

Alzheimer's Disease Research Review

Better Health Through Research

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What Turns Tau into a Neuron Killer?

Answer emerges from research supported by Alzheimer's Disease Research

A scientist sponsored by Alzheimer's Disease Research has helped to show that the memory loss from Alzheimer's disease may be caused not by cell death but by the buildup of tau protein in "dendritic spines," the parts of nerve cells that store memories.

Under normal conditions, tau contributes to a cell's supportive framework of proteins. By contrast, in an Alzheimer's disease brain, according to Dr. Dezhi Liao and his colleagues at the University of Minnesota, tau proteins are forced toward the dendrites, where they form clumps that disrupt communication from other neurons.

However, when researchers used genetically modified tau proteins that couldn't be clumped, they were able to block the buildup of damaging tau protein in rat nerve cells.

The research, published in the journal *Neuron*, raises the possibility of developing new drugs that could stop tau from entering the dendritic spines, potentially halting the memory loss associated with early stage Alzheimer's disease.

"The work of Dr. Liao and his colleagues has given us a critical window into how dementia initially disrupts neurons," says Dr. Brian K. Regan, Chairman, Board of Directors of Alzheimer's Disease Research. "This could lead ultimately to therapies that block Alzheimer's disease in its earliest stages."

Alzheimer's Disease Research has contributed \$150,000 toward Dr. Liao's research.

Alzheimer's Brain Loses Ability to Clear Beta-Amyloid Plaque

Findings could shape future drug therapies

Scientists with Washington University School of Medicine may have resolved a major question: do rising levels of beta-amyloid plaque in the Alzheimer's disease brain mean that the brain is producing more plaque or failing to clear plaque?

A research team led by Dr. Randall Bateman compared a group of 12 patients with early Alzheimer's disease to 12 cognitively healthy patients of the same age. Both groups produced beta-amyloid protein at the same average rate, but the patients with Alzheimer's disease cleared 30 percent less of the protein. Over 10 years, scientists estimate, this deficit would cause a beta-amyloid buildup equal to that seen in the brains of Alzheimer's disease patients.



“These findings support the idea that impaired a-beta clearance is fundamentally linked to Alzheimer's disease,” Bateman says.

As scientists learn more about how the brain breaks down and disposes of beta-amyloid, Bateman adds, they may be able to diagnose and treat Alzheimer's disease before symptoms develop. Alzheimer's Disease Research has previously contributed \$150,000 to Dr. Bateman's work.

Chairman's Corner

Catching it early

One of the most insidious features of Alzheimer's disease is how quietly it steals over the human brain. Many months or even years may pass before symptoms appear — and all the while the assailant is tightening its grip.

The more we know about the disease's infancy, then, the better chance we have of stopping it before it does serious damage.

Fortunately, as this issue of **Alzheimer's Disease Research Review** makes clear, scientists are opening up a window on those earliest moments.

One of the researchers we've funded in the past has shown how the brain, under the influence of Alzheimer's disease, loses its ability to shed toxic-amyloid protein. Another has shown how tau proteins begin clumping in the cell's memory sites, laying the groundwork for the devastation ahead.

Taken together, these findings raise the hope that we can one day catch Alzheimer's disease earliest footprints in the human brain — and stop it before it takes another step.

Research Roundup

Diabetes may heighten Alzheimer's risk

Diabetes may impair the brain's ability to produce cholesterol, leaving diabetes patients at greater risk of developing Alzheimer's disease, according to scientists at Joslin Diabetes Center in Boston.

"Since cholesterol is required by neurons to form connections with other cells, this decrease in cholesterol could affect how nerves function for appetite regulation, behavior, memory and even pain and motor activity," says Dr. C. Ronald Kahn. "Thus, this has broad implications for people with diabetes."

The findings add to a mounting body of evidence that people with diabetes are more prone to memory loss and altered brain function. Dr. Kahn points out that the brain contains more cholesterol than any other organ in the human body and won't function normally if it can't produce enough.

Gene therapy could prevent memory loss

Scientists at the Gladstone Institute of Neurological Disease in San Francisco have developed a new gene therapy that appears to prevent memory problems in mice with Alzheimer's disease.

The therapy is aimed at boosting an enzyme called EphB2, which regulates neurotransmission in the brain's memory centers. Beta-amyloid proteins directly bind to the enzyme and degrade it, which explains why it is found at reduced levels in people with Alzheimer's disease.

"What we were most curious about, of course, was whether normalizing EphB2 levels could fix memory problems caused by amyloid proteins," says senior author Lennart Mucke. "We were absolutely thrilled to discover that it did."

"Based on our results, we think that blocking amyloid proteins from binding to EphB2 and enhancing EphB2 levels or functions with drugs might be of benefit in Alzheimer's disease. We are excited about these possibilities and look forward to pursuing them in future studies," says Lennart Mucke.

Breaking the amyloid-antioxidant link

Scientists with the University of California, San Diego, have found a way to prevent beta-amyloid from disrupting a key enzyme that clears away excess oxidants in the brain.

"We were able to determine that amyloid beta and this anti-oxidant enzyme, catalase, interact," says report author Lila Habib, "and that this interaction harmed catalase so it wasn't able to perform its physiological function: to degrade hydrogen peroxide into oxygen and water."

However, by coating the amyloid with a small molecule to prevent its interaction with other proteins, scientists were able to restore the activity of the catalase and return hydrogen peroxide to normal levels.



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Monthly giving helps reduce overhead

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Automatic payments are particularly effective because they save us the cost of stamps and envelopes — reducing our overhead and allowing us to allocate more of every dollar to the fight against Alzheimer's disease.

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