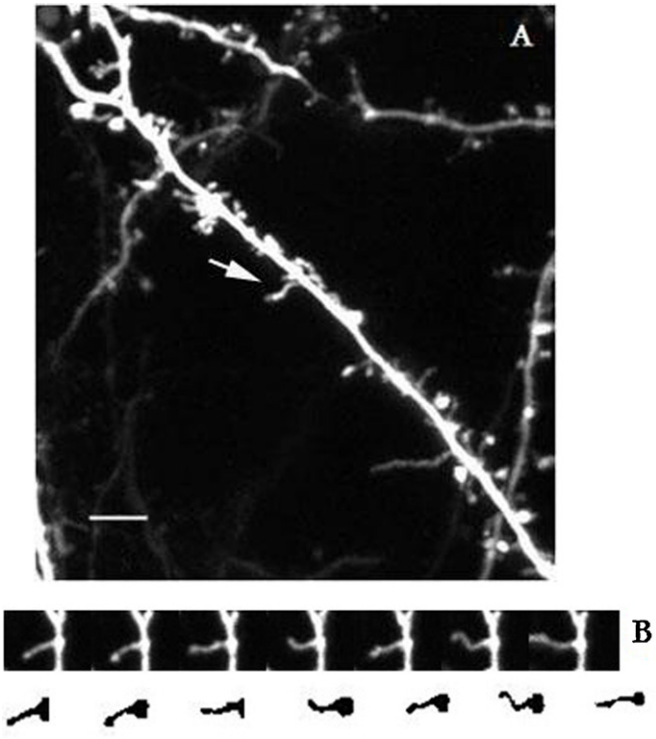

Fig. 2. (A) Dendrite with spines from P10 mice (control). High magnification (60× objective; zoom 4). Time-lapse imaging. Arrow indicates the spine with motility index 2.0. Scale bar = 4 μm. (B) The most different 7 z-stacks of motile spine.

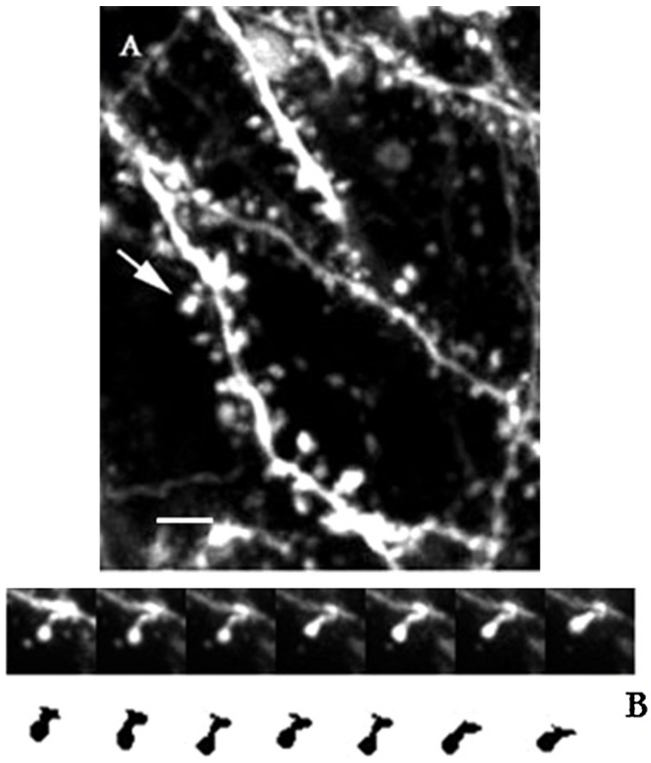

Fig. 3. (A) Dendrite with spines from P30 mice (control). High magnification (60× objective; zoom 4). Time-lapse imaging. Arrow indicates the spine with motility index 1.6. Scale bar = 3 μm. (B) The most different 7 z-stacks of motile spine.

Fig. 4. Spine motility index chart of P10 and P30 mice, control group (slices treated with CMF-PBS); 80 spines (from 10 cells) in each group; blue column – P10; red column – P30; spine motility is significantly decreased in P10 mice ($p < 0.01$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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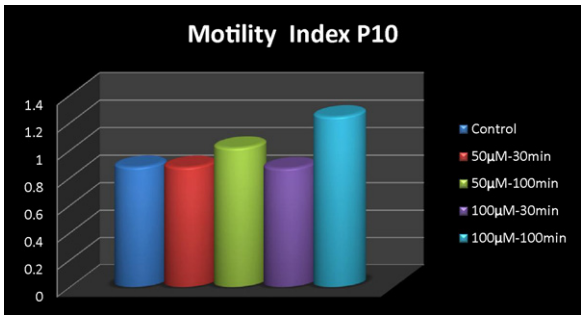

Fig. 5. Spine motility index chart of P10 mice. 80 spines (from 8 to 10 cells) in each group. blue column – control (slices treated with CMF-PBS); red column – slices treated with 50 μM KA for 30 min; green column – slices treated with 50 μM KA for 100 min; violet – slices treated with 100 μM KA for 30 min; Baby-blue column – slices treated with 100 μM KA for 100 min; There is a significant increase in spine motility index in slices treated with 100 μM KA for 100 min compared to control ($p = 0.03$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 6. Spine motility index chart of P30 mice. 80 pines (from 8 to 10 cells) in each group. Blue column – control (slices treated with CMF-PBS); red column – slices treated with 50 μM KA for 30 min; green column – slices treated with 50 μM KA for 100 min; violet – slices treated with 100 μM KA for 30 min; baby-blue column – slices treated with 100 μM KA for 100 min; There is significant increase in spine motility index in slices treated with 100 μM KA for 100 min compared to –100 μM KA for 30 min ($p < 0.04$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

100 min incubation, as compared to control ($p = 0.002$) (MI in P10–100 μM/100 min was 1.2429 ± 0.5823) (Fig. 5). In this group motility index was augmented by 41.5%, as compared to control group. There was also an increase in spine motility after KA acid treatment using 50 μM for 100 min (1.0167 ± 0.3187), but these data were not statistically significant compared to control. Less significant changes, specifically very slight decrease in spine motility, were obtained during short-time exposure (30 min) of slices to KA (0.8767 ± 0.2897 and 0.8683 ± 0.3197, respectively in 50 and 100 μM solution) (Fig. 5).

These results are supported by the existing literature reporting that in the somatosensory cortex the sensory-deprivation induced decrease in spine dynamics occurs at a time of peak synaptogenesis, while in the visual cortex the synapses are already in place and are undergoing activity-dependent rearrangements. In support of this interpretation, in the somatosensory cortex of young adult mice where synapses are already established, sensory deprivation leads to an increase in transient, thin dendritic spines (Trachtenberg et al., 2002). Thus, alteration in the activity of neurons with sensory deprivation might cause the destabilization and thus increased dynamics of dendritic spines (Lippman and Dunaevsky, 2005).

At the later stage of development (P30) when synaptogenesis goes to its end and spines are more stabilized, the effect of KA on spine motility was somewhat different from that in P10 mice. There was a decrease in spine motility in slices treated with 50 μM (0.6857 ± 0.2043) and 100 μM (0.6595 ± 0.2285) KA for 30 min, as compared to control (0.7286 ± 0.2110) (Fig. 6). For 100 min of KA exposure, there was considerable increase is spine motility in both experimental groups treated with 50 μM and 100 μM KA (0.7738 ± 0.2490 and 0.7524 ± 0.1784, respectively). However, these variations in spine motility were not statistically significant compared to control ($p = 0.15$; $p = 0.66$) (Fig. 6).

Our results indicate an importance of duration of KA exposure on hippocampal dendritic spine motility. The most apparent alterations in spine motility in both age groups (P10, P30) were observed after long-term treatment (100 min) with KA, so we can conclude that the effect of KA on dendritic spine motility is more time- rather than concentration-dependent. According to the data obtained from the literature glutamate is the major fast excitatory amino acid transmitter in the CNS, and exerts its action through receptors that function as ion channels such as NMDA receptors, AMPA receptors, and kainate receptors, and also through signaling cascades via metabotropic receptors (Bloss and Hunter, 2010). It has been demonstrated that filopodial motility of hippocampal mossy fibers is differentially regulated by kainite receptors: synaptic stimulation of kainite receptors enhances motility in younger slices, but inhibits it in mature slices (Tashiro et al., 2003). Two different types of motility – vertical and head morphing – should be considered, as it is detected in immature brain that filopodia predominantly express vertical motility, while in mature spines head morphing is prevalent. Thus we can speculate that KA has different effect on these two types of spine motility. Based on our data we can conclude that KA, which is a structural analog of glutamate, effects spine motility; this effect is developmentally regulated. In immature filopodia, released glutamate could stimulate high-affinity KA receptors and induce filopodial motility. In immature filopodia the induction of motility could help them to explore their environment and find potential synaptic target. As for mature spines, with a synaptic contact, released glutamate would activate low-affinity KA receptors or cause a sustained stimulation of the same high-affinity receptors, such that spines are stabilized and actually prevented from moving. 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%.

The blockade of NMDA and AMPA receptors with bath applied antagonists induces a decrease in the density and turnover of dendritic filopodia. Local puffs of small amounts of glutamate close (100–200 μm) to dendritic filopodia have been reported to have different effects. In some cases, the motility of the filopodium was blocked by glutamate activation, whereas filopodia of more than 4 μm in length exhibited a small increase in length (Portera-Cailliau et al., 2003).

In contrast, chronic blockade with NMDA receptor antagonists on mature dendritic spines results in no significant change in the density of dendritic spines but many long (2 μm) thin dendritic protrusions resembling filopodia are formed similar to the structures noted in immature hippocampus (McKinney et al., 1999).

Filopodia-like processes are thought to actively initiate synaptic contacts with axons in close proximity. Insufficient NMDA receptor activation appears to return the spines of CA1 pyramidal cells to an early development scenario whereby they actively search for presynaptic boutons with which to form synapses (McKinney, 2010).

It has been shown in hippocampal cultures that spine dynamics are inhibited by activation of glutamatergic receptors, while antagonists to NMDA receptors have no effect on spine motility (Fischer et al., 2000). Interestingly, spine motility is not correlated with the developmental expression of AMPA and NMDA receptors or with the ability to flux calcium ions which would stabilize the cytoskeletal network. One can conclude that spine motility is

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affected by glutamate receptor activity but surprisingly not by glutamate receptor composition (McKinney, 2010).

In conclusion, we hypothesize that long-term (100 min) exposure of slices to KA can cause AMPA and kainate receptor desensitization, which results in the enhancement of dendritic spine motility. This augmentation is more obvious at the early stage of synaptogenesis as compared to the later stages of brain development.

Acknowledgments

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