Alzheimer's protein detected in brain fluid of healthy mice

September 21 2011, By Michael C. Purdy

Postdoctoral research scholar Kaoru Yamada, PhD, right, was lead author on a new study that detected an Alzheimer's protein where it wasn't expected to be found: in the brain fluid of healthy mice. Mary Beth Finn, senior research technician, was a co-author.

(Medical Xpress) -- One of the most promising markers of Alzheimer's disease, previously thought only to be inside nerve cells, now appears to be normally released from nerve cells throughout life, according to researchers at Washington University School of Medicine in St. Louis.

Scientists found evidence in mice that healthy brain cells regularly secrete tau protein into surrounding brain fluids. Before now, the major

known role for tau in healthy biology was as a component of the cytoskeleton, or railroad tracks that allow for the transport of material inside cells in the central nervous system.

The new report appears online in *The* Journal of Neuroscience.

In Alzheimer's disease, tau seems to play a pivotal role. Tau is the main ingredient of neurofibrillary tangles, which are abnormal clumps of material inside nerve cells and a hallmark of the disease. Increased tau in the spinal fluid appears to be a sign of early Alzheimer's disease, and the protein is one of several indicators researchers are investigating as they attempt to treat Alzheimer's before patients develop dementia.

"Our new technique for measuring tau in the living brains of animal models has the potential to help us determine how it is secreted, which could be very important to fully understanding the Alzheimer's disease process," says lead author Kaoru Yamada, PhD, a postdoctoral research scholar. "It's also going to help us test new drugs for Alzheimer's."

Tau protein comes in several different forms. Depending upon how a tau protein is assembled and folded, it may stay suspended in the fluid within and between cells (soluble) or drop out of those fluids and clump together with other copies of the tau protein to create tangles (insoluble). Soluble tau can bind to parts of the cell cytoskeleton to give them added strength and flexibility and to allow for the transport of material inside nerve cells.

Recent studies have revealed that clumps of insoluble tau can form inside cells, leave the cells and be taken up by other cells. But until now, soluble tau has not been described as leaving nerve cells inside a living brain.

Yamada and others in the laboratory of David Holtzman, MD, the

Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology, modified a technique they had developed to measure amyloid beta, the main ingredient of amyloid plaques, another hallmark of Alzheimer's.

They found that tau was present in brain fluid of normal mice at levels up to ten times higher than tau levels in the spinal fluid. These levels did not change as the mice aged.

Next, researchers tested mice genetically altered to make more tau, which causes them to develop neurofibrillary tangles as they get older. Levels of tau in brain fluids decreased as these mice aged, dropping from 250 nanograms per milliliter in young mice to 80 nanograms per milliliter in older mice.

This may be because the soluble tau in brain fluids is being converted into insoluble forms of the tau protein that then form neurofibrillary tangles. When researchers injected copies of tau shortened to contain only the protein's biochemically "stickiest" region, potentially seeding the formation of new insoluble clumps of tau, levels of the protein in brain fluid dropped even in young mice.

"We speculate that there are unknown metabolic processes that regulate levels of soluble tau in brain fluid, and the aggregation of tau into neurofibrillary tangles is disrupting these processes," Holtzman says.

Yamada notes that the new technique currently can only measure single soluble copies of tau. Multiple copies of soluble tau can stick together, and further adaptations of the assessment technique are needed to see if such chains are present in the fluids between brain cells before and after tangles begin to form.

Scientists also plan further investigations into how and why brain cells

secrete soluble tau.

More information: Yamada K, Cirrito JR, Stewart FR, Jiang H, Finn MB, Holmes BB, Binder LI, Mandelkow E-M, Diamond MI, Lee VM-Y, Holtzman DM. In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice. *The Journal of Neuroscience*.

Provided by Washington University School of Medicine in St. Louis