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Experimental drug blocks toxic ion flow linked to Alzheimer's disease

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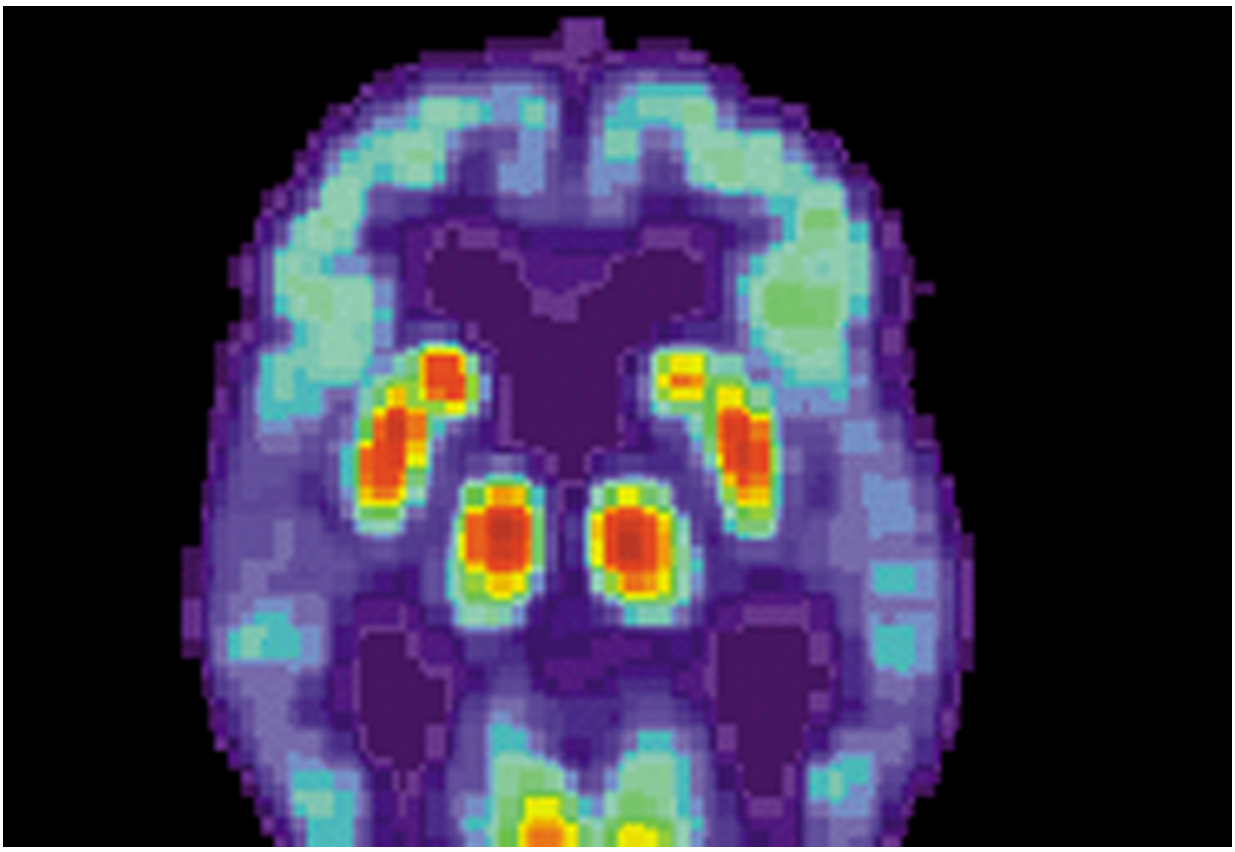

PET scan of a human brain with Alzheimer's disease. Credit: public domain

An international team of researchers has shown that a new small-molecule drug can restore brain function and memory in a mouse model of Alzheimer's disease. The drug works by stopping toxic ion flow in the

brain that is known to trigger nerve cell death. Scientists envision that this drug could be used to treat Alzheimer's and other neurodegenerative diseases such as Parkinson's and ALS.

"This is the first drug molecule that can regulate memory loss by directly blocking ions from leaking through nerve cell membranes," said Ratnesh Lal, a professor of bioengineering at the University of California San Diego and co-senior author of the study.

Various studies have linked Alzheimer's disease to the accumulation of two particular proteins in the brain called amyloid-beta and tau. One theory is that these protein clusters create pores in nerve cell membranes that allow ions to travel in and out uncontrollably. This would alter ion levels inside the cells and in turn trigger neuronal dysfunction and cell death.

The new drug, a small molecule called anle138b, blocks these pores from moving ions in and out of nerve cells. Anle138b attaches to both amyloid-beta and tau protein clusters and deactivates the pores created by these clusters.

Researchers administered anle138b to mice with a genetic predisposition for developing an Alzheimer's-like condition. The mice had symptoms such as abnormal brain function, impaired memory and high levels of either amyloid-beta or tau proteins in the brain. Treatment with anle138b normalized brain activity and improved learning ability in mice.

The study was led by the German Center for Neurodegenerative Diseases, the University Medical Center Göttingen, the Braunschweig University of Technology, the Max Planck Institute for Biophysical Chemistry, the Center for Nanoscale Microscopy and Molecular Physiology of the Brain in Göttingen, Germany, and the University of California San Diego. Researchers published their findings on Dec. 5 in

EMBO Molecular Medicine.

Christian Griesinger, a professor at the Max Planck Institute for Biophysical Chemistry and co-senior author of the study, noted, "The drug is able to reach the brain when taken orally. Therefore, it is easy to administer, and we are currently performing toxicology studies to eventually be able to apply anle138b to humans."

The team cautions that since the drug has so far only been tested in mice, it is unclear how well it would perform in humans. "I would like to emphasize that none of the current animal models fully recapitulate the symptoms seen in Alzheimer's patients. Thus, care has to be taken when interpreting such data. However, our study offers evidence that anle138b has potential for neuroprotection," said André Fischer, a senior researcher at the German Center for Neurodegenerative Diseases and the University Medical Center Göttingen, who is also a co-senior author of the study.

While collaborators in Germany will be pursuing clinical studies in human patients with neurodegenerative diseases, Lal and his research group at the UC San Diego Jacobs School of Engineering are particularly interested in testing anle138b on a variety of other diseases that are linked to toxic ion flow caused by amyloid proteins, including diabetes, tuberculosis and certain types of cancer. Lal's group has performed extensive research on amyloid ion channels and their roles in these diseases. "Blocking the ion leakiness of amyloid channels using anle138b could be an effective therapy for various diseases," Lal said.

Lal serves as co-director for the Center of Excellence for Nanomedicine and Engineering, a subcenter of the Institute of Engineering in Medicine at UC San Diego. His research group will also work on targeted delivery of the drug using their patent pending "nanobowls," which are magnetically guided nanoparticles that can be packed with drugs and

diagnostic molecules, deliver them to particular sites in the body and release them on demand. Future studies will focus on using these nanobowls to deliver anle138b to the brain, as well as other diseased tissues and organs affected by toxic amyloid-beta ion channels.

More information: "The diphenylpyrazole compound anle138b blocks Aβ channels and rescues disease phenotypes in a mouse model for amyloid pathology." *EMBO Molecular Medicine* (2017). DOI: 10.15252/emmm.201707825

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