

Current Literature

In Basic Science



Less is More: Reducing Tau Ameliorates Seizures in Epilepsy Models

Tau Loss Attenuates Neuronal Network Hyperexcitability in Mouse and *Drosophila* Genetic Models of Epilepsy.

Holth JK, Bomben VC, Reed JG, Inoue T, Younkin L, Younkin SG, Pautler RG, Botas J, Noebels JL. *J Neurosci* 2013;33:1651–1649.

Neuronal network hyperexcitability underlies the pathogenesis of seizures and is a component of some degenerative neurological disorders such as Alzheimer's disease (AD). Recently, the microtubule-binding protein tau has been implicated in the regulation of network synchronization. Genetic removal of *Mapt*, the gene encoding tau, in AD models overexpressing amyloid- β (A β) decreases hyperexcitability and normalizes the excitation/inhibition imbalance. Whether this effect of tau removal is specific to A β mouse models remains to be determined. Here, we examined tau as an excitability modifier in the non-AD nervous system using genetic deletion of tau in mouse and *Drosophila* models of hyperexcitability. *Kcna1*^{-/-} mice lack Kv1.1-delayed rectifier currents and exhibit severe spontaneous seizures, early lethality, and megencephaly. Young *Kcna1*^{-/-} mice retained wild-type levels of A β , tau, and tau phospho-Thr²³¹. Decreasing tau in *Kcna1*^{-/-} mice reduced hyperexcitability and alleviated seizure-related comorbidities. Tau reduction decreased *Kcna1*^{-/-} video-EEG recorded seizure frequency and duration as well as normalized *Kcna1*^{-/-} hippocampal network hyperexcitability in vitro. Additionally, tau reduction increased *Kcna1*^{-/-} survival and prevented megencephaly and hippocampal hypertrophy, as determined by MRI. Bang-sensitive *Drosophila* mutants display paralysis and seizures in response to mechanical stimulation, providing a complementary excitability assay for epistatic interactions. We found that tau reduction significantly decreased seizure sensitivity in two independent bang-sensitive mutant models, *kcc* and *eas*. Our results indicate that tau plays a general role in regulating intrinsic neuronal network hyperexcitability independently of A β overexpression and suggest that reducing tau function could be a viable target for therapeutic intervention in seizure disorders and antiepileptogenesis.

Commentary

The observed coincidence of epilepsy among patients with early-onset Alzheimer's disease suggested a possible connection between Alzheimer's disease and epilepsy. Alzheimer's disease patients with early onset between the ages of 50–59 years have an 87-fold increased risk of seizures compared to the general population (1). Although familial Alzheimer's disease cases represent a significant proportion of the early-onset cases, sporadic early-onset cases also have increased seizure risk (2). Further evidence for a link between Alzheimer's disease and epilepsy came from studies of transgenic mice that model genetic forms of Alzheimer's disease. A number of transgenic Alzheimer's disease models exhibit seizures or increased seizure susceptibility (3). This suggests that network hyperexcitability may be a common pathogenic effect underlying neurodegeneration and seizures, although the exact mechanisms have not been delineated. A possible key molecule linking neurodegeneration and seizures is microtubule

associated protein tau (tau), based on the observation that deletion of tau in Alzheimer's disease mouse models results in reduced seizures (4).

In the current study, Holth and colleagues sought to determine if reducing tau would improve the phenotype in models of epilepsy not related to Alzheimer's disease. They used the *Kcna1*^{-/-} knockout mouse model of temporal lobe epilepsy and bang-sensitive *Drosophila* mutants. *Kcna1*^{-/-} knockout mice lack the Kv1.1 potassium channel and have severe spontaneous seizures beginning in the third week of life, megencephaly, and early lethality (5). The authors crossed *Kcna1* knockout mice with tau knockout mice to generate double mutants. Double-mutant mice lacking tau exhibited a 94% reduction in seizure frequency and approximately 60% reduction in abnormal electrographic activity. *Kcna1*^{-/-} single-mutant mice exhibit elevated hippocampal network excitability, which was returned to wild-type levels by reduction of tau in the double-mutant mice. Tau loss also had a dose-dependent protective effect on the premature lethality phenotype of *Kcna1*^{-/-} mice. Single-mutant *Kcna1*^{-/-} mice have only 30% survival at 10 weeks of age, while *Kcna1*^{-/-};*Tau*^{+/-} mice had 59% survival at 10 weeks and *Kcna1*^{-/-};*Tau*^{-/-} had 74% survival at 10 weeks of age. Overall, these results demonstrate a significant

Epilepsy Currents, Vol. 13, No. 4 (July/August) 2013 pp. 184–185
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protective effect of tau reduction on network excitability, seizures, and survival.

To determine if the protective effect of tau reduction would generalize to other seizure models, Holth and colleagues performed additional experiments using bang-sensitive *Drosophila* mutants. Bang-sensitive *Drosophila* mutants exhibit increased propensity for behavioral seizures following mechanical stimulation (6). They used two different bang-sensitive *Drosophila* mutants: *kcc* that carries a mutation in a K⁺/Cl⁻ cotransporter, and *eas* that carries a mutation in ethanolamine kinase. In both mutants, genetic reduction of tau resulted in reduced bang sensitivity, demonstrating that tau reduction is protective in hyperexcitability models with different underlying mechanisms.

The results of the current study and other studies with Alzheimer's disease-related transgenic models clearly demonstrate that removal of tau is neuroprotective in mutants with hyperexcitability phenotypes (4). Although the pathogenic effect of tau hyperphosphorylation and aggregation into neurofibrillary tangles has long been appreciated in Alzheimer's disease and frontotemporal dementia (FTD), the protective effect of tau removal suggests that it contributes to the regulation of neuronal excitability in the normal brain. The precise mechanism by which tau deletion reduces seizures in transgenic Alzheimer's disease models—and in the epilepsy models studied by Holth and colleagues—is not clear. One potential mechanism may be through the interaction of tau with fyn kinase and the NMDA receptor. In the absence of tau, postsynaptic localization of fyn is reduced, resulting in decreased phosphorylation of NMDA receptors, destabilization of NMDA-PSD95 complexes, and reduced excitotoxicity (7). Additional work will be necessary to determine the specific mechanism(s) and assess the suitability of this pathway for therapeutic intervention.

For tau removal to be a viable therapeutic strategy, it is critical to understand the effects of tau removal under otherwise normal conditions. Genetic deletion of tau in mice does not result in an overt deleterious phenotype, but there are subtle behavioral alterations and changes in neuronal migration and morphology. When cultured *in vitro*, neurons from *tau*^{-/-} mice exhibit delays in neuronal migration and reduced process length (8). Behavioral evaluation of *tau*^{-/-} mice revealed subtle deficits, including open field hyperactivity, impaired balance, and mild muscle weakness in wire hang tests (9). Consistent with the mouse data, deletion of tau homologs in *C. elegans* and *Drosophila* does not result in overt adverse phenotypes

(10). Although the currently available studies suggest that the consequences of tau removal are limited, more extensive behavioral and neurophysiological studies are required to rule out more subtle adverse phenotypes.

The current study broadens the therapeutic potential of tau reduction to epilepsy and possibly other non-Alzheimer's disease disorders of excitability. The broadening of potential therapeutic indications could result in synergy between seemingly disparate areas of research and may ultimately accelerate the development of novel treatments.

by Jennifer A. Kearney, PhD

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