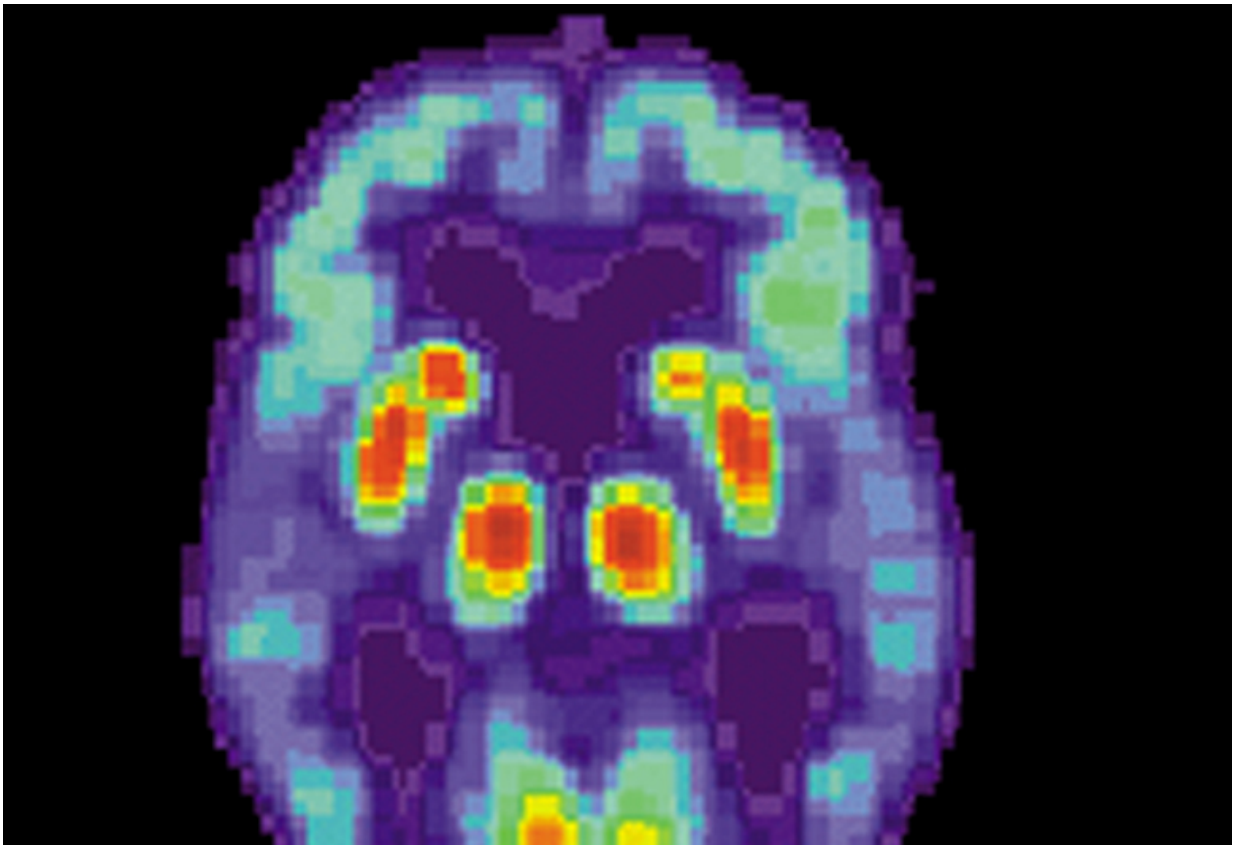
A new way of thinking about tau kinetics, an essential component of Alzheimer's disease

March 21 2018



PET scan of a human brain with Alzheimer's disease. Credit: public domain

Alzheimer's disease is most often characterized by two different pathologies in the brain: plaque deposits of a protein called beta-amyloid and tangles of another protein called tau. A paper appearing March 21 in

the journal *Neuron* brings new insights into how tau proteins are processed in the human central nervous system. Researchers found that tau production and secretion from nerve cells appears to be an active process in the natural course of Alzheimer's disease. This may explain why experimental treatments targeting tau have had disappointing results, as the current focus of these drugs assumes that the protein is primarily released from dying nerve cells.

"This study changes our way of thinking about tau in the context of neurodegenerative diseases," says senior author, Randall Bateman, the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis. "Contrary to the idea that tau is a product released by dying neurons, we have shown that the release of tau is an active and controlled activity that appears to be an important part of the disease process."

In the study, the investigators used mass spectrometry and a method called stable isotope labeling kinetics to study tau in the cerebrospinal fluid (CSF) of people who were known to have Alzheimer's and healthy controls. This enabled them to measure the tau turnover rate and its half-life in the human nervous system as well as to analyze the different forms of the protein. Their findings revealed that certain forms of tau have faster turnover rates than others, suggesting that they may have unique biological activities. In addition, they found that production rate of tau was higher in people with Alzheimer's, suggesting a biological link between the presence of amyloid plaques and tau kinetics.

"We've known for a long time that CSF tau is increased in Alzheimer's disease, but until this study, we didn't know if tau production was increased or if clearance was decreased," says Chihiro Sato, a member of the Bateman lab and one of the paper's co-first authors. "Our results showing that tau production is increased suggest that we might want to target tau production therapeutically."

The researchers also looked at tau production in human neurons made from induced pluripotent stem cells (iPSCs). "The research with the iPSCs was really valuable, because we were able to ask questions about human neurons that we wouldn't be able to ask in living subjects," says Celeste Karch, an Assistant Professor of Psychiatry at Washington University School of Medicine and one of the study's co- authors. "We found that inside neurons some forms of tau are turned over more quickly than others. Interestingly, the forms of tau that are turned over more quickly are also those that are prone to misfold and aggregate in the context of Alzheimer's disease and other tauopathies."

"Using mass spectrometry, we found that tau is truncated in CSF in healthy people and Alzheimer's patients," says Nicolas Barthélemy, a member of the Bateman lab and the other co-first author. "Truncated tau is released differently from full-length tau, supporting our hypothesis that tau is actively processed under physiological and pathological conditions."

The investigators say the knowledge gained from this study not only helps to understand more about Alzheimer's disease, but other diseases characterized by the aggregation of tau as well. "We expect these findings will help us to distinguish between Alzheimer's and other types of tauopathies in future," Bateman says. The investigators plan to expand their research to patients with some of these other diseases, including progressive supranuclear palsy and corticobasal degeneration, to determine whether there are different forms of tau in the cerebrospinal fluid and different kinetics underlying the changes that are observed.

"It's hard to do clinical research on tauopathies right now, because we don't have good tests for diagnosing these other diseases, such as frontotemporal dementia," Bateman adds. "Having an accurate diagnosis helps not only in the clinic but also in clinical trials, to ensure that we've included the right patients in our studies."

More information: *Neuron*, Sato et al. "Tau Kinetics in Neurons and the Human Central Nervous System." www.cell.com/neuron/fulltext/S0896-6273(18)30136-3 , DOI: 10.1016/j.neuron.2018.02.015

Provided by Cell Press