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Does Epileptiform Activity Contribute to Cognitive Impairment in Alzheimer's Disease?

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Alzheimer's disease is a devastating neurological disorder. The role of hyperexcitability in the disease's cognitive decline is not completely understood. In this issue of *Neuron*, Palop et al. report both limbic seizures and presumed homeostatic responses to seizures in an animal model of Alzheimer's.

Alzheimer's disease (AD) is the most common cause of dementia, or loss of intellectual function, among people aged 65 and older. This loss of cognitive function is the most devastating feature of AD, and the progressive failures of declarative and nondeclarative memory are attributed to the dysfunction of nerve cells in entorhinal-hippocampal circuitry. Currently approved treatments for AD are either cholinesterase inhibitors or the N-methyl-D-aspartate (NMDA) blocker memantine. Unfortunately, the cognitive benefits of these drugs have been modest, and they are not aimed at the essential causes of AD. Understanding the cellular and molecular mechanisms underlying the cognitive impairments in AD may lead to better forms of treatment for the debilitating aspects of this disease.

Converging lines of evidence support the hypothesis that accumulation of the amyloid peptides (Aβ) contributes to the pathogenesis of AD (Walsh and Selkoe, 2004). Aβ is formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein of undetermined function. Familial autosomal-dominant mutations in APP cause hereditary early-onset Alzheimer's disease (FAD), likely as a result of altered proteolytic processing and the production of aberrant amyloid peptides (Goedert and Spillantini, 2006). The progressive accumulation of Aβ in brain regions such as the hippocampus is theorized to contribute to the cognitive decline in AD. Here, Palop et al. (2007) report that transgenic overexpression of Aβ peptide causes epileptiform activity within the entorhinal-hippocampal circuitry. They propose that the epileptiform activity together with homeostatic responses to this epileptiform activity may contribute to dysfunction of the circuitry that underlies memory formation.

The authors study several lines of transgenic mice overexpressing a mutant form of human APP ($hAPP_{FAD}$). When overexpressed in mice, $hAPP_{FAD}$ is sufficient to recapitulate some of the biochemical and behavioral features of AD. Most importantly, these animal models exhibit impairments in learning and memory. Palop et al. (2003) previously reported reduced expression of calbindin, a calcium binding protein, in the dentate granule cells of hippocampus of $hAPP_{FAD}$ mice as well as in humans with AD. Here, the authors confirm these observations and further report increases in neuropeptide Y (NPY) immunoreactivity in the mossy fiber axons and cell bodies of the dentate granule cells (DGCs) and in the molecular layer of the dentate gyrus of the $hAPP_{FAD}$ mice. The colocalization of the NPY with somatostatin immunoreactive fibers in the molecular layer suggests localization to axons originating from inhibitory interneurons of the dentate hilus, as well as termination of these inhibitory afferents on the dendrites of the granule cells. Axonal sprouting of the excitatory granule cells was also identified in which their mossy fiber terminals decorated presumed GABAergic interneurons, suggesting enhanced recurrent inhibition of the granule cells themselves. Consistent with the predictions of the immunohistochemical findings, whole-cell patch-clamp recordings revealed increased frequency and amplitude of mIPSCs in hippocampal slices isolated from the $hAPP_{FAD}$ compared to control mice. Analyses of multiple transgenic lines correlated these findings with accumulation of Aβ peptide rather than with plaques or APP itself.

What might cause these interesting plasticities of the dentate granule cells? Previous observations by other investigators raised the possibility that both the immunohistochemical and electrophysiological abnormalities of the granule cells reflected homeostatic responses to recurrent limbic seizures. That is, Tonder et al. (1994) reported identical plasticities of NPY and calbindin immunoreactivity in the dentate gyrus 1 day, but not 1 month, following recurrent seizures in the kindling model and proposed that this represented homeostatic responses to the recurrent seizures. Likewise, increased frequency and amplitude of mIPSCs were found in the dentate granule cells in slices isolated one day following recurrent seizures in the kindling model (Nusser et al., 1998). As predicted, Palop et al. (2007) discovered impressive epileptiform activity in $hAPP_{FAD}$, but not control mice,

using video-EEG monitoring. The epileptiform activity included frequent interictal (between seizure) spikes as well as limbic seizures. Importantly, the behaviors of the limbic seizures consisted merely of immobility, rather than overt tonic or clonic contractions of musculature typical of seizures propagating widely throughout the brain. Together with the findings of Tonder et al. (1994) and Nusser et al. (1998), this strongly supports the authors' assertion that the immunohistochemical and electrophysiological abnormalities represent homeostatic responses to the increased neuronal excitability evidenced by both interictal abnormalities and frank seizure activity.

The authors advance an interesting idea, namely that both the recurrent seizure activity and homeostatic responses to this seizure activity contribute to malfunction of the entorhinal-hippocampal circuitry, specifically to some of the memory impairments of the $hAPP_{FAD}$ mice and possibly in AD in humans as well. This idea is both eminently plausible and testable in the $hAPP_{FAD}$ mice. That is, distinct antiseizure drugs can be administered chronically with the expectation of suppressing both recurrent seizure activity as well as interictal epileptiform abnormalities. The key question is whether inhibiting the epileptiform activity in the $hAPP_{FAD}$ prevents these immunohistochemical and electrophysiological abnormalities in the dentate gyrus and, most importantly, whether this improves cognitive function in the $hAPP_{FAD}$ mice.

If successful, such a finding in the $hAPP_{FAD}$ mice would raise the possibility that similar treatments may benefit cognitive function in humans with AD. Here the question arises as to how commonly limbic seizures and epileptiform EEG activity are associated with AD in humans. Certainly, the subtlety of nonconvulsive limbic seizures obscures their detection in some instances in humans, and one could imagine even greater problems with detection in a cognitively impaired individual. That said, epileptiform abnormalities on EEG and complex partial seizures are uncommon features of sporadic Alzheimer's disease, at least in its early stages, afflicting perhaps 10%–20% of patients (Lehtovirta et al., 1996; Hesdorffer et al., 1996). The occurrence of complex partial seizures may be substantially higher in some familial forms of AD (Cabrejo et al., 2006; Takao et al., 2001). It seems plausible that the phenotype of $hAPP_{FAD}$ mice more accurately mirrors that of rare familial forms with APP mutations than sporadic AD. If careful video-EEG monitoring of patients with rare familial forms of AD reveal epileptiform activity, this would warrant careful study to determine whether pharmacological inhibition of increased excitability improves cognitive function.

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