Early role of mitochondria in AD may help explain limitations to current beta amyloid hypothesis

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Before Alzheimer's patients experience memory loss, the brain's neurons have already suffered harm for years.

A new study in mouse models by researchers at Columbia University Medical Center has found that the brain's mitochondria -- the powerhouses of the cell -- are one of the earliest casualties of the disease. The study, which appeared in the online Early Edition of PNAS, also found that impaired mitochondria then injure the neurons' synapses, which are necessary for normal brain function.

"The damage to synapses is one of the earliest events in Alzheimer's disease, but we haven't been able to work out the events that lead to the damage," says the study's principle investigator, ShiDu Yan, M.D., professor of clinical pathology and cell biology in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center. "Our new findings, along with previous research, suggest that mitochondrial changes harm the synapses, and that we may be able to slow down Alzheimer's at a very early stage by improving mitochondrial function."

Drugs that restore mitochondria function may be able to treat Alzheimer's disease in its earliest stages. One potential drug, cyclosporin, is already used in organ transplant and autoimmune patients. Cyclosporin suppresses the immune system, but it also blocks amyloid beta (Aβ)

peptides-induced mitochondrial injury, Dr. Yan has found in previous studies (Du et al. Nature Medicine, 2008).

Cyclosporin, however, has too many toxic side effects for long term use in other patients. Dr. Yan is currently trying to alter the chemical structure of the drug to reduce its toxicity and to improve its ability to cross the blood brain barrier but preserve its protective effect on Aβ-mediated toxicity.

Most Alzheimer's researchers initially believed that Aβ peptides caused the disease after aggregating together in large, extracellular plaques, a defining feature of Alzheimer's-affected brains. But Dr.Yan's findings, along with those of many other scientists, now point to an earlier role for Aβ peptides inside the brain's neurons.

The mitochondria are damaged, the researchers found, when (Aβ) peptides breach the mitochondria's walls and accumulate on the inside. Even low concentrations of Aβ peptides, equivalent to the levels found in cells years before symptoms appear, impair the mitochondria, particularly mitochondria that supply power to the neuron's synapses.

When filled with Aβ peptides, these synaptic mitochondria were unable to travel down the neurons' long axons to reach, and fuel, the synapse. And the mitochondria that did make the journey failed to provide adequate energy to operate the synapses. Without operating synapses, neurons are unable to function.

"Since cyclosporin is already FDA approved for use in organ transplant and autoimmune patients, this research has the potential to lead to more rapid clinical trials and progress quickly," said Dr. Yan.

Next, Dr. Yan and her team also plan to do more research on the role of tau, which like beta amyloid, is the protein associated most with the

plaques and tangles seen at autopsy in the brains of those with Alzheimer's.

Provided by Columbia University Medical Center