Epilepsy and Cognitive Impairments in Alzheimer Disease

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Alzheimer disease (AD) is associated with cognitive decline and increased incidence of seizures. Seizure activity in AD has been widely interpreted as a secondary process resulting from advanced stages of neurodegeneration, perhaps in combination with other age-related factors. However, recent findings in animal models of AD have challenged this notion, raising the possibility that aberrant excitatory neuronal activity represents a primary upstream mechanism that may contribute to cognitive deficits in these models. The following observations suggest that such activity may play a similar role in humans with AD: (1) patients with sporadic AD have an increased incidence of seizures that appears to be independent of disease stage and highest in cases with early onset; (2) seizures are part of the natural history of many pedigrees with autosomal dominant early-onset AD, including those with mutations in presenilin-1, presenilin-2, or the amyloid precursor protein, or with duplications of wild-type amyloid precursor protein; (3) inheritance of the major known genetic risk factor for AD, apolipoprotein E4, is associated with subclinical epileptiform activity in carriers without dementia; and (4) some cases of episodic amnestic wandering and disorientation in AD are associated with epileptiform activity and can be prevented with antiepileptic drugs. Here we review recent experimental data demonstrating that high levels of β-amyloid in the brain can cause epileptiform activity and cognitive deficits in transgenic mouse models of AD. We conclude that β-amyloid peptides may contribute to cognitive decline in AD by eliciting similar aberrant neuronal activity in humans and discuss potential clinical and therapeutic implications of this hypothesis.

Obviously mice are not people, just as apples are not planets. Nonetheless, because apples and planets both have mass, falling apples allowed Newton to elucidate the forces underlying planetary movements. In a similar vein, mice and people share several characteristics that make mice reasonable models for exploring human diseases. Indeed, evolutionary pressures have preserved many processes across mammalian species. An example is spatial learning and memory, which are essential for any species that must return to its home after foraging for food. Humans with AD and hAPP transgenic mice both show navigational deficits that are closely related to impairments of the hippocampus and entorhinal cortex.6,7 Although mice never develop AD-like pathology spontaneously, the murine brain is similar enough to the human brain to develop many AD-like changes when exposed to high levels of human Aβ, including amyloid plaques, neuritic dystrophy, gliosis, synaptic deficits, and a range of cognitive and noncognitive behavioral alterations.8-17 Notably, some alterations or associations were discovered in hAPP mice and subsequently identified for the first time in humans with AD, including loss of calbindin levels in the dentate gyrus18 and the relation between transforming growth factor β and cerebral amyloid angiopathy.19

While none of the available singly transgenic models recapitulates the full spectrum of the human disease, they make it possible to dissect the complexity of AD and to assess the relative pathogenic impact of individual factors in vivo. Compound transgenic mice combining different factors suspected of pathogenic roles in AD or related conditions have shed light on synergisms between Aβ and apolipoprotein (apo) E4,19 Aβ and tau,5,20 and Aβ and α-synuclein.21 We recently used hAPP mice to determine the effect of high Aβ levels on neural network activity and the dependence of this effect on tau.

**HIGH LEVELS OF Aβ CAUSE EPILEPSY AND COGNITIVE DEFICITS**

The brain is characterized by multiple levels of complexity, ranging from molecules and individual synapses to circuits and interconnected networks. Activities in lower levels determine activities in higher levels and vice versa. Consequently, molecular and synaptic alterations can affect the function of networks and, in turn, alterations in network functions can affect individual synapses and molecules. It is well known that Aβ causes depression of excitatory neurotransmission at specific synaptic connections (Figure 1),14,15,24,26 but the net effect of Aβ on the activity of microcircuits and broader neural networks had been unknown.

To shed light on this issue, we continually monitored neuronal activity in cortical and hippocampal net-
works by video electroencephalography (EEG) recordings in hAPP mice (J20 line; hAPPJ20), which have behavioral and synaptic deficits but no obvious neuronal loss. These recordings revealed frequent epileptiform activity including spikes and sharp waves (Figure 1). The hAPPJ20 mice also had intermittent unprovoked seizures involving diverse regions of the neocortex and hippocampus that were not accompanied by tonic or clonic motor activity (Figure 1). These results suggest that high levels of Aβ are sufficient to elicit epileptiform activity in vivo in the absence of frank neurodegeneration. Therefore, aberrant network synchronization appears to be a primary effect of high Aβ levels rather than a secondary consequence of extensive neurodegeneration. Electroencephalographic epileptiform activity has subsequently been identified in independent transgenic mouse models of AD, including hAPPJ9/FYN mice (unpublished data), Tg2576 mice, and hAPP/PS1 mice, underlining the robustness of this Aβ effect.

Several lines of evidence suggest that Aβ-induced aberrant neuronal activity could contribute to cognitive deficits in hAPP mice and in AD. Epileptic activity triggers a variety of inhibitory compensatory responses in hippocampal circuits to counteract imbalances in network activity (Figure 2). Although these compensatory inhibitory mechanisms may dampen aberrant increases in network activity, they may also interfere with normal neuronal and synaptic functions required for learning and memory. In hAPP mice, Aβ-induced epileptic activity was associated with sprouting of inhibitory axonal terminals in the molecular layer of the dentate gyrus, enhanced synaptic inhibition, and alterations in several calcium- and activity-regulated proteins in granule cells including calbindin, Fos, and Arc (Figure 2B). Importantly, these alterations correlated tightly with each other and with deficits in learning and memory, suggesting that Aβ-induced aberrant neuronal activity and associated compensatory inhibitory responses may be causally linked to cognitive decline (Figure 2A). We further assessed this possibility by crossing hAPP mice onto a tau-deficient (tau−/−) background, a genetic manipulation that blocks Aβ- and excitotoxin-induced overexcitation. Reducing tau levels in hAPP mice prevented learning and memory deficits, compensatory inhibitory responses, premature mortality, and most evidence for aberrant network activity without affecting either hAPP or Aβ (Figure 3). These results are consistent with our hypothesis that Aβ-induced aberrant neuronal activity contributes causally to learning and memory deficits in hAPP mice and possibly in AD.

**INFREQUENT SEIZURES IN SPORADIC AD AND MORE PROMINENT EPILEPSY IN FAMILIAL EARLY-ONSET AD**

The incidence of unprovoked seizures is clearly higher in sporadic AD than in reference populations, and the increase appears to be independent of disease stage. However, just as in hAPP mice, frank convulsive seizures are rather infrequent in AD. Nonetheless, 7% to 21% of patients with sporadic AD are estimated to have at least 1 unprovoked clinically apparent seizure during their illness. The relative risk of unprovoked seizures markedly increases in patients with early-onset AD, reaching 3−20−, and 87-fold with dementia onset when aged 70−79, 60−69, or 50−59 years, respectively.

The relationship between clinically apparent seizures and AD is even stronger in autosomal dominant early-onset AD, which can be caused by mutations in hAPP (≥23 mutations), presenilin-1 (≥17 mutations), or presenilin-2 (≥14 mutations) and by duplications of wild-type hAPP (≥7 duplications). These genetic alterations either increase Aβ42 production or the Aβ42:Aβ40 ratio or promote Aβ aggregation, providing strong evidence for a causal role of Aβ in AD. Notably, more than 30 mutations in presenilin-1 are associated with...
epilepsy, and 56% of patients with early-onset AD with APP duplications have seizures. Around 83% of pedigrees with very early onset of dementia (<40 years of age) show frank seizures or epilepsy. Most cases of Down syndrome have an extra copy of the hAPP gene and develop early-onset AD; notably, 84% of those cases also have frank seizures.

These clinical observations are consistent with our experimental findings and with our hypothesis that Aβ is an important cause of aberrant neural network synchronization in AD.

**APOLIPOPROTEIN E4 IS ASSOCIATED WITH SUBCLINICAL EPILEPTIFORM ACTIVITY IN CARRIERS WITHOUT DEMENTIA**

Apolipoprotein is the most important known genetic risk factor for sporadic AD. Although the mechanisms underlying this link remain to be fully elucidated, much evidence suggests that ApoE4 contributes to AD pathogenesis through both Aβ-dependent and Aβ-independent pathways. Aberrant increases in network excitability may represent a critical convergence point for the adverse effects of ApoE4 and Aβ in the pathogenesis of AD. In contrast to noncarriers, ApoE4 carriers without dementia showed signs of epileptiform activity and sharp waves on their EEGs after hyperventilation, although their EEGs were normal under resting conditions. Similar changes have been found in subjects with high familial risk of developing AD, such as first-order relatives of patients with early-onset AD. Apolipoprotein E4 also exacerbates epilepsy and promotes memory impairment in patients with long-standing intractable temporal lobe epilepsy. These data indicate that major genetic risk factors for developing AD are associated with increased network excitability in individuals without dementia, suggesting that this type of network dysfunction might play an early role in the establishment of pathogenic cascades leading to AD.

**AMNESTIC WANDERING AND DISORIENTATION IN AD CAN BE ASSOCIATED WITH EPILEPTIFORM ACTIVITY**

Many patients with AD experience fluctuations in cognitive functions such as transient episodes of amnestic wandering and disorientation. The intermittent inability to retrieve memories cannot be easily explained by relatively protracted processes such as neuronal loss, plaque deposition, or tangle formation. It seems more likely that abnormal neuronal network activity is to blame. Interestingly, amnestic episodes in patients with AD have been associated with epileptiform EEG discharges such as spikes and sharp waves. What is more, these specific cognitive disturbances and the associated epileptiform EEG discharges could be prevented by antiepileptic treatment. Epileptiform discharges in patients with temporal lobe epilepsy can also lead to transient amnesia and even simulate AD-like memory disturbances. Therefore, nonconvulsive epileptiform activity could underlie at least some of the cognitive impairments observed in AD. Prospective clinical investigations focusing on hard-to-detect forms of epileptic activity are needed to further test this hypothesis in the clinic.

**THERAPEUTIC IMPLICATIONS**

Many drugs for AD currently in clinical trials aim to reduce Aβ levels. However, the efficacy and long-term safety of these drugs have not yet been established. The studies discussed above suggest that reducing aberrant synchronization of neuronal activity may effectively pro-

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**Figure 3.** Tau reduction prevents β-amyloid (Aβ) toxicity in vivo. Thioflavin-S staining (A) and anti-Aβ immunostaining (B) of hippocampal amyloid plaques in mice with human amyloid precursor protein transgenic mice (hAPPJ20) with 2 (tau+/−) or no (tau−/-) functional tau alleles revealed that tau reduction did not alter plaque loads in hAPP mice. However, tau reduction effectively prevented Aβ-induced depletion of calbindin (CB) (C) and increases in neuropeptide Y (NPY) (D) in the dentate gyrus as well as spatial memory deficits in the Morris water maze (E). The representative path tracings in (E) were obtained in a probe trial (platform removed) 24 hours after 3 days of hidden platform training. Tau reduction markedly increased focused search activity in the target quadrant (light gray) and over the platform location (dark gray), suggesting improved spatial memory retention. Adapted from *Neuron* and *Science*. ©2009 American Medical Association. All rights reserved.
tect the brain against Aβ’s adverse effects on cognitive functions and thus could provide a complementary or alternative therapeutic strategy. We specifically hypothesize that cognitive deficits in hAPP mice, and perhaps in humans with AD, result from the combination of aberrant excitatory neuronal activity and of compensatory inhibitory responses that reduce overexcitation but end up constraining the functional agility of processes required for learning and memory (Figure 2A). Combination treatments may be required to block the contributions of overexcitation and overinhibition to AD-related cognitive deficits, although it seems reasonable to speculate that blocking the former should prevent, and might reverse, the latter.

Low doses of the γ-aminobutyric acid A (GABA_A) receptor antagonist picrotoxin prevented long-term potentiation deficits in the dentate gyrus and cognitive impairments in hAPP/presenilin 1 mice as well as in T65Dn mice, a mouse model of Down syndrome.43 These results indicate that inhibition in the dentate gyrus may critically contribute to cognitive impairments in these overlapping disorders. However, blocking inhibition with GABA_A receptor antagonists can also exacerbate or precipitate seizures in hAPP mice,44 making this therapeutic intervention risky, at least as a monotherapy. Blocking overexcitation might provide a more effective upstream approach. A key question is whether any of the available Food and Drug administration–approved antiepileptic drugs could prevent or ameliorate Aβ-induced aberrant network excitation. Notably, some of the most commonly used antiepileptic drugs actually worsened seizure activity in hAPPJ20 mice,46 underlining the need to carefully evaluate these agents at the preclinical level before designing clinical trials for people with AD or mild cognitive impairment. Consistent with this notion, the few clinical trials of antiepileptic drugs that have been conducted in AD so far have yielded disappointing results, but they were small and focused mostly on behavioral abnormalities in late stages of the disease.47

Up to one-third of patients with seizures without AD do not respond satisfactorily to medication and develop refractory epilepsy.48 Antiepileptic drugs can also aggregate or precipitate certain types of seizures.49 Thus, the efficacy of antiepileptic drugs in AD will likely depend on the exact mechanisms of Aβ-induced dysrhythmias, which are currently unknown. Some antiepileptic drugs may elicit beneficial effects, whereas others may exacerbate aberrant network activity and cognitive decline. It is also possible that novel drugs may have to be developed to specifically block Aβ-induced dysrhythmias in AD. Our experimental data suggest that reducing tau levels is highly effective in preventing Aβ-induced network dysfunction and cognitive deficits in vivo (Figure 3).43 However, much more research is needed to further assess the efficacy and safety of this novel therapeutic strategy.

Accepted for Publication: September 10, 2008.
Published Online: February 9, 2009 (doi:10.1001/archneurol.2009.15).
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**Author Contributions:** Study concept and design: Palop and Mucke. Acquisition of data: Palop. Analysis and interpretation of data: Palop and Mucke. Drafting of the manuscript: Palop and Mucke. Critical revision of the manuscript for important intellectual content: Palop and Mucke. Obtained funding: Mucke. Administrative, technical, and material support: Palop and Mucke. Study supervision: Mucke.

**Financial Disclosure:** Dr Mucke being a consultant for Merck.

**Funding/Support:** This study was supported by grants NS041787 and AG023501 from the National Institutes of Health (Dr Mucke).

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