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Researchers find agents that speed up destruction of proteins linked to Alzheimer's

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Taking a new approach to the treatment and prevention of Alzheimer's disease, a research team led by investigators at the Mayo Clinic campus in Florida has shown that druglike compounds can speed up destruction of the amyloid beta (A-beta) proteins that form plaque in the brains of patients with the disorder.

Researchers say their study, published in the April 22 online issue of *PLoS ONE*, demonstrates that this strategy is a viable and exciting alternative to the approach most drug designers have taken to date.

"Historically, a lot of effort has been made at stopping initial production of A-beta in order to halt development of Alzheimer's disease, but we are interested in what happens to A-beta after it is produced," says the study's lead researcher, Malcolm Leissring, Ph.D., from Mayo's Department of Neuroscience.

The researchers found two chemicals that could speed up activity of a molecule, insulin-degrading enzyme (IDE), which helps chew up A-beta proteins produced in the brain.

In laboratory experiments, they found that one agent, dubbed Ia1, increased the activity of IDE by about 700 percent, while the second compound, Ia2, increased it by almost 400 percent.

"This study describes the first examples of synthetic small-molecule activators of IDE, showing that activation of this important enzyme with

druglike compounds is achievable," Dr. Leissring says.

"If it is possible to generate drugs for human use that stimulate the activity of IDE, these agents might offer therapeutic benefit for treating and preventing Alzheimer's disease," he says.

Since IDE also chews up excess insulin in the body, the role for which it is primarily known, small molecule activators might also be useful in controlling diabetes, he says.

A-beta is produced when a larger protein, known as the amyloid precursor protein (APP), is cut into smaller pieces by other enzymes known as beta-secretase and gamma-secretase.

Not much is known about what happens to A-beta after it is produced, says Dr. Leissring. What is known is that A-beta proteins, especially those of a certain length, are found sticking to each other in clumps of plaque in the brains of patients with Alzheimer's disease. Because of this, drug designers have taken the tack of trying to inhibit the cutting of APP by beta-secretase and gamma-secretase, reasoning that if A-beta isn't produced, plaques won't form. But, to date, this and other approaches have not yet resulted in clearly beneficial therapies.

This group of researchers is focused, instead, on what ultimately happens to A-beta produced in a normal brain, and have found that, surprisingly, more than 99 percent of all A-beta is destroyed immediately, Dr. Leissring says.

"Normally, there is a balance between production and elimination of A-beta in the brain," he says. "We don't know why that balance is skewed in individuals that develop Alzheimer's disease, but one hypothesis is that, as we age, activity of the enzymes that destroy A-beta goes down."

IDE was the first degrading enzyme, or protease, implicated in this imbalance, Dr. Leissring says. The enzyme is shaped like a clamshell that opens and shuts, like the well-known video game protagonist, Pac-Man, he says. A-beta fits inside the open enzyme, which then closes and gobbles up the protein inside.

In this study, the research team screened tens of thousands of chemicals looking for ones that could bind to IDE and modulate its activity. That led to discovery and testing of Ia1 and Ia2.

Dr. Leissring says that the findings don't suggest that these compounds should be tested in humans. Rather, he says they have shown that activating IDE in a test tube is possible and that further work is needed on this new approach.

"The story that is emerging now is that the level of activity of A-beta degrading enzymes may play a significant role in the development of Alzheimer's disease," he says. "We are actively pursuing the next chapter."

Source: Mayo Clinic (news : web)