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DENDRITIC SPINE PATHOLOGY IN EPILEPSY: CAUSE OR CONSEQUENCE?

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Abstract—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. Dendritic spine abnormalities may promote hyperexcitable circuits and seizures in some types of epilepsy, especially in specific genetic syndromes with documented dendritic pathology, but in these cases it is difficult to differentiate their effects on seizures versus other comorbidities, such as cognitive deficits and autism. In other situations, seizures themselves may cause damage to dendrites and dendritic spines and this seizure-induced brain injury may then contribute to progressive epileptogenesis, memory problems and other neurological deficits in epilepsy patients. The mechanistic basis of dendritic spine abnormalities in epilepsy has begun to be elucidated and suggests novel therapeutic strategies for treating epilepsy and its complications.

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Key words: seizure, epilepsy, epileptogenesis, dendrite, actin.

INTRODUCTION

Epilepsy is a common neurological disorder, affecting about 1% of all people, and is associated with significant morbidity and mortality. Seizures, the cardinal symptom of epilepsy, are dangerous and disabling in themselves. In addition, learning disabilities, memory problems, autism, and other neuropsychiatric disorders frequently occur in epilepsy patients and sometimes exhibit a progressive course, often correlating with worsening seizure control (Dodrill, 2002; Elger et al., 2004). As epilepsy may be caused by numerous other underlying neurological diseases, the mechanisms promoting epileptogenesis and the comorbidities of epilepsy are diverse and multifactorial, including a variety of biological, environmental, and psychosocial factors. Once established, seizures themselves may in some cases cause further brain injury, contributing to a cyclical or progressive process of worsening epilepsy and neurological deficits. From the biological perspective, there is increasing interest in identifying intrinsic mechanisms of epileptogenesis and seizure-induced brain injury. Understanding such mechanisms may help to promote development of novel therapies that can prevent or reverse the detrimental neurocognitive consequences of seizures and retard progressive epileptogenesis.

Dendritic spines represent critical structural and functional components of neurons that could be involved in the pathophysiology of epilepsy and its comorbidities (Swann et al., 2000; Wong, 2005). Spines normally receive and integrate the majority of excitatory synaptic inputs in the mammalian cortex and hippocampus and thus could directly influence neuronal excitability and seizures under pathological conditions. Furthermore, changes in the morphology or number of dendritic spines are strongly implicated in mechanisms of synaptic plasticity, learning, and memory, such as long-term potentiation (LTP) and long-term depression (LTD) (Segal, 2005; Kasai et al., 2010); thus, abnormalities in dendritic spines could cause or contribute to cognitive deficits observed in epilepsy patients. There is substantial pathological evidence for dendritic spine abnormalities in brain specimens from epilepsy patients, most commonly obtained from surgical resections as treatment for medically-refractory epilepsy. Direct examination of the epileptic focus in neocortex or hippocampus has identified a number of abnormalities in dendrites, including changes in both structure and number of dendritic spines (Fig. 1). A significant decrease in dendritic spine density is frequently seen in hippocampal pyramidal neurons and dentate granule cells in patients with temporal lobe epilepsy (Scheibel et al., 1974; Isokawa and Levesque, 1991; Belichenko and Dahlstrom, 1995; von Campe et al., 1997; Blumcke et al., 1999; Freiman et al., 2011). Spine loss may occur in isolation or be associated with varicose swelling of the dendritic branches. Similar findings of spine loss and dendritic swelling have also been observed in pyramidal neurons of neocortex, including sites distant from the primary epileptogenic focus (Multani et al., 1994; Kitaura et al., 2011). Less common dendritic abnormalities also documented in neocortical and hippocampal tissue of epilepsy patients include changes in dendritic length, shape, and branching patterns, as well as a focal increase in dendritic spines (Multani et al., 1994; Belichenko et al., 1994b; Isokawa,

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Abbreviations: LTD, long-term depression; LTP, long-term potentiation; MECP2, methyl-CpG-binding protein-2; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; TSC, tuberous sclerosis complex.

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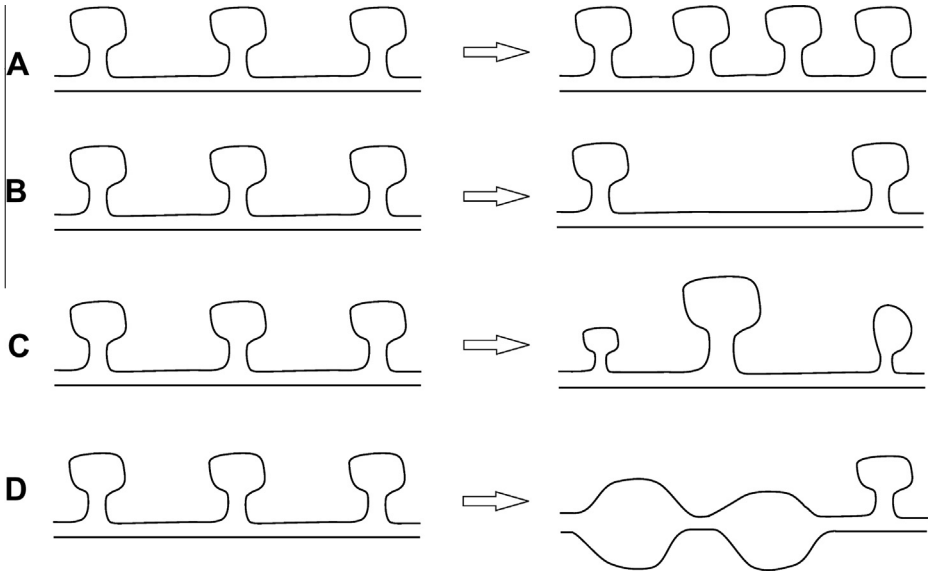

Fig. 1. Common pathological changes in dendritic spines in epilepsy. (A) Increase in spine density. (B) Decrease in spine density. (C) Change in size or morphology of spines. (D) Spine loss with dendritic beading.

1997; von Campe et al., 1997; Blumcke et al., 1999; Freiman et al., 2011).

In addition to pathological specimens from patients with epilepsy, animal models of epilepsy also display similar dendritic defects. Traditional histological studies demonstrate primarily a loss of dendritic spines and varicose swelling of dendrites in a variety of animal models involving either acute seizures or chronic epilepsy, induced by electrical kindling, toxins, or other chemoconvulsant drugs (Willmore et al., 1980; Nishizuka et al., 1991; Isokawa, 1998; Jiang et al., 1998; Gonzalez-Burgos et al., 2004; Ampuero et al., 2007). Other dendritic changes, including an increase in dendritic spines, have been less commonly reported (Bundman et al., 1994; Suzuki et al., 1997; Spigelman et al., 1998).

Overall, these common, related abnormalities in dendrites observed in different types of both human epilepsy and animal models strongly suggest that dendritic spine abnormalities represent an important, central pathophysiological mechanism in epilepsy. However, the specific pathogenic role and clinical consequences of this dendritic pathology for epilepsy are not fully understood. It is unclear whether these dendritic abnormalities are more related to the cause or consequence of seizures, and this may differ depending on the type of epilepsy. Furthermore, in certain progressive epilepsies, it is possible that dendritic pathology is both the cause and result of seizures. This may constitute a repetitive, cyclical process whereby seizures lead to dendritic injury which promotes further seizures and dendritic injury. On the other hand, dendritic changes could contribute to a compensatory response, as a form of homeostatic plasticity, to try and dampen excessive neuronal excitability in the face of epilepsy. Besides epilepsy per se, dendritic spine loss could also be a basis for seizure-induced brain injury leading to memory problems and other cognitive deficits or could simply represent epiphenomena related to these comorbidities independent of the seizures. In the remainder of this review, evidence for the pathophysiological role and mechanisms of dendritic spine abnormalities in epilepsy will be analyzed.

DENDRITIC SPINE PATHOLOGY AS A CAUSE OF EPILEPSY

Dendritic spines represent the major site of anatomical contact for excitatory, usually glutamatergic, synaptic inputs to cortical neurons and thus play an integral role in excitatory neuronal signaling in the brain. As epilepsy is primarily a disorder of electrical excitability, it is very rational to hypothesize that dendritic spine abnormalities could promote epileptogenesis and the generation of seizures. There is a delicate balance between excitatory and inhibitory forces in the brain and any disruption of this balance could result in hyperexcitability and seizures. Alterations in dendritic spine structure or function could affect the processing of synaptic inputs and ultimately the excitability of neurons. While a loss of dendritic spines and corresponding excitatory inputs might simplistically be predicted to lead to decreased excitability on the cellular level, the ultimate effect on the outputs of neuronal circuits is likely more complex. For example, if loss of excitatory input ultimately had a larger effect on inhibitory networks, the net effect on circuit output might be increased excitability and a tendency toward seizures.

Although abnormalities in dendritic spines have been clearly documented in both pathological specimens from epilepsy patients and animal models of epilepsy, establishing that these dendritic abnormalities actually cause or contribute to epileptogenesis and seizure generation is more difficult. The potential role of dendritic pathology in causing seizures will almost certainly depend on the type and etiology of the epilepsy. While epilepsy is generally defined as a neurological disorder characterized by recurrent seizures, there are numerous types and etiologies of epilepsy, including structural lesions of the brain (e.g.