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Scientific Discovery Could Lead to New Types of Drugs for Alzheimer's and Other Degenerative Diseases

A ground-breaking new research approach to understanding the cellular processes of Alzheimer's and other degenerative diseases has revealed a promising pathway to the development of new types of drugs for these diseases.

The discovery, made in the laboratory of Ratnesh Lal, research scientist in the Neuroscience Research Institute (NRI) at the University of California, Santa Barbara, is published in this week's online issue of the Proceedings of the National Academy of Sciences (PNAS).

The research describes a new way of understanding the degeneration of brain cells in patients with Alzheimer's, Huntington's, and Parkinson's diseases, as well as other degenerative diseases. Misfolded proteins in the cell membrane, and subsequent changes in the electrical properties of cells, provide the explanation for the cell degeneration. Specific three-dimensional structures of misfolded proteins are embedded in the cell membrane.

"It has long been thought that amyloid plaque, which has been studied for more than 30 years, was the cause of Alzheimer's disease," said Lal. "Plaque isn't the cause." He explained that the fibers of plaque are too large to directly affect small cells.

The answers may come from small globs of misshapen, misfolded proteins that make well-defined holes in cell membranes and disrupt their electrical activity, according to the study.

Amyloid protein is a sticky, globular substance created when normal cellular proteins become twisted and contorted into abnormal shapes. While amyloid formation has been associated with diseases like Alzheimer's, Parkinson's, and Huntington's, scientists have puzzled over whether and how it actually kills cells and causes disease. To gain insight into this mysterious process, Lal and his research team examined the three-dimensional structure of several different proteins associated with these diseases. The researchers observed that all of the proteins folded into structures resembling ion channels, or pores within cell membranes. These pores control the electrical properties of the cell by regulating the flow of charged particles (ions) such as calcium.

When embedded into artificial membranes, the misfolded proteins were able to produce electrical currents, confirming their similarity to ion channels. Since abnormal ion balance is known to disrupt cell function and cause degeneration, these results provide proof of a possible mechanism by which amyloid formation may lead to the cellular destruction seen in these neurodegenerative diseases.

"These ion channels could serve as a model system for designing preventive and therapeutic drugs," said Lal. "You don't need large aggregates of these amyloid proteins, the plaque, to have this disruption. Rather, small aggregates, when in contact with membrane, form ion channels and allow passage of ion current. By controlling activity and designing specific drugs to regulate these channels, we might be able to prevent and/or treat various diseases related to the amyloids."

These findings provide a major piece of the puzzle about the underlying protein misfolding associated with these degenerative diseases. Besides the diseases already mentioned, other degenerative diseases that also result from misfolded proteins include cystic fibrosis, type II diabetes, cerebrovascular dementia, arthritis, tuberculosis, as well as British and Danish famial dementias.

The researchers used atomic force microscopy (AFM) to view the ion channels. By using the AFM they were able to view these "bio-nano" molecules. The AFM allows for a look at these very small channels, which would be very difficult if not impossible to see in their native, cell-like environment with electron microscopy.

In addition to Lal, the authors of this path-breaking paper are: Arjan Quist and Ivo Doudevski of the NRI at UCSB; Hai Lin of the University of Pittsburgh; Rushana Azimova and Bruce Kagan of the University of California, Los Angeles; and Douglas Ng, Blas Frangione, and Jorge Ghiso of New York University.

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