Central trafficking compartment in neurons malfunctions in majority of Alzheimer's patients

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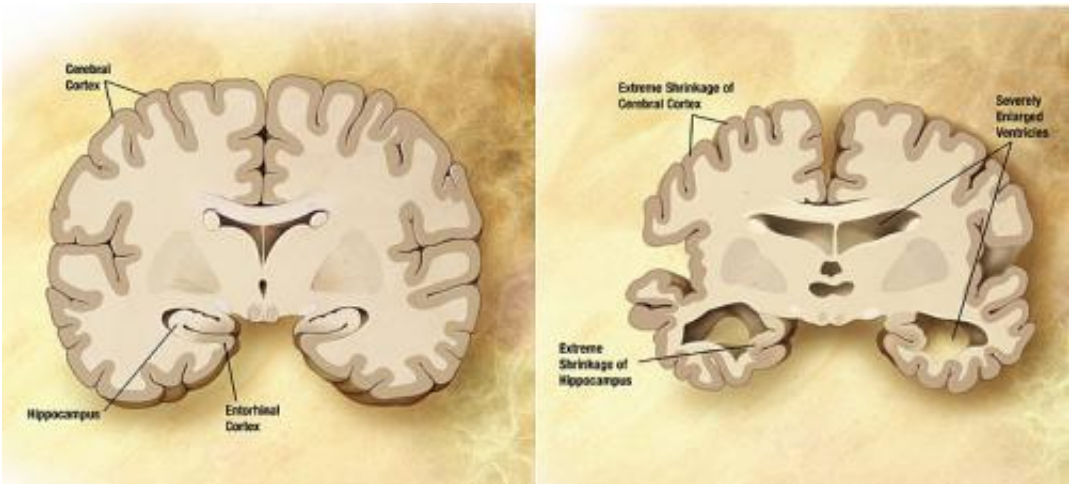

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Decades before the first symptoms of Alzheimer's appear, the brain's neurons start secreting tau proteins, one of the first changes known to occur in the course of the disease.

High levels of secreted forms of tau—which can be detected in spinal fluid and, as recently reported, in blood—are known to be the most reliable predictor of who will eventually develop Alzheimer's disease.

But a critical question about tau has remained unanswered: Why are neurons secreting tau in Alzheimer's disease?

"Since tau secretion is one of the earliest events in Alzheimer's, figuring out why that happens can tell us about the underlying mechanisms of the disease, which is critical for developing therapies. If tau is the smoke, in other words, what is the fire?" says Scott Small, MD, Ph.D., the Boris and Rose Katz Professor of Neurology at Columbia University Vagelos College of Physicians and Surgeons and director of the Alzheimer's Disease Research Center at Columbia University.

The Neuron's 'Grand Central Station' Is Commonly Defective in Alzheimer's

A new study from Small's laboratory found that, in many patients, tau secretion arises from tiny malfunctioning compartments inside the brain's neurons, suggesting that these malfunctional compartments are commonly involved in the appearance of Alzheimer's disease.

These tiny compartments, called endosomes, function as a 'grand central station' and traffic proteins throughout a cell. The new study provides evidence that endosomal trafficking is disrupted in about 70% of the patients it examined, including those only displaying the first signs of Alzheimer's.

The results provide the first direct evidence that endosomal traffic disruption—which Small, Richard Mayeux, MD, chair of neurology at Columbia, and others had previously identified as one of Alzheimer's root causes—is commonly defective among patients with the disease.

"There was no question that endosomal dysfunction is a component of Alzheimer's, but just how often it's involved had been unknown," says Sabrina Simoes, Ph.D., assistant professor of neurological sciences at

Columbia University Vagelos College of Physicians and Surgeons, who led the study.

"Our study suggests that if drugs that restore endosomal dysfunction can slow Alzheimer's, those drugs could help a large proportion of patients."

Moreover, the study's results and new biomarker tools can be used to investigate which predisposing genes or comorbid diseases, such as obesity and diabetes, disrupt endosomal trafficking and raise the risk of developing Alzheimer's.

What the Study Did

The researchers were looking for biomarkers of endosomal trafficking dysfunction to determine its presence in Alzheimer's patients. Using mice with the same endosomal trafficking defect, the researchers searched the animals' spinal fluid for proteins that differed from that in normal animals. Three proteins stood out: Two were cleaved proteins that are known to be secreted by endosomes, called n-APLP1 and n-CHL1. The third was tau.

The study then examined the spinal fluid of people. First, investigators from Janssen Pharmaceuticals, collaborators in the study, developed new biomarkers of n-APLP1 and n-CHL1. Armed with accurate new biomarkers of these two proteins and with established biomarkers of tau (those that are in current use to diagnose patients), the investigators examined their relationship in healthy people. They found a remarkably tight relationship among the three proteins, suggesting that tau is normally secreted from the endosomal pathway.

The researcher then looked for the proteins in Alzheimer's patients and found that all three proteins are abnormally elevated in spinal fluid in approximately 70% of patients, even in those in the early "prodromal"

stage of the disease.

Can Alzheimer's Be Slowed by Restoring Endosome Trafficking?

The study's identification of three new biomarkers of endosomal trafficking disruption can be used to accelerate Alzheimer's drug discovery and clinical trials by identifying patients with malfunctioning endosomes and measuring a drug candidate's ability to restore endosomal operations.

Researchers in Small's lab are working to find ways to improve endosomal trafficking and slow Alzheimer's disease. Several years ago, they identified compounds that do just that in neurons in a dish, and are now trying to develop these compounds as therapeutics. They are also developing gene therapies that can correct endosomal trafficking disruption in the brain.

The researchers are testing these therapeutics to see if they can improve the endosome's trafficking function in animal models of Alzheimer's disease.

The study appears in a paper titled, "Tau and other proteins found in Alzheimer's Disease spinal fluid are linked to retromer-mediated endosomal traffic," published online Nov. 25 in *Science Translational Medicine*.

More information: "Tau and other proteins found in Alzheimer's disease spinal fluid are linked to retromer-mediated endosomal traffic in mice and humans" *Science Translational Medicine* (2020). stm.sciencemag.org/lookup/doi/ … scitranslmed.aba6334