MedicalXpress

Molecule that spurs cell's recycling center may help Alzheimer's patients

March 16 2011

Cells, which employ a process called autophagy to clean up and reuse protein debris leftover from biological processes, were the original recyclers. A team of scientists from Paul Greengard's Rockefeller University laboratory have linked a molecule that stimulates autophagy with the reduction of one of Alzheimer's disease's major hallmarks, amyloid peptide. Their finding suggests a mechanism that could be used to eliminate built-up proteins in diseases such as Alzheimer's, Down syndrome, Huntingdon's and Parkinson's.

The molecule, called SMER28, spurs autophagy, which in turn eliminates unwanted materials such as amyloid-beta, the protein aggregates that cause Alzheimer's plaques. Increasing autophagy, either through a drug or a natural process such as diet, could improve the outcome for people with neurodegenerative diseases, the researchers report in the FASEB Journal.

"Much effort has been carried out to prevent the formation of amyloid-beta without much success," says Greengard, who is Vincent Astor Professor and head of the Laboratory of Molecular and Cellular Neuroscience. "In order to develop better-suited therapies, alternative approaches are clearly needed. One approach would be the identification of potential therapeutic targets that enhance the removal of amyloid-beta, for example, by increasing autophagy."

Most prior strategies to develop Alzheimer's disease drugs were designed to inhibit the formation of the toxic amyloid-beta. Greengard, who

directs the Fisher Center for Research on Alzheimer's Disease at Rockefeller, and his colleagues propose a radically different approach: boosting a cellular mechanism to enhance their clearance. This approach, says Marc Flajolet, a research assistant professor in Greengard's lab, may also be beneficial for targeting a hallmark of advanced Alzheimer's disease, twisted fibers of tau protein that build up inside nerve cells and cause tangles.

The researchers, led by Yuan Tian, a postdoctoral fellow in Greengard's lab, tested various compounds for their ability to reduce the buildup of amyloid-beta by exposing cultured cells to compounds known to activate autophagy. They then compared the effect of these compounds by removing growth factors from the culture medium, a well-established stimulant of autophagy known as "starvation."

The researchers found that SMER28 was the most effective compound, and focused their studies on it to characterize the cellular components involved in this phenomenon. They compared the effect of SMER28 on amyloid-beta formation using normal cells or cells where the expression of genes known to be involved in autophagy was reduced or abolished. They found that three important autophagic players were involved, and one of them was essential for SMER28's effect.

Identifying a cure for Alzheimer's disease remains a major challenge. Four drugs are currently approved by the Food and Drug Administration to treat Alzheimer patients. Unfortunately none of these drugs halt progression of the disease and their impact on cognitive defects are minimal. On top of that, current strategies are associated with severe side effects. This limitation was highlighted recently by failures in various clinical trials.

"Our work demonstrates that small molecules can be developed as therapies, by activating a cellular function called autophagy, to prevent

Alzheimer's disease," says Flajolet. "By increasing our understanding of autophagy, it might be possible to stimulate it, pharmacologically or naturally, to improve the quality of life for aging people."

The results also suggest the power of diet to prevent damage to neurons. It has been known that a low calorie diet is beneficial for longer life expectancy as well as for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. "Our results suggest that a low calorie diet might lead to a higher autophagy activity that might delay or prevent aging and neurodegenerative diseases," says Flajolet.

Provided by Rockefeller University