Medical Xpress

Researchers find the roots of tau tangles in Alzheimer's disease

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An experimental drug can reduce the toxic changes in tau proteins

known to damage neurons in brains with Alzheimer's disease, researchers from Yale School of Medicine and Johns Hopkins University report.

While much research related to Alzheimer's disease has concentrated on identifying ways to reduce the buildup of amyloid plaques—which form when sticky protein fragments known as amyloid beta collect in the brain—the new study focuses on slowing harmful changes in a molecule called tau, which can lead to tangles and neuronal degeneration. In particular, the phosphorylation of tau, in which phosphate groups are added to the tau peptide, is a key early event that triggers neurological damage, the researchers found.

The research suggests that inflammatory processes in the aging brain contribute to the phosphorylation of tau in the common, late-onset form of Alzheimer's disease.

"We were able to reduce the phosphorylation of tau by restoring regulatory actions that are lost with age and inflammation," said senior author Amy Arnsten, the Albert E. Kent Professor of Neuroscience at Yale School of Medicine and professor of neurobiology and psychology in Yale's Faculty of Arts and Sciences. "The mechanism of protection is different from other approaches undertaken so far."

The study was published in the journal *Alzheimer's & Dementia: Translational Research & Clinical Interventions*.

In their research, members of Arnsten's lab investigated ways to reduce tau phosphorylation early in progression of the disease, before damage is done to neurons.

Specifically, they focused on the role of a brain enzyme involved in inflammation called GCPll (glutamate-carboxypeptidase-II). This

enzyme erodes the protective effects provided by mGluR3, a receptor on neurons that facilitates higher cognitive functions.

The researchers found that a GCPII inhibitor called 2-MPPA (synthesized by the Johns Hopkins Drug Discovery program) reduced tau phosphorylation in older monkeys with naturally occurring tau pathology.

The goal now is to develop a compound that can be used in humans.

"We hope to develop a GCPll inhibitor that can be taken orally and is safe for human use," said Barbara Slusher, director of Johns Hopkins Drug Discovery and co-author of the study. "We believe this mechanism has great potential."

More information: Shveta Bathla et al, Chronic GCPII (glutamate-carboxypeptidase-II) inhibition reduces pT217Tau levels in the entorhinal and dorsolateral prefrontal cortices of aged macaques, *Alzheimer's & Dementia: Translational Research & Clinical Interventions* (2023). DOI: 10.1002/trc2.12431

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