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Less tau reduces seizures and sudden death in severe epilepsy

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Deleting or reducing expression of a gene that carries the code for tau, a protein associated with Alzheimer's disease, can prevent seizures in a severe type of epilepsy linked to sudden death, said researchers at Baylor College of Medicine and the Mayo Clinic in Jacksonville, Fla., in a report in the current issue of the *Journal of Neuroscience*.

A growing understanding of the link between epilepsy and some forms of inherited Alzheimer's disease led to the finding that could point the way toward new drugs for seizure disorders said Dr. Jeffrey Noebels, professor of neurology at BCM, and director of the Blue Bird Circle Developmental Neurogenetics Laboratory.

In her research, Jerrah Holth, a graduate student in molecular and human genetics at BCM who was working with mice with the severe form of epilepsy in Noebel's laboratory, deleted the gene for tau. She found that reducing or eliminating tau also prevented the seizures in a severe form of epilepsy that has been associated with sudden death and reduced deaths in the animals.

In an earlier experiment, Noebels, in collaboration with Dr. Lennart Mucke at the Gladstone Research Laboratory at the University of California San Francisco, found that mice who carried a human gene that leads to accumulation of the beta amyloid protein and the amyloid plaques that accumulate in the brains of people with Alzheimer's disease, also had epileptic seizures arising in the hippocampus, the region of the brain associated with memory storage and retrieval.

"This led to the paradigm-shifting hypothesis that excessive neuronal network activity, rather than too little, may contribute to lower cognitive performance and dementia in some forms of Alzheimer's disease. When this happens, the progression of memory loss may accelerate," said Noebels.

The finding also demonstrated the two disorders may share defects in signaling within brain memory circuits.

The two labs went on to show that deleting the second gene for tau ameliorated both cognitive losses and seizures in the mice whose inherited disorder mimicked Alzheimer's disease found in humans.

Holth's finding demonstrates that tau is involved in a far broader range of epilepsy than previously suspected, said Noebels. The type of epilepsy she studied resulted from an inherited potassium ion channel defect that affects the flow of the potassium in and out of nerve cells. She found that removing the gene encoding Tau not only dramatically reduced seizures, but prevented the mice from dying early, which typically happens in these animals.

"Even a partial reduction of the amount of tau protein by 50 percent was highly effective," said Holth. Her finding suggests developing new drugs that lower the normal interactions of the tau protein may reduce seizures and sudden unexpected death for persons with intractable epilepsies, a problem in nearly one-third of the 5 million Americans with this disorder.

Currently, Noebels and his colleagues in the Blue Bird Laboratory are studying whether the loss of tau can correct a seizure disorder once it is already established. If these studies prove fruitful, "the pharmacological discovery programs under development for treatment of Alzheimer's disease may one day find their way to the epilepsy clinic," said Noebels.

Provided by Baylor College of Medicine