Researchers discover weak link in Alzheimer's drug candidates

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Ratnesh Lal, a UCSD bioengineering and mechanical engineering professor, led a multi-disciplinary team of researchers in a breakthrough discovery relating to Alzheimer's disease. Credit: UC San Diego

Some current therapies being investigated for Alzheimer's disease may cause further neural degeneration and cell death, according to a breakthrough discovery by UC San Diego researchers.

By combining three dimensional computer simulations with high resolution atomic force microscopy membrane protein and cell imaging, electrical recording and various cellular assays, UCSD nano-biophysicist Ratnesh Lal and his colleagues investigated the structure and function of truncated peptides, known as nonamyloidgenic peptides, formed by some Alzheimer's drug candidates. The researchers found that the nonamyloidgenic peptides formed active ion channels that caused the

cells to take in very high levels of calcium ions, which damaged synaptic efficiency and eventually killed neurons, neurons that are linked to memory loss in human brain.

As a result of their current findings and related previous work, Lal and his colleagues believe that aggregate-forming amyloidogenic peptides promote neurological diseases by forming holes or channels in cell membranes, disturbing ionic homeostasis by allowing unwanted ion flow in-and-out of cells, and most importantly allowing toxic amounts of calcium ions into neural cells. Truncated, shorter non-amyloidogenic peptide fragments that also form ion channels and alter neuronal viability, are assumed by biomedical researchers to be non-toxic and are currently targeted to treat Alzheimer's disease patients. Details of their research were recently published in a paper entitled "Truncated β-amyloid peptide channels provide an alternative mechanism for Alzheimer's Disease and Down syndrome" in the *Proceedings of the National Academy of Sciences.*

"There are several drugs to treat Alzheimer's in Trials I and II, but we don't believe that they will be adopted for clinical usage," said Lal, a joint professor in the UCSD Jacobs School of Engineering's Department of Mechanical and Aerospace Engineering and Bioengineering. We believe we are providing the most direct mechanism of Alzheimer's disease and Down Syndrome pathology. Through our research we have provided a structure and mechanism (an ion channel) that can account for the pathology. The strategy to control the activity of this structure - the opening and closing of the channel - should be targeted for an effective treatment."

Lal and his colleagues are now working on a 3D structural model of the ion channel using their data to identify the domains (or sites) of the channel for designing effective therapeutics. Lal said the use of advanced nanotechnology and biology combined with a multi

disciplinary approach, aided in the researchers' breakthrough discovery.

"Without advances in technology and a multi disciplinary approach this kind of complex research would not move forward," said Lal, a trained physicist and neurobiologist who joined the UCSD faculty in January 2010 from the University of Chicago. "My goal is to provide practical solutions for effective human health management using advances in nanoscience and technology with a multidisciplinary and multi-scale (nano-to-translational) integrated approach," he added.

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