Gladstone scientists identify process by which Alzheimer's disease creeps through the brain

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Scientists at the Gladstone Institute of Neurological Disease (GIND) have offered new information about the events that underlie the "spread" of Alzheimer's disease (AD) throughout the brain. The research, published in the November 4th issue of the journal *Neuron,* follows disease progression from a vulnerable brain region that is affected early in the disease to interconnected brain regions that are affected in later stages. The findings may contribute to design of therapeutic interventions, as targeting the brain region where AD originates might be simpler than targeting multiple brain areas.

An alteration in brain levels of amyloid ? proteins (A?) plays a major role in AD, a devastating neurodegenerative disorder that causes progressive cognitive impairment and memory loss. AD is characterized by abnormal accumulation of A? in the brain, which leads to the formation of protein aggregates that are toxic to neurons. A? peptides are generated when a large protein called amyloid precursor protein (APP) is cut up into smaller pieces.

One of the first brain regions affected in AD is the entorhinal cortex (EC). Connections between the EC and another brain region called hippocampus are critical for memory, and disruption of this circuit may play a role in memory impairment in the beginning stages of AD.

"It is not clear how EC dysfunction contributes to cognitive decline in AD or whether early vulnerability of the EC initiates the spread of dysfunction through interconnected neural networks," explained senior study author and GIND director Lennart Mucke , MD. "To address these questions, we studied transgenic mice with mutant APP expressed primarily in neurons of the EC."

The majority of current mouse models of AD express mutant proteins throughout the brain, making it difficult to identify the role of any specific brain region in AD-related dysfunction.

Dr. Mucke and colleagues found that expressing mutant APP and A? selectively in the EC led to age-dependent deficits in learning and memory, and other behavioral deficits including hyperactivity and disinhibition. Importantly, these abnormalities are similar to those observed in mouse models of AD with mutant APP expression throughout the brain. The researchers also observed abnormalities in parts of the hippocampus that receive input from the EC, including dysfunction of synapses and A? deposits.

"Our findings directly support the hypothesis that AD-related dysfunction is propagated through networks of neurons, with the EC as an important hub region of early vulnerability," concluded Dr. Julie Harris, the lead author of the study. "Although additional studies are needed to better understand how events in the EC are related to AD, it is conceivable that early interference in the EC might be of therapeutic benefit, perhaps halting disease progression."

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