Scientists discover a missing link between tau and memory loss

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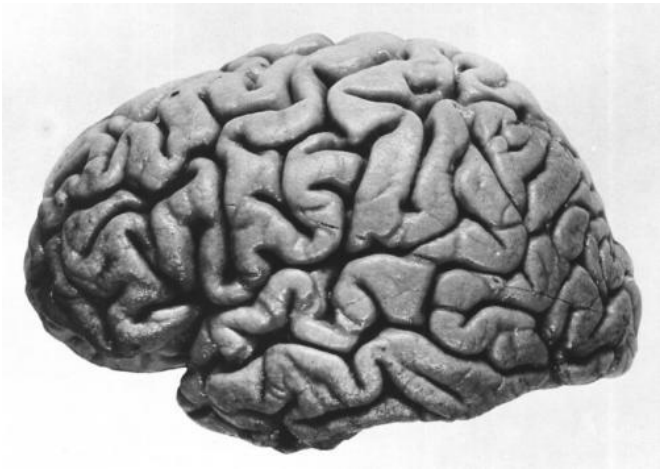

Left hemisphere of J. Pi?sudski's brain, lateral view.
Credit: public domain

Scientists have long known that the protein tau is involved in dementia, but how it hinders cognitive function has remained uncertain. In a study published in the journal *Neuron*, researchers at the Gladstone Institutes reveal how tau disrupts the ability of brain cells to strengthen connections with other brain cells, preventing new memories from forming.

"Understanding why and how tau is toxic to neurons is the first step in repairing or preventing the damage it causes in Alzheimer's disease," said senior author Li Gan, PhD, a senior investigator at Gladstone. "We learned that tau disrupts memory in models of Alzheimer's disease by depleting another protein, KIBRA, which is critical for memory formation. With this knowledge, we can explore ways to increase KIBRA with drugs that block the harmful effects of tau."

Memories are formed when chemical signals strengthen the connection between neurons. To maintain the memories, neurons physically change, recruiting more chemical receptors to the surface where the connections are made (the synapse) to increase the strength of incoming signals. If the connections among neurons weaken or are lost, so is the memory.

In the current study, the scientists discovered that, in a mouse model of Alzheimer's disease, the accumulation of tau in neurons disrupts the cells' ability to strengthen their connections with other neurons, preventing them from stabilizing new memories. This is because a natural chemical modification of tau called acetylation that is exacerbated in Alzheimer's disease results in tau moving from its normal location in the neuron to the synapse. At the synapse, tau depletes another protein called KIBRA (KIdney/BRAin protein), a process that prevents neurons from adapting and strengthening their connections. Increasing KIBRA levels reversed the harmful effects of acetylated tau and restored the cells' ability to form memories.

Supporting the clinical relevance of this finding, the researchers also found that KIBRA is decreased in the brains of patients with Alzheimer's disease, which correlated with an increase in acetylated tau.

"Our findings suggest that KIBRA may be the missing link between tau and memory loss in Alzheimer's disease," said first author Tara Tracy, PhD, a postdoctoral scholar at Gladstone. "The next step is to determine precisely how acetylated tau causes KIBRA levels to drop, and to explore whether our findings may help develop better treatments for Alzheimer's disease."

Provided by Gladstone Institutes