Some neurological conditions manifest themselves early in life. Others, such as Alzheimer’s disease, afflict people at the opposite end of life’s spectrum. Alzheimer’s is a form of dementia that usually strikes after age 65, gradually destroying its victims’ memory, reasoning and judgment. It robs them of personality, identity and, eventually, life itself. Most Alzheimer’s sufferers die within about five years after being diagnosed with the disease, but some can linger for as long as 20 years, causing untold heartbreak and financial hardship to themselves and their families.

Since it was first identified by Dr. Alois Alzheimer more than 100 years ago, the disease has been associated with the atrophy and death of nerve cells (neurons) in the brain, accompanied by deposits of tiny, fibrous clumps of material called plaques that collect between the neurons. Both of these conditions are visible in the brains of autopsied Alzheimer’s patients. From the beginning, most researchers studying the disease believed that the plaques were the cause of the disease. But the plaques are sometimes seen in the autopsied brains of people who never had the disease. And the number of plaques deposited in the brain doesn’t correlate well with the number of neurons that die. In other words, numerous dead neurons aren’t necessarily accompanied by numerous plaques.

The Real Culprit
Several years ago, some studies suggested that the plaques themselves weren’t causing the disease. Rather, they suggested that the material from which the plaques form is directly responsible for weakening and killing neurons before it ever precipitates into plaques. But this suggestion poses a problem because this material, called Amyloid Beta or Abeta (pronounced AY BAYtuh), occurs naturally in the brain and may be an important part of normal brain function.

It Starts in the Synapses
In 2003, CSHL researchers Flavio Kamenetz, Helen Hsieh and Roberto Malinow, collaborating with other researchers, were able to show that an overabundance of Abeta in the brains of mice weakens the synapses—the parts of the neuron that connect to other neurons and allow them to communicate with one another. “Basically,” said Dr. Malinow, “we found that Abeta, which [has been implicated] as a causative agent in Alzheimer’s disease, directly causes weakening of synapses. That had been suggested by other studies, but this was the first direct demonstration of that,” he said. They also found that the more active a neuron is, the more Abeta it makes.
the more Abeta it makes.

Since Abeta occurs naturally in the brain, the findings by Kamenetz, Hsieh, Malinow, and the others led to the assumption that, under normal conditions, neurons produce Abeta in small amounts to help keep synaptic activity in balance and prevent overstimulation. Over the next few years, Malinow, Hsieh, Jannic Boehm, and other scientists conducted research to test this assumption and, sure enough, they found evidence that Abeta taps into some normal physiological processes that weaken synapses. These most recent findings were published in the December 2006 edition of the journal *Neuron*.

### Disappearing Receptors

Memories are formed in the brain when brain activity selectively strengthens some synapses while weakening others. Malinow’s group found that Abeta uses some of the normal machinery that the brain uses to weaken synapses. “We found that Abeta triggers a sequence of events that leads to the removal of receptors in the synapses,” said Malinow. Receptors are proteins that sit at the surface of a synapse, like lily pads on a pond. A neuron removes a receptor from its synapse by causing its surface, or membrane, to rise above the receptor, engulf it, and basically swallow it up inside the cell. “That’s a normal process that occurs in the brain,” explained Malinow, “but an overabundance of Abeta in the brain seems to turn that process on too much.” He added that, if the condition persists and the neuron removes enough receptors in a particular synapse, the cell will eventually remove the entire synapse.

### New Hope

These discoveries about the mechanism of synapse weakening and the role Abeta plays in this process may point the way to new therapies to treat Alzheimer’s patients. Finding an Abeta-specific receptor could eventually lead to the development of a drug that blocks Abeta from interacting with such a receptor.

In the meantime, Malinow suggests the use of genetically engineered receptors that are resistant to Abeta’s effects. “If we can generate mutant receptors that are not subject to this kind of regulation,” he said, “it will prevent Abeta from weakening or destroying the synapse.” This type of therapy is a strong contender because Malinow and other researchers are aware of such a receptor. “We know of a mutant receptor that is resistant to the normal physiological regulation,” he said. “We tested it to see if it would block the removal of receptors by Abeta, and it did.”

Other possible therapies involve using drugs that are known to interfere with the sequence of events, begun by Abeta, that lead to receptor removal.

### The Road Ahead

The discoveries by Malinow’s team enrich the entire field of Alzheimer’s research by strengthening the view that synapses are important in the disease process and by focusing interest on how the misregulation of synapses can occur. The search is now on for an Abeta-specific receptor that may be responsible for triggering synaptic degeneration.

Malinow and his team plan to follow other avenues of research in the Alzheimer’s field as well. “We’re interested in knowing how it is that [a neuron’s] activity causes the cell to produce more Abeta,” he said. He believes that if they can find that out, they might be able to understand why the level of Abeta increases without increased neuron activity and becomes misregulated as might be the case in Alzheimer’s disease.

“We’re figuring out all the molecular constituents and targets of this process,” said Malinow, “and we’re getting closer to identifying how some of the initial things that go wrong in the disease are occurring. There are still many open questions,” he cautioned, “but we’re figuring out some of the basic ones.”

---

**Amyloid Beta at Work**

In healthy brain tissue (left), brain activity and secretion of β-amyloid control each other in a balanced manner.

In Alzheimer’s disease (right), abnormal production of β-amyloid (Aβ42) results in abnormal decreases in brain activity.