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Review

The effects of early-life seizures on hippocampal dendrite development and later-life learning and memory

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ABSTRACT

Severe childhood epilepsy is commonly associated with intellectual developmental disabilities. The reasons for these cognitive deficits are likely multifactorial and will vary between epilepsy syndromes and even among children with the same syndrome. However, one factor these children have in common is the recurring seizures they experience – sometimes on a daily basis. Supporting the idea that the seizures themselves can contribute to intellectual disabilities are laboratory results demonstrating spatial learning and memory deficits in normal mice and rats that have experienced recurrent seizures in infancy. Studies reviewed here have shown that seizures *in vivo* and electrographic seizure activity *in vitro* both suppress the growth of hippocampal pyramidal cell dendrites. A simplification of dendritic arborization and a resulting decrease in the number and/or properties of the excitatory synapses on them could help explain the observed cognitive disabilities. There are a wide variety of candidate mechanisms that could be involved in seizure-induced growth suppression. The challenge is designing experiments that will help focus research on a limited number of potential molecular events. Thus far, results suggest that growth suppression is NMDA receptor-dependent and associated with a decrease in activation of the transcription factor CREB. The latter result is intriguing since CREB is known to play an important role in dendrite growth. Seizure-induced dendrite growth suppression may not occur as a single process in which pyramidal cells dendrites simply stop growing or grow slower compared to normal neurons. Instead, recent results suggest that after only a few hours of synchronized epileptiform activity *in vitro* dendrites appear to partially retract. This acute response is also NMDA receptor dependent and appears to be mediated by the Ca^{+2}/calmodulin-dependent phosphatase, calcineurin. An understanding of the staging of seizure-induced growth suppression and the underlying molecular mechanisms will likely prove crucial for developing therapeutic strategies aimed at ameliorating the intellectual developmental disabilities associated with intractable childhood epilepsy.

This article is part of a Special Issue entitled 'Dendrites and Disease'.

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1. Introduction

Integrating the myriad of synaptic inputs that dendrites receive is critical for not only proper neuronal function but also network operations and ultimately animal and human behavior. For instance, neurons in somatosensory cortex assimilate not only peripheral information relayed through ascending sensory pathways but also local circuit synaptic inputs to interpret environmental stimuli. Within the hippocampus, physiological signals arising from the occipital, temporal and parietal lobes, posterior cingulate cortex and the contralateral hippocampus all converge on hippocampal neurons through the medial, lateral perforant pathways and the anterior commissure (Aggleton, 2012). Within the hippocampus, additional synaptic integration arising from local recurrent excitatory networks and feedforward and recurrent inhibitory connections are thought to contribute to the acquisition of new episodic memories (Scoville and Milner, 1957; Schmolck et al., 2002). It is thought that the dendrites of principal excitatory neurons of the hippocampus and their attendant synapses play a particularly important role in learning and the formation of memories. The soma of these neurons have a characteristic pyramidal morphology with dendritic processes extending from the pyramidal apex and base termed apical and basolateral dendrites, respectively.

Often in human epilepsy, alterations in these dendritic trees are observed. Commonly neurons are examined in tissue that has been surgically removed to stop seizures. For instance in a quantitative Golgi study, the dendrites of neocortical pyramidal layer from layer 3 were reconstructed. The tissue examined was from patients with focal seizures but the region was judged to be remote from the site of seizure generation based on intraoperative EEG recordings and histopathological characterization. Pyramidal cells were found to have fewer dendritic branch points and fewer proximal dendritic branches compared to pyramidal cells obtained from autopsied tissue or post operative surgical samples removed following brain trauma (Multani et al., 1994). In addition, the small actin rich dendritic protrusions that receive presynaptic signals, termed spines, were found to be reduced in number and density. Moreover, dendritic spine density was found to progressively decrease with increasing duration of the epilepsy. While these investigators did not attempt to correlate dendritic abnormalities with the age of seizure onset, the demographic data presented clearly shows that the patients with longer duration of epilepsy were ones with onset in infancy and early childhood. Among other conclusion the authors suggested that the dendritic anatomical alterations could help to explain the intellectual disabilities often associated with intractable seizure disorders. Similar alterations in dendritic anatomy and spine density have been described in hippocampal tissue that was surgically removed to control temporal lobe epilepsy (Scheibel et al., 1974). Moreover experiments in several animal models, including focal epilepsy in non-human primates, have consistently described dendritic spine loss and a reduction in dendrite branching as a feature of epileptic brain tissue (Westrum et al., 1964; Willmore et al., 1980; Swann et al., 2000).

Intellectual disabilities are a common neurobehavioral comorbidities of epilepsy – particularly in childhood epilepsy (Hermann and Seidenberg, 2007; Hermann et al., 2008). Studies of a variety of epilepsies have reported intellectual ability to be below that considered normal for age (Nordli, 2002; Camfield and Camfield, 2002; Hermann and Seidenberg, 2007). The nervous system of children may be particularly vulnerable to the effects of recurring seizures. Numerous studies have compared the risk of comorbidities in adults as a function of age of onset of epilepsy (Hermann et al., 2002a,b, 2006). Results have shown that the earlier the age of onset the poorer the cognitive abilities. These observations have led investigators to propose a neurodevelopmental origin for the comorbidities of epilepsy and that epilepsy in early-life negatively impact the normal growth and maturation of the nervous system (Camfield and Camfield, 2002; Elger et al., 2004). With the development of imaging technologies such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), our appreciation of the neuroanatomical abnormalities associated with epilepsy has increased. Despite the variety of etiologies that can lead to the synchronous neuronal hyperactivity that characterizes seizures, volumetric alterations of the white and gray matter of the neocortex have been commonly observed (Hermann et al., 2002b). For instance, in pediatric patients diagnosed with temporal lobe epilepsy, reduced white matter tracts (Kimiwada et al., 2006) of the temporal lobe have been observed. Additionally, pediatric epilepsy is also associated with reduced hippocampal and temporal gray matter volumes (Cormack et al., 2005). Some of these effects appear to be progressive as recent longitudinal studies have illustrated significant reductions in cortical white matter volume after a 2-year follow-up (Hermann et al., 2010). These results suggest that seizures impair normal brain growth which conceivably could contribute to learning and memory deficits.

2. Synaptic plasticity and activity-dependent dendrite growth: shared molecular mechanisms

The molecular correlates of learned experiences involve both presynaptic changes that modify transmitter release and post-synaptic modifications of spines that cover the dendritic trees. *In vivo* and *in vitro* animal models utilizing hippocampal slices have demonstrated rapid (<30 min) increases in post synaptic spine density and spine head volume following repetitive stimulation (Matsuzaki et al., 2004). These increases correlate with increased AMPA receptor subunit insertion and increased AMPA receptor channel conductances (Malenka and Bear, 2004). Modifications of the pre-synaptic machinery following a learned experience include increases in synaptic quantal size, release probability and the readily releasable pool (Emptage et al., 2003; Lauri et al., 2007). Together the pre- and post-synaptic modifications increase the efficiency of synaptic transmission and have been termed long term potentiation, LTP (Malenka and Bear, 2004). Conversely, by reducing the strength and duration of the applied stimulation, modifications such as increased AMPA receptor endocytosis and reductions in spine head volume are thought to limit the strength of synaptic efficiency (Winder and Sweatt, 2001; Colledge et al., 2003; Zhou et al., 2004). This has been referred to as long term depression (LTD) and together with LTP provide support for a Hebbian model of synaptic plasticity.

Our understanding of how changes in the activity of numerous kinases, phosphatases, and proteases are orchestrated to produce the biphasic alterations in synaptic efficacy of LTP and LTD have been greatly expanded over the past two decades. Upon the release of glutamate from presynaptic nerve terminals and its binding to post-synaptic AMPA receptors, the influx of sodium depolarizes the postsynaptic plasma membrane and alleviates the noncompetitive extracellular magnesium ion block of NMDA receptors, which subsequently allows calcium entry into the postsynaptic neuron. The elevation of calcium through NMDA receptor activation and voltage-dependent calcium channels leads to the activation of numerous, highly regulated signaling pathways culminating in the structural and molecular changes associated with synaptic plasticity. One widely studied molecule, the serine/threonine protein kinase, Ca^{+2}/calmodulin-dependent protein kinase (CAMKII) is activated when calcium bound calmodulin alters the CaMKII conformation allowing for its autophosphorylation at T286 (Kolodziej et al., 2000; Rellos et al., 2010; Lisman et al., 2012). Activated CAMKII then phosphorylates the AMPA binding protein stargazin