Two defective proteins conspire to impair the nerve cell's 'powerhouse' in Alzheimer's disease

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Two proteins that are abnormally modified in the brains of patients with Alzheimer disease collude, resulting in ill effects on the crucial energy centers of brain cells, according to new findings published online in *Neurobiology of Aging*.

The research raises the possibility that pathological forms of two proteins, amyloid beta and tau, which make up the pathological hallmarks of the brains of Alzheimer patients – plaques and tangles – may work in tandem to decrease the survival of brain cells.

The findings come as part of a bundle of results from several laboratories that are putting cellular components known as mitochondria under increasing scrutiny in the development of a range of brain conditions, including Alzheimer, Huntington and Parkinson diseases.

Mitochondria are like tiny little energy plants inside neurons and other cells, constantly on the move, churning out the energy that cells need to survive. Mitochondria are also master controllers as they perform additional jobs such as keeping calcium levels normal. A cell with damaged mitochondria is unable to produce sufficient energy to keep the cell going, cannot buffer calcium correctly, and releases oxidative molecules that damage the cell. These types of events may be occurring in the Alzheimer disease brain, resulting in nerve cells that don't function properly.

"The idea that amyloid beta and tau may work together to cause mischief in the brain has been an evolving theme among scientists for a number of years," said Gail Johnson, Ph.D., professor of Anesthesiology and the corresponding author of the paper. "The precise relationship between the two pathologies is unclear, but there may be a synergy between the two when it comes to their effects on mitochondria in Alzheimer disease."

Johnson's group took a particularly close look at a pathological form of the protein known as tau, which helps stabilize a network of highway-like tracks called microtubules in neurons. In recent years scientists like Johnson have been focusing on an abnormally shortened form of the protein, known as truncated tau, as one that likely has a role in Alzheimer disease.

Johnson's team looked at the performance of mitochondria in rat neurons during exposure to amyloid beta, to the regular tau protein, to the truncated version of tau, and to combinations of amyloid beta and the two versions of tau. Among the experiments was one in which scientists tracked the movement of mitochondria, snapping a new image every 10 seconds during a five-minute span to track the movements of the organelles within neurons.

The biggest changes to mitochondria occurred when amyloid beta and truncated tau were present together. Effects included:

- The ability of mitochondria to maintain their electrical potential, which is needed to produce energy efficiently, was severely impaired. They had only one-third of the electrical potential of mitochondria in control cells.

- Mitochondria usually are highly mobile and distributed throughout the cell. However, in the presence of truncated tau

and amyloid beta, mitochondria clumped together abnormally in some parts of neurons and failed to get to other parts of neurons, such as the synapses, like they normally do. Overall, only about half the mitochondria were mobile compared to their counterparts not exposed to the pathological proteins.

- Cells that were exposed to both truncated tau and amyloid beta were less able than usual to respond to cellular stress. The number of harmful molecules known as reactive oxygen species or free radicals was boosted 60 percent in these cells.

- Mitochondria exposed to amyloid beta and truncated tau were fragmented, with the average length just half that of normal mitochondria.

The cellular changes that Johnson is looking at likely occur before a patient begins to experience symptoms like memory loss. Most scientists believe that changes in the brains of Alzheimer patients begin years or even decades before the signs of Alzheimer disease become apparent.

"By the time the cells are dead, it's far too late to do much," said Johnson, who is also a professor in the Department of Pharmacology and Physiology and a scientist in the Center for Neural Development and Disease. "Therefore, in the field of Alzheimer research, investigators are looking for early markers and indicators of disease so that patients could be identified before significant nerve cell death has occurred. In addition, studies in many labs are ongoing to identify treatments that could target these early events.

"Perhaps," Johnson adds, "the new information on mitochondrial dysfunction in Alzheimer disease can be used to fight the disease, as it is likely an important target for therapeutic intervention. Given the fact that Alzheimer disease is a very complex disease, a monotherapeutic

approach may not be as effective as a combinatorial treatment strategy, as is the case for treating other diseases including cancer and diabetes. Further studies on why and how mitochondria are compromised in Alzheimer disease as well as other neurodegenerative conditions are needed to develop effective treatments which will increase mitochondrial function and improve the health of the brain cells."

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