Laboratory research shows promising approach to preventing Alzheimer's

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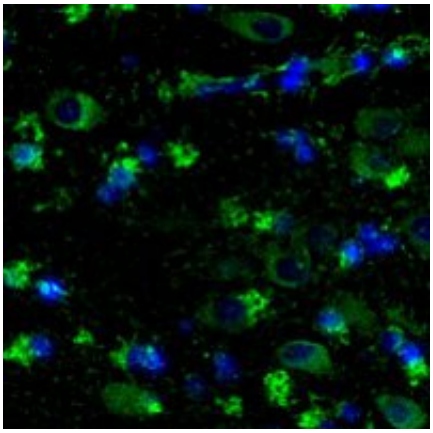

The image shows that the enzymes ATase1 and ATase2 are abundantly present in the brains of Alzheimer's disease patients. The green color labels the ATases while the blue labels the nuclei. Both neurons and glial cells are shown.

(Medical Xpress) -- As scientists struggle to find an effective way to prevent Alzheimer's disease, researchers at the University of Wisconsin School of Medicine and Public health may have found a new approach to interrupting the process that leads to the devastating disease.

Building on their knowledge of two enzymes that control an "uber" enzyme critical to the development of the disease, the scientists found that the two enzymes are present in the brains of Alzheimer's patients. And by screening some 15,000 compounds, they discovered two that lower activity of the enzymes in test tubes.

The research, published in the Jan. 20 issue of *The Journal of Biological Chemistry*, offers hope for a novel approach to preventing Alzheimer's disease (AD). No other research team has focused on the two enzymes and the way they affect the uber enzyme.

More than 5 million people in the United State may have Alzheimer's, a complicated disease that has been a challenge to understand. Many researchers have zeroed in on amyloid, which accumulates in the brains of patients with Alzheimer's, as one of the main culprits.

Amyloid originates from a protein called amyloid precursor protein, or APP. An enzyme called beta-site APP cleaving enzyme, or BACE1, cuts APP to produce amyloid and another small fragment called AICD. Both amyloid and AICD are toxic to nerve cells and have been linked to AD.

The current research, under the direction of Dr. Luigi Puglielli, associate professor of medicine at the UW School of Medicine and Public Health (SMPH), centers generally on BACE1. Elevated levels of this enzyme, which rise normally during aging, may lead to high levels of amyloid.

"The prediction is that if you prevent the up-regulation of BACE1 caused by aging, you could prevent the increased risk of Alzheimer's disease that is also associated with aging," says Puglielli, of the Geriatric Research and Education Center at the William S. Middleton Memorial Veterans Hospital in Madison.

Drugs to block BACE1 could, in theory, prevent the build-up of amyloid and help slow or stop the disease. A handful of companies are devoting resources to finding various ways to block BACE1; the Wisconsin Alumni Research Foundation (WARF) has filed a patent for the compounds Puglielli has discovered to be effective.

In 2007, Puglielli and his colleagues discovered that regulation of BACE1 occurs when it undergoes a molecular process called acetylation, which changes its structure. If BACE1 is acetylated, it can travel through the cell in a series of steps to produce the amyloid precursor. If it isn't acetylated, it takes another path toward degradation.

The School of Medicine and Public Health team set out to find what makes the acetylation occur, and in 2009 found that two enzymes-ATase1 and ATase2-are responsible.

In the current paper, the researchers found that both ATase1 and ATase2 are expressed in neurons and glial cells. The enzymes are also up-regulated in the brains of AD patients. The researchers looked for compounds that could shut down ATase1 and ATase2, creating an assay to measure the enzyme levels in test tubes so they could screen about 15,000 compounds. The experiments showed that 186 compounds could do the trick.

The scientists then introduced the compounds into several kinds of cellular systems to see if they could reach ATase1 and ATase2 inside the cells.

"We ended up with two compounds that could affect the enzymes in living cells-compound 9 and compound 19," Puglielli says.

Analyzing the biochemistry and cell biology of the compounds, the scientists found that they shut down ATase1 and 2, which in turn resulted in less acetylation of BACE1 - and therefore less production of the amyloid precursor protein.

The UW-Madison scientists are now testing the compounds in an animal model of Alzheimer's disease. Preliminary results are encouraging.

"Alzheimer's is a complex disease, but finding compounds that affect BACE1 through these two enzymes gives us hope that we are making progress with a novel approach to preventing the disease," Puglielli says.

Provided by University of Wisconsin-Madison