SAVING A LIFETIME OF MEMORIES

BY JENNIFER NEJMAN BOHONAK
Neuroscience

photo: Stu Rosner

NEW BWH STUDY FINDS PROTEIN FRAGMENTS CAN DISRUPT MEMORY

As researchers work to advance the treatment of Alzheimer's disease, they seek to uncover the chain of events in the brain that causes this disorder.

"You need a detailed understanding of the disease mechanism to create treatments," says Dennis Selkoe, MD, who co-directs the Center for Neurologic Diseases in the Department of Neurology at Brigham and Women's Hospital and Harvard Medical School.

It's been many decades since scientists discovered that amyloid plaques accumulate in the brains of Alzheimer's patients. They've wondered what role these plaques play in this neurological disease that destroys brain cells, shrinks the brain, and steals one's memory, personality, and ability to live independently.

Amyloid plaques are chiefly composed of long polymers of amyloid-beta protein that clump together, building a cement-like mass that cannot easily float around brain cells.

A point of debate in the field is whether the plaques are toxic, or whether some other form of amyloid-beta protein or another agent is at work.

THE PUZZLE

Selkoe has worked on the Alzheimer's puzzle for 25 years. He helped construct the knowledge base of amyloid-beta protein that has driven much of the research on Alzheimer's today. During the last decade, Selkoe, his colleagues, and other labs have proposed that the amyloid plaques act as "jails" for much smaller assemblies of amyloid-beta protein—and it's these smaller assemblies that cause trouble in the brain. He believes that the creation of these plaques is an attempt by the brain to sequester the "bad guys" and keep them locked up. "But it doesn't really protect the patients in the long run," he adds.

Research published in the summer of 2008 by medical student Ganesh Shankar, PhD, Selkoe, and their colleagues points the finger at a small aggregate of amyloid-beta protein called a "dimer" as the possible initial culprit that leads to Alzheimer's disease.

Dennis Selkoe, MD (right), and medical student Ganesh Shankar, PhD (left), published research that is helping scientists understand the chain of events that leads to a person developing Alzheimer's disease.

The chain of events that Shankar and Selkoe believe eventually leads to Alzheimer's begins before the dimer forms. They start the story with amyloid precursor protein, a protein that sits in cell membranes and normally helps neurons grow and function. Neurons are the brain cells responsible for storing information, like memory.

Over the last two decades, Selkoe and other scientists have shown that certain enzymes in the brain act like scissors and cut this precursor protein into smaller parts—one of which is amyloid beta. If the brain does not get rid of amyloid beta efficiently, it can float around and stick to other amyloid-beta proteins to make clusters. These clusters can nestle against brain cells, apparently changing the cells' biochemical balance and, perhaps, eventually killing them.

Over time, the brain produces more and more amyloid beta, only some of which can aggregate into very large masses—the plaques. Eventually, there are too many dimers, trimers, and other groupings for the plaques to contain. This leaves the excess to float freely—potentially exposing the neurons to an injury that Shankar and Selkoe believe could lead to symptoms of memory loss and ultimately Alzheimer's disease.

WHAT IS STEALING OUR MEMORY?

Amyloid-beta protein is generated as a monomer, Shankar explains. He compares the protein in this state to a single Lego block. These single Lego blocks of protein can bond together, forming groups of two called dimers, groups of three called trimers, and so on.

Researchers would like to pinpoint which form of amyloid beta is most toxic to neurons. They want to know precisely what affects the neurons' ability to communicate, and as a result, steals our memory. Is it one Lego block, a monomer? Is it two Lego blocks, a dimer? Or is it some larger form?

What Shankar and Selkoe found in their study, which used extracts from postmortem brain tissue typical of Alzheimer's disease patients, is that the two-molecule aggregate, the amyloid-beta dimer, was able to strongly hinder access points of communication between neurons.

They then collaborated with researchers at University College Dublin in Ireland to test the human amyloid-beta's effect on behavior. Researchers injected the free-floating amyloid-beta protein, taken from the brains of Alzheimer's subjects, into the brains of rats. The rats had been trained to avoid a dark chamber, but the free-floating amyloid-beta made them forget and go back into the dark chamber as if they had never been trained, Shankar says.

Notably, this finding may help explain why some people who are later diagnosed with Alzheimer's disease experience brief, transient episodes of memory loss five to 10 years before they develop clear-cut dementia. One explanation is that small amounts of amyloid-beta dimers are affecting neurons, Shankar says.

The study suggested that a person could have amyloid plaques containing many amyloid-beta dimers in the brain, but unless that person also had free-floating or diffusible amyloid-beta dimers, the person would not exhibit significant impairment in brain function, and thus, symptoms of Alzheimer's-type dementia. The plaques, in essence, appear to be sequestering the potentially toxic diffusible amyloid-beta dimers.

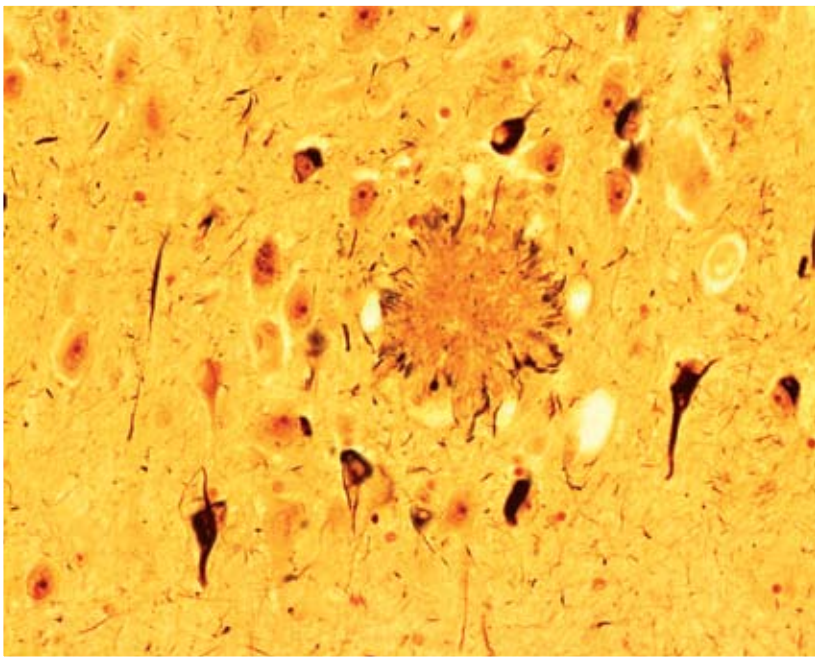
Shankar believes it's important to target the exact form of amyloid beta that is the first bad guy in Alzheimer's. Throwing drugs at the wrong form may not help patients as efficiently, he says.

The next step, Selkoe says, is to understand precisely how free-floating dimers bind to the brain's neurons. Understanding this event in Alzheimer's would help researchers figure out how to specifically block the effect of amyloid-beta protein on the neurons' communication system.

Catching Alzheimer's early, before it erodes a person's ability to remember, is believed to be the best hope to halt the disease. "It's all part of our steady march toward prevention," Selkoe says. ●

(Below) Amyloid plaques are chiefly composed of long polymers of amyloid-beta protein that clump together, building a cement-like mass that cannot easily float around brain cells. This glass slide of brain tissue has been stained to show the plaques and tangles of Alzheimer's disease.

(Right) Alzheimer's disease is known for affecting the brain in a way that interferes with normal activity and memory. The top image is a brain that has been affected by Alzheimer's disease. The bottom image shows a normal brain.



photos: Dennis Selkoe, MD; James Cavallini/Photo Researchers, Inc.

IS AN ALZHEIMER'S VACCINE ON THE HORIZON?

A type of Alzheimer's disease vaccine that is now in clinical trials should help blunt the strike against a patient's memory, if the theory proposed in a recent study is correct.

Ganesh Shankar, PhD, a medical student, and Dennis Selkoe, MD, co-director of the Center for Neurologic Diseases at Brigham and Women's Hospital and Harvard Medical School, researched certain antibodies that can recognize and neutralize the effects of free-floating amyloid-beta, a protein in the brain believed necessary to initiate the progression of Alzheimer's disease.

The goal of this type of immune therapy is to enable the body to neutralize smaller forms of amyloid beta, called dimers, Shankar says. Shankar and Selkoe's recent study found that these dimers are particularly toxic to the brain's memory systems and may initiate the process that leads to Alzheimer's disease.

Their research found that antibodies directed to a specific region of amyloid beta, the "N" terminus, were able to neutralize the effects of amyloid beta on memory processes much better than antibodies directed to other regions. If the theory is correct, then it's possible that an amyloid-beta antibody, called Bapineuzumab, which is directed at the "N" terminus, could work to slow or halt the progression of Alzheimer's in some patients.

Bapineuzumab is the first antibody in late-stage patient trials as a potential Alzheimer's disease treatment. The drug is designed to clear toxic amyloid beta from the brain, according to the two companies collaborating on the product, Elan Corp. and Wyeth Pharmaceuticals, the latter of which is now part of Pfizer. ●