# Putting the squeeze on Alzheimer's (w/ Video)

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Brain cells exposed to a form of the amyloid beta protein, the molecule linked to Alzheimer's disease, become stiffer and bend less under pressure, researchers at UC Davis have found. The results reveal one mechanism by which the amyloid protein damages the brain, a finding that could lead to new ways to screen drugs for Alzheimer's and similar diseases.

The researchers, led by Gang-Yu Liu, professor of chemistry, and Lee-Way Jin, associate professor of pathology and a researcher at the UC Davis Alzheimer's Disease Center, used a cutting-edge microscope to measure how cells respond to physical pressure. Their findings are published this month in the Proceedings of the National Academy of Sciences.

The microscope, located at UC Davis' Spectral Imaging Facility, combines an atomic force microscope and a confocal microscope. It is one of a handful in the United States and one of the most advanced of its type, Liu said.

An atomic force microscope uses a fine needle to visualize the features of a surface with exquisite resolution and precision; it is used more often in materials science than in cellular biology. A confocal microscope can view living cells in culture media and in three dimensions.

The team put a glass microbead on the tip of the AFM needle and used it to press down on living cells. By measuring the forces required to

squeeze the cell under the bead, they could calculate the stiffness of both the cell membrane and the cell contents.

"This is a simple method for measuring the stiffness of a cell — like pushing down on a spring," Liu said.

Amyloid-beta peptide is found in tangled fibrils and plaques in the brains of Alzheimer's patients and is thought to be the cause of the disease and similar conditions, such as "mad cow" disease. It can exist in different forms: as individual peptide units (monomers); as short chains of peptides (oligomers); and as fibrils.

Liu and Jin exposed cultured neurons (brain cells) to the three different types of amyloid, and measured their response to pressure. They found that the intermediate, oligomer, form had the greatest effect in stiffening the cells.

From the measurements, Liu and Jin deduced that the amyloid oligomers probably insert themselves into the cell membrane, changing its properties. Some of the molecules cross the membrane completely and affect the network of proteins that provides a "skeleton" within the cell.

They also found that when the cells were treated with amyloid oligomers, other ions flooded into the cell, showing that the membrane's function had been damaged.

The "squeeze" test could be used as a screening method for potential drugs for Alzheimer's and other diseases, Liu and Jin predicted.

Normal brain cells are the "squishiest" among the cell types they have tested with the technique, Liu said. The cells readily deform under pressure, but recover. At the other end of the scale, skin cells (keratinocytes) are very stiff and resistant to pressure, but shatter under

stress.

Provided by University of California - Davis