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GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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GLADSTONE SCIENTISTS UNCOVER NOVEL MECHANISM FOR THE MAJOR GENETIC RISK FACTOR OF ALZHEIMER'S DISEASE

ApoE4 causes GABAergic interneuron impairment, leading to learning and memory deficits

SAN FRANCISCO, CA—OCT. 13, 2010 -- Alzheimer's disease (AD) is an extremely complicated disease. Several proteins seem to be involved in its cause and progression. For example, the lipid-transport protein apolipoprotein E4 (apoE4) is the major genetic risk factor for AD, and apoE4 carriers account for 65–80% of all Alzheimer's cases, but exactly how apoE4 contributes to the disease is unclear.

Scientists at the Gladstone Institutes of Neurological Disease (GIND) have provided new insights into how apoE4 might be involved. In a study published today online in the *Journal of Neuroscience*, researchers led by led by Yadong Huang, MD, PhD reported that apoE4-dependent learning and memory deficits are caused by loss of a specific type of neuron in the learning and memory center of the brain.

“We found that mice that had been genetically engineered to produce human apoE4 lost a specific kind of cells and that loss of these cells correlated with the extent of learning and memory deficits,” said Yaisa Andrews-Zwilling, PhD, postdoctoral fellow and lead author of the study.

Those key cells are called GABAergic interneurons in the hilus of the hippocampus, an area of the brain involved in learning and memory and affected by AD. GABA is an important

neurotransmitter released from GABAergic interneurons. As one component of a delicately balanced system for regulating brain activity, GABA functions to inhibit brain activity. AD brains seem to have low levels of GABA.

“Importantly, apoE4 causes GABAergic interneuron loss and learning and memory deficits in the absence of A β peptide accumulation, a widely suspected toxin in Alzheimer’s disease,” said Dr. Huang, senior author of the study. “This demonstrates clearly that apoE4 plays A β -independent roles in Alzheimer’s disease.”

To try to overcome the decrease of GABAergic interneuron function, the Gladstone team treated the apoE4 mice with daily injections of pentobarbital, a compound that enhances GABA action. They found that the injections rescued the learning and memory deficits in the mice. They also examined the effects of apoE4 on tau, another protein implicated in Alzheimer’s disease. When they genetically eliminated the mouse’s own tau, the loss of the GABAergic interneuron was halted and the learning and memory deficits were prevented.

“We previously showed that suppressing the protein tau can prevent A β from causing memory deficits and other abnormalities in mouse models of Alzheimer’s disease,” said Dr. Lennart Mucke, GIND director. “This new study demonstrates that tau also acts downstream of apoE4. Thus, tau might be a general causative factor in Alzheimer’s disease pathogenesis.”

ApoE4 seems to increase the concentration of a particular species of tau—phosphorylated tau known to be toxic in some kinds of neurodegeneration. Increases in the levels of phosphorylated tau eventually kill the GABAergic interneurons, and this loss leads to learning and memory deficits. The Gladstone team showed that giving the mice pentobarbital to boost the GABA function could stop this chain of events. In effect, they were providing a product of a reaction downstream from where apoE4 disrupts the pathway.

“Clinical studies have shown that apoE4 is associated with increased activity in the hippocampus at rest and in response to memory tasks in humans. Our study suggests that this may reflect the impaired GABAergic inhibitory neuronal functions in the presence of apoE4,” said Dr. Huang.

“Our study also demonstrates that increasing GABA signaling and reducing tau are potential strategies to treat or prevent apoE4-related Alzheimer’s disease.”

The team also included Gladstone's Nga Bien-Ly, Qin Xu, Gang Li, Aubrey Bernardo, Seo Yeon Yoon, Daniel Zwilling, Tonya Xue Yan, and Ligong Chen.

The research was supported in part by NIH.

Yadong Huang’s primary affiliation is with the Gladstone Institute of Neurological Disease, where he is associate investigator and where his laboratory is located and his research is conducted. He is also an associate professor of Pathology and Neurology at UCSF.

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