Alzheimer’s Findings Resolve Dispute Over How Disease Kills Brain Cells

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For a decade, Alzheimer's disease researchers have been entrenched in debate about one of the mechanisms believed to be responsible for brain cell death and memory loss in the illness.

Now a team of researchers at UC San Diego and the University of Michigan have settled the dispute, an achievement which will improve understanding of the disease and could one day lead to better treatments.

Michael Mayer, an assistant professor in the U-M departments of Biomedical Engineering and Chemical Engineering, and Jerry Yang, an assistant professor in the Department of Chemistry and Biochemistry at UCSD, and their colleagues found a flaw in earlier studies supporting one side of the debate. Their findings are published online in the *Journal of Neurotoxicity Research* and will appear in the journal's May print edition.

Their results clarify how small proteins called amyloid-beta peptides damage brain cell membranes, allowing extra calcium ions to enter the neurons. An ion is an electrically-charged particle. An ion imbalance in a cell can trigger its suicide.

Amyloid-beta peptides are the prime suspects for causing cell death in Alzheimer's, although other mechanisms could also be to blame. The disease is not well understood.

The researchers confirmed evidence found by others that amyloid-beta peptides prick pores into brain cell membranes, opening channels where calcium ions can rush in. This was one mechanism the field had contemplated, but other evidence suggested a different scenario. Some researchers believed that the peptide caused a general thinning of the cell membranes and these thinned membranes lost their ability to keep calcium ions out of brain cells. Mayer and Yang disproved this latter theory.

"When you understand these mechanisms better, you have a better chance of being able to pharmaceutically counteract them as a possible treatment. For instance, if amyloid-beta thins membranes, this general effect might be difficult to treat. On the other hand, if it forms pores, this effect might be treatable with pore blockers. Ion channel blockers are medications sold today to treat a variety of diseases," Mayer said. He cautions that much research is needed before it is known whether such medications are effective and safe to treat Alzheimer's.

Mayer and Yang were able to explain the other experimental results that blamed cell membrane thinning for uncontrolled calcium ion fluctuations. It turns out that in these studies, trace amounts of residual solvent used to prepare the peptide had a dramatic effect. The Michigan- and UCSD-led team reproduced these experimental results using only the solvent, without the peptide. The solvent is called Hexafluoroisopropanol, or HFIP.

"HFIP is a good solvent used to break up clumps of the peptide to prepare for experiments, but it's toxic and membrane-active. What we found was that the reported preparation procedure did not remove the solvent effectively," Mayer said. "Our findings are watertight since we could reproduce the thinning effect in the absence of amyloid-beta peptides by this solvent alone."

Yang and Mayer carried out these experiments by examining how the electric current fluctuates across artificial membranes and live human cancer cell membranes in the presence of the amyloid-beta peptide. (Cancer cells are often used in biological experiments because they reproduce rapidly.) They also measured the fluctuation of ions in mouse brain cells and in genetically-modified mouse brain cells that produce human amyloid-beta peptide.

In all these trials, the electrodes measuring across the cell membrane registered spikes in electric current consistent with what researchers would expect from the formation of pores in the cell membrane and not from thinning of membranes.

To cross-check that the spikes in electric current were caused by amyloid pores, they added zinc to the specimens that hadn't been exposed to the solvent. Zinc is known to act as a blocker to clog amyloid pores in cell membranes. Sure enough, the electrical current through the cell membrane held steadier, suggesting that the zinc was blocking the pores.

"This ongoing controversy has slowed our own progress in Alzheimer's research as well as progress in other labs," Mayer said. "It is our hope that putting this disagreement to rest by showing that amyloid beta peptides do not thin membranes but instead form discrete pores in membrane can help the field move forward at a more rapid pace."

The team's paper is titled "Amyloid-beta-induced ion flux in artificial lipid bilayers and neuronal cells: Resolving a controversy." Members of Mayer's and Yang's research groups contributed to this study, as did the research group of R. Scott Turner, an associate professor of neurology at the U-M Medical School. The study was funded by the Wallace H. Coulter Foundation, the National Science Foundation, the Alzheimer's Disease Research Center and the Alzheimer's Association. UCSD and U-M are seeking commercial partners to license and develop these innovations into useful products. Further information can be found at: http://invent.ucsd.edu/technology/cases/2007/SD2007-018.shtml and http://invent.ucsd.edu/index.shtml

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